

BMJ Open Elucidating bidirectional relationship between metabolic syndrome and elevated faecal haemoglobin concentration: a Taiwanese community-based cohort study

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ABSTRACT

Objectives To elucidate the bidirectional temporal relationship between elevated faecal haemoglobin (f-Hb) concentration and metabolic syndrome (MetS).

Design A longitudinal cohort study was conducted by utilising data on community-based periodical screening for colorectal cancer with faecal immunochemical test (FIT) and health check-up for MetS.

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

Participants We enrolled a total of 62,293 community residents aged 40–79 years.

Main outcomes and measures Bidirectional outcomes of FIT-positive and MetS were measured.

Results The presence of MetS at baseline led to a statistically significant 31% elevated risk of being incident FIT-positive (adjusted HR, (aHR)=1.31, 95% CI: 1.14 to 1.51) whereas the effect of those with FIT-positive at baseline on incident MetS was not statistically significant (aHR=1.06, 95% CI: 0.89 to 1.25) after adjusting for relevant confounders. Such an effect was particularly noted for three individual components (abnormal waist circumference, higher fasting plasma glucose and lower high-density lipoprotein).

Conclusions Our finding on the presence of MetS before FIT-positive based on bidirectional relationship assessment suggests the control of MetS may contribute to reducing the risk of colorectal neoplasia through the early surveillance of f-Hb. However, such a temporal epidemiological finding still needs to be verified by using other external data.

INTRODUCTION

While faecal immunological test (FIT) has been widely used worldwide to demonstrate a significant mortality reduction of colorectal cancer,^{1–3} additional values of faecal haemoglobin (f-Hb) concentration derived from FIT for predicting the risk of colorectal neoplasia and also its mortality have been corroborated in a dose–response manner in several previous studies.^{4–10} Such a favourable

Strengths and limitations of this study

- This is a prospective cohort study elucidating bidirectional relationships regarding the effect of both faecal immunochemical test (FIT) and metabolic syndrome (MeTS) status collected at baseline since 2001 on the incident outcome of each counterpart following over time until 2009.
- This is the first study disentangling the temporal sequence between MetS and FIT-positive that is very informative to design and plan appropriate primary prevention programme of colorectal neoplasia.
- Other unmeasured confounding factors, such as aspirin intakes, family history of colorectal cancer and the amount of physical activities should be taken into account in future studies.
- Other longitudinal cohort studies are required to verify these epidemiological associations.

predictive validity for colorectal neoplasia with f-Hb raised the possibility of using f-Hb as a quantitative surrogate biomarker for early prediction of colorectal neoplasia so as to dispense with the use of a longitudinal follow-up study for ascertaining colorectal neoplasia.

Better use of information on f-Hb may also be useful for elucidating bidirectional relationship between elevated f-Hb and metabolic syndrome (MetS), an emerging risk factor responsible for the risk of colorectal neoplasia that has been supported by epidemiological findings,^{11–14} molecular studies on obesity that predisposes to the development of insulin resistance via immunological pathway^{15–18} and others supporting the significant relationship between inflammation and tumorigenesis.^{19,20}

From the viewpoint of primary prevention of colorectal neoplasia, clarifying the

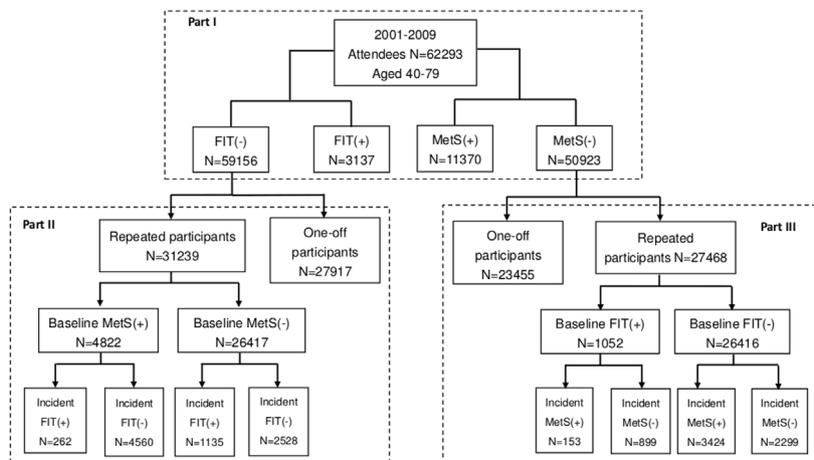


Figure 1 The flow chart for bidirectional prospective normal cohort study design (free of metabolic syndrome (MetS) or faecal immunological test (FIT) (+)). MetS, metabolic syndrome; FIT, Faecal immunological test.

temporal relationship between high f-Hb and metabolic syndrome would provide an insight into appropriate early primary prevention programmes. Lifestyle modification for the adequate control of those biomarkers in relation to MetS would be prioritised if MetS precedes the elevated f-Hb. On the other hand, if the reverse temporal relationship is demonstrated, how to reduce the level of f-Hb through the possible improvement of serum haemoglobin level²¹ may need to be considered.

We thus aimed to elucidate the bidirectional temporal relationship between high f-Hb and MetS utilising data on a population-based periodical screening for colorectal cancer with FIT and also health check-up for MetS.

METHODS

Study design

The flowchart of study framework is diagrammed in figure 1, which consists of three main parts based on the outcome of incident FIT-positive or incident MetS. In part I, a cross-sectional analysis was conducted to investigate the relationship between prevalent (first screen) FIT-positive and MetS. We further conducted a longitudinal cohort study containing part II and part III for elucidating the bidirectional relationship between FIT and MetS. Notably, only those with negative-FIT or non-MetS who underwent repeated screening were included in the long-term follow-up study in part II and part III.

The long-term follow-up of FIT-negative (part II in figure 1) and MetS-free (part III in figure 1) cohorts enables us to elucidate the bidirectional temporal relationship between the two factors. Considering FIT-positive as dependent variable and MetS status as an independent variable, the cohort of FIT-negative subjects with long-term follow-up and ascertainment of subsequent FIT-positive results was analysed (part II, figure 1). Regarding the study using incident MetS as dependent variable and FIT status as an independent variable, the MetS-free cohort was followed over time to ascertain incident MetS (part III, figure 1).

Study population and screening data collection

The Keelung Community Integrated Screening (KCIS) programme, which provided chronic diseases and neoplasia screening simultaneously, facilitated the elucidation of the temporal sequence between MetS and elevated f-Hb concentration after considering the demographic and lifestyle factors. Our study subjects were derived from a cohort invited to the KCIS programme for colorectal neoplasia service screening. The KCIS programme comprised multiple screening strategies, including five types of non-neoplastic diseases (including diabetes, hypertension, hyperlipidaemia, obesity, periodontal disease) and five types of neoplastic diseases (oral, cervical, breast, colorectal, liver cancers). The service of screening for multiple diseases along with the referral of attendees with positive results for confirmatory diagnosis was provided in an organised and integrated manner.¹¹

The screening population was composed of residents aged 40–79 years who had been screened annually until 2008 and then biennially since then. Only those free of colorectal cancer were eligible for attending the screening programme. In addition, we excluded those who was prevalent cases of positive FIT test result (part II, figure 1) or MetS (part III, figure 1) depending on which is the main outcome of interest in our bidirectional study design in order to elucidate the temporal sequence of the two phenotypes. Only those with negative-FIT or non-MetS who underwent repeated screening were included in the long-term follow-up study. This cohort was followed up from the time when f-Hb information was available in 2001 until the end of 2009 or the occurrence of colorectal cancer (CRC) or death, whichever came first. Both death and CRC were considered as censored event. Apart from information on f-Hb concentration, we also documented individual components of MetS, including waist circumference, weight, height, blood pressure and other biochemistry index such as fasting glucose, triglyceride and high-density lipoprotein cholesterol. In addition, the baseline information relevant to MetS or FIT (including

educational levels and dietary habits of fruits, vegetable and meat intake) were collected by questionnaires. The dietary habits considering the amount of daily consumption of fruit, vegetable and meat intake were categorised into three levels (none, 1–2 unit, and ≥ 3 unit). Food modes and standard dishes or containers of each food were displayed as the portion sizes to assist the estimation of the volume of daily consumption. Individual informed consents were obtained before screening.

Faecal immunochemical test measurement

In our colorectal cancer screening programme, f-Hb concentration measurement was based on OC-SENSOR method (Eiken Chemical Company, Tokyo, Japan), a ubiquitous method for quantitatively measuring f-Hb. Details of the procedure have been described elsewhere.⁵ A standard single faecal sample with 10 mg per specimen collection device was collected and preserved in 2 mL buffer by trained nurses following the standard procedures. Collected samples were stored at room temperature (23°C–26°C) and were sent to the community health centre in 3 days. They were then refrigerated at 4°C. All samples were further sent to the central laboratory for analysis within 7 days of screening. The quantitative values of f-Hb results were recorded with the unit of ng Hb/mL (5 ng Hb/mL = 1 µg Hb/g faeces). The cut-off for identifying subjects requiring further colonoscopy examination was 100 ng Hb/mL. As a result, subjects with f-Hb concentrations above 100 ng Hb/mL were considered as FIT-positive.

Measurement of MetS and its components

Metabolic syndrome (MetS) was defined according to the International Diabetes Federation Consensus criteria²² from which the presence of at least three of the following criteria was derived: central obesity (waist circumference ≥ 80 cm for female, and ≥ 90 cm for male), hypertriglyceride (triglyceride ≥ 150 mg/dL), a low level of high-density lipoprotein cholesterol (HDL-C) (HDL-C < 50 mg/dL for women and < 40 mg/dL for men), an elevated blood pressure (systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg) and hyperglycaemia (fasting glucose ≥ 100 mg/dL).

Statistical analysis

For descriptive analysis, we reported the percentage for positive-FIT result by different characteristics including demographic features, lifestyle factors, dietary habits and individual components of MetS. A post-hoc analysis was performed by comparing at least three levels of categorical variables as indicated in [table 1](#) using Bonferroni correction. Regarding the part of cross-sectional study (part I, [figure 1](#)), a logistic regression analysis was applied to investigating the association between prevalent MetS status and f-Hb concentration, with the dependent variable defined by a binary outcome, such as f-Hb ≥ 100 (positive FIT result) and < 100 ng Hb/mL (negative FIT result). The multiple-variable analysis was also carried out

to adjust for confounding factors including age, gender, educational levels, cigarette smoking, alcohol drinking and intake of vegetable, fruit and meat. The results were presented by crude OR or adjusted OR.

We further used Cox proportional hazards regression model with the time scale of month for subjects with negative f-Hb result or non-MetS status and the interval from the time of entry to screen until the occurrence of bidirectional outcomes of MetS and FIT-positive. Recall that while assessing bidirectional relationship, the temporal relationship between MetS status (including score and 5 components of MetS) and the occurrence of FIT-positive followed the study design in [figure 1](#) as mentioned above.

The multinomial logistic regression was also used to evaluate the effects of baseline MetS on quartiles of f-Hb measures (Q1: first quartile, Q2: second quartile (median), Q3: third quartile) in subsequent screen, and to examine the trend effect of MetS on f-Hb levels.

Given the assumption of constant incidence rate, Poisson regression model was applied to estimating the adjusted cumulative incidence of FIT-positive by baseline MetS status and also the cumulative incidence of MetS by the presence of FIT-positive.

Patient and public involvement

The patient and public involvement in this study was achieved by the inclusion of the personnel in the local public health sector and Public Health Bureau in Keelung City responsible for the monitoring of the health indicators including MetS and FIT-positive. They also responsible for the consultation and provision of screening service in the communities of Keelung City. Our study subjects were enrolled through the community-based screening programme.

The results of this study will be disseminated to the public in community through the personnel of the Public Health Bureau of Keelung City.

RESULTS

A total of 62 293 subjects aged 40–79 years were enrolled in this study from 2001 to 2009. Among them, 3137 were detected with FIT-positive given the criterion that f-Hb was greater than 100. The overall positive rate of FIT was 5.0%. [Table 1](#) shows the distribution of positive rates by demographic characteristics (age, gender, educational levels and marital status), lifestyle factors (cigarette smoking, alcohol drinking, and intakes of vegetable, fruit and meat) and metabolic syndrome. Positive rate increased with age and was higher in men than women ([table 1](#)). The level of education was inversely associated with the positive rate of FIT. The widowed/divorced had also higher positive rate compared with the married/single. As far as lifestyle factors are concerned, current smoker (6.4%), ever drinker (6.4%), low vegetable intake (5.9%) and high fruit consumption (5.6%) exhibited higher positive rate compared with the counterpart of each factor. The elevated positive rates of 6.4%, 5.8%,

**Table 1** The distribution of FIT-positive result by demographic and lifestyle factors

Characteristic	f-Hb \geq 100 (ng/mL)/Total (n)	Positive rate (%)	Overall p value	P value (Post-hoc)*
Age (year)			<0.0001	
40–49	902/24410	3.7		–
50–59	725/17616	4.1		–
60–69	805/12607	6.4		–
70–79	705/7660	9.2		–
Total	3137/62293	5.0		
Gender			<0.0001	
Female	1665/37637	4.4		–
Male	1472/24656	6.0		–
Education level			<0.0001	
Elementary/Illiterate (1)	1577/25677	6.1		–
Junior/Seniorhigh (2)	1187/27174	4.4		(2) vs (1), <0.0001
University/Graduate (3)	373/9422	4.0		(3) vs (1), <0.0001
Marital Status			<0.0001	
Widowed/Divorced	597/10062	5.9		–
Married	2400/49713	4.8		Married vs Widowed/Divorced, <0.0001
Single	140/2515	5.6		NS
Cigarette smoking			<0.0001	
Non-smoker	2105/45235	4.7		–
Ex-smoker	223/4353	5.1		Ex-smoker vs Non-smokers, 0.0062
Current smoker	775/12062	6.4		Current smoker vs Non-smokers, <0.0001
Alcohol drinking			<0.0001	
Non-drinker	2247/46948	4.8		Non-drinker vs Current drinker, <0.0001
Ex-drinker	156/2420	6.4		Ex-drinker vs Current drinker, 0.0006
Current drinker	691/11969	5.8		–
Intake of vegetable			0.0486	
Low	65/1106	5.9		NS
Medium	2455/48433	5.1		NS
High	500/10754	4.6		NS
Intake of fruit			0.0076	
Low	882/18386	4.8		Low vs High, 0.0048
Medium	1395/28400	4.9		Medium vs High, 0.0104
High	720/12864	5.6		–
Intake of meat			0.1587	
Low (1)	684/12791	5.3		NS
Medium (2)	2179/44266	4.9		NS
High (3)	148/2976	5.0		NS
Metabolic syndrome			<0.0001	
Non-MetS	2404/50922	4.7		–
MetS (Score \geq 3)	733/11371	6.4		–
Waist circumference(cm)†			<0.0001	
Normal	1836/39963	4.6		–
Abnormal	1271/21745	5.8		–

Continued

Table 1 Continued

Characteristic	f-Hb \geq 100 (ng/mL)/Total (n)	Positive rate (%)	Overall p value	P value (Post-hoc)*
Blood pressure \ddagger			<0.0001	
Normal	2447/51323	4.8		–
Abnormal	690/10970	6.3		–
AC Sugar(mg/dL) \S			<0.0001	
Normal	2133/45880	4.6		–
Abnormal	985/16095	6.1		–
Triglycerides(mg/dL) \P			<0.0001	
Normal	2063/43578	4.7		–
Abnormal	1050/18357	5.7		–
HDL-C (mg/dL)**			<0.0001	
Normal	2344/48751	4.8		–
Abnormal	769/13183	5.8		–

*Post-hoc test for groups using Bonferroni correction, only significant comparisons were listed.

\ddagger Waist circumference: Abnormal: \geq 90 cm (men) or \geq 80 cm (women), Normal: $<$ 90 cm (men) or $<$ 80 cm (women).

\ddagger Blood pressure: Abnormal: SBP \geq 130(mm Hg) or DBP \geq 85(mm Hg) or Hypertension history, Normal: SBP $<$ 130 (mm Hg) and DBP $<$ 85 (mm Hg).

\S AC Sugar (fasting plasma glucose, FPG): Abnormal: FPG \geq 100(mg/dL) or DM history, Normal: FPG $<$ 100(mg/dL).

\P Triglycerides: Abnormal: \geq 150 (mg/dL), Normal: $<$ 150 (mg/dl).

**HDL-C: Abnormal: $<$ 40 (mg/dL), Normal: \geq 40 (mg/dL).

f-Hb, faecal haemoglobin ; FIT, faecal immunisation test; MetS, metabolic syndrome.

6.3%, 6.1%, 5.7% and 5.8% were noted in those with MetS, abnormal waist, elevated blood pressure, pre-diabetes/diabetes mellitus, triglyceride \geq 150mg/dL and lowered HDL-C, respectively (table 1).

The significant results of post-hoc analysis are also listed in table 1. As far as the variable ‘Intake of fruit’ is concerned, there was a significant difference in FIT positive rates between low vs high ($p=0.0048$) and medium vs high ($p=0.0104$). Significant differences in the FIT-positive rate between non-drinker vs current drinker ($p<0.0001$) and ex-drinker and current drinker ($p=0.0006$) were noted. There were significant differences in ex-smoker vs non-smoker ($p=0.0062$) and current smoker vs non-smoker ($p<0.0001$). Significant comparisons in post-hoc analysis are also listed for levels of education and marital status.

MetS and Prevalent FIT-positive

Online supplementary table 1 shows the crude and adjusted odds ratios for FIT-positive in association with MetS by using binary categorisation (Yes vs No), score, and each of the five individual components for MetS. In univariate analysis, those with MetS led to a 40% (OR=1.40, 95% CI, 1.28–1.52; $p<0.0001$) increased risk of being FIT-positive compared with those free of MetS. The similar results were also observed for a 16% incremental risk per score and 23%–35% elevated risk for various five individual components of MetS.

The significant elevated risk persisted after adjusting for potential confounding factors such as age, gender, education, alcohol drinking, cigarette smoking and fruit consumption for the presence of MetS (aOR=1.19, 95%

CI=1.08–1.30; $P=0.0002$) and MetS score (aOR=1.08, 95% CI=1.05 to 1.12; $p<0.0001$). Among the five individual components of MetS, higher fasting plasma glucose (aOR=1.09, 95% CI=1.00–1.19; $p=0.04$) and lower HDL-C (aOR=1.21, 95% CI 1.10 to 1.32, $p=0.0002$) increased the odds of yielding FIT-positive. Considering the severity of MetS in terms of total score, we found a significant trend in association with the risk of FIT-positive (online supplementary figure 1a, $p<0.0001$ in trend test).

Effect of baseline MetS on incident FIT-positive

In part II analysis as shown in figure 1, there were 31 239 subjects who attended subsequent colorectal cancer screen. We used the Cox proportional hazards regression model to assess the effect of baseline MetS on positive FIT result among subjects with the negative result of FIT at first screen. Table 2 shows the results of the association between baseline MetS and subsequent incident FIT-positive. The presence of MetS increased the risk of yielding incident FIT-positive in univariate analysis (HR =1.58, 95% CI=1.38 to 1.81; $p<0.0001$) and multi-variable regression analysis (aHR=1.31, 95% CI=1.14 to 1.51; $p=0.0001$), after adjusting for potential confounding factors. Abnormal waist circumference (aHR=1.27, 95% CI=1.13 to 1.43; $p<0.0001$), higher fasting plasma glucose (aHR=1.13, 95% CI=1.00 to 1.29; $p=0.0547$) and lower HDL-C (aHR=1.27, 95% CI=1.09 to 1.47; $p<0.0001$) were those significant individual components contributing to the effect of MetS on incident FIT-positive.

In addition to incident positive FIT results, the effects of baseline MetS on the quartile of f-Hb measures with multi-nomial logistic regression are listed in

Table 2 Crude and adjusted HRs (aHR) for incident FIT-positive result associated with baseline metabolic syndrome

Variable	f-Hb positive (≥ 100 ng/mL)			
	HR	95% CI	aHR	(95% CI)
Metabolic syndrome				
Yes vs no	1.58	(1.38 to 1.81)	1.31	(1.14 to 1.51)
Score	1.22	(1.17 to 1.27)	1.13	(1.08 to 1.18)
Score=1 vs Score=0	1.24	(1.08 to 1.42)	1.09	(0.94 to 1.25)
Score=2 vs Score=0	1.60	(1.38 to 1.85)	1.30	(1.11 to 1.51)
Score=3 vs Score=0	1.78	(1.50 to 2.12)	1.37	(1.14 to 1.65)
Score=4 vs Score=0	2.13	(1.65 to 2.73)	1.61	(1.24 to 2.09)
Score=5 vs Score=0	2.43	(1.50 to 3.95)	1.88	(1.16 to 3.07)
Individual components				
Waist circumference (cm)*				
Abnormal vs Normal	1.52	(1.37 to 1.70)	1.27	(1.13 to 1.43)
High blood pressure†				
Abnormal vs Normal	1.26	(1.10 to 1.44)	0.90	(0.79 to 1.02)
AC Sugar (mg/dL)‡				
Abnormal vs Normal	1.42	(1.26 to 1.59)	1.13	(1.00 to 1.29)
Triglycerides (mg/dL)§				
Abnormal vs Normal	1.34	(1.20 to 1.50)	1.07	(0.94 to 1.21)
HDL-C (mg/dL)¶				
Abnormal vs Normal	1.33	(1.16 to 1.52)	1.27	(1.09 to 1.47)
Confounders				
Age (year)				
50–59 vs 40–49	1.14	(0.98 to 1.31)	1.09	(0.93 to 1.27)
60–69 vs 40–49	1.80	(1.57 to 2.07)	1.61	(1.37 to 1.89)
70–79 vs 40–49	3.84	(3.28 to 4.49)	3.28	(2.73 to 3.94)
Sex				
Male vs Female	1.62	(1.46 to 1.80)	1.34	(1.16 to 1.54)
Education				
Junior/Senior high vs Elementary/Illiterate	1.10	(0.91 to 1.31)	1.09	(0.90 to 1.31)
University/Graduate vs Elementary/Illiterate	1.49	(1.25 to 1.78)	1.29	(1.09 to 1.51)
Drinking status				
Ex-drinker vs Non-drinker	1.40	(1.08 to 1.81)	1.04	(0.79 to 1.38)
Current drinker vs Non-drinker	1.21	(1.06 to 1.38)	0.97	(0.84 to 1.14)
Smoking				
Ex-smoker vs Non-smoker	1.31	(1.07 to 1.60)	1.06	(0.84 to 1.34)
Current smoker vs Non-smoker	1.62	(1.43 to 1.85)	1.29	(1.09 to 1.51)
Vegetable intake	0.72	(0.64 to 0.81)	0.74	(0.66 to 0.83)
Meat intake	1.08	(0.98 to 1.19)	–	
Fruit intake	0.97	(0.89 to 1.05)	–	

*Waist circumference: Abnormal: ≥ 90 cm (male) or ≥ 80 cm (female), Normal: < 90 cm (male) or < 80 cm (female).

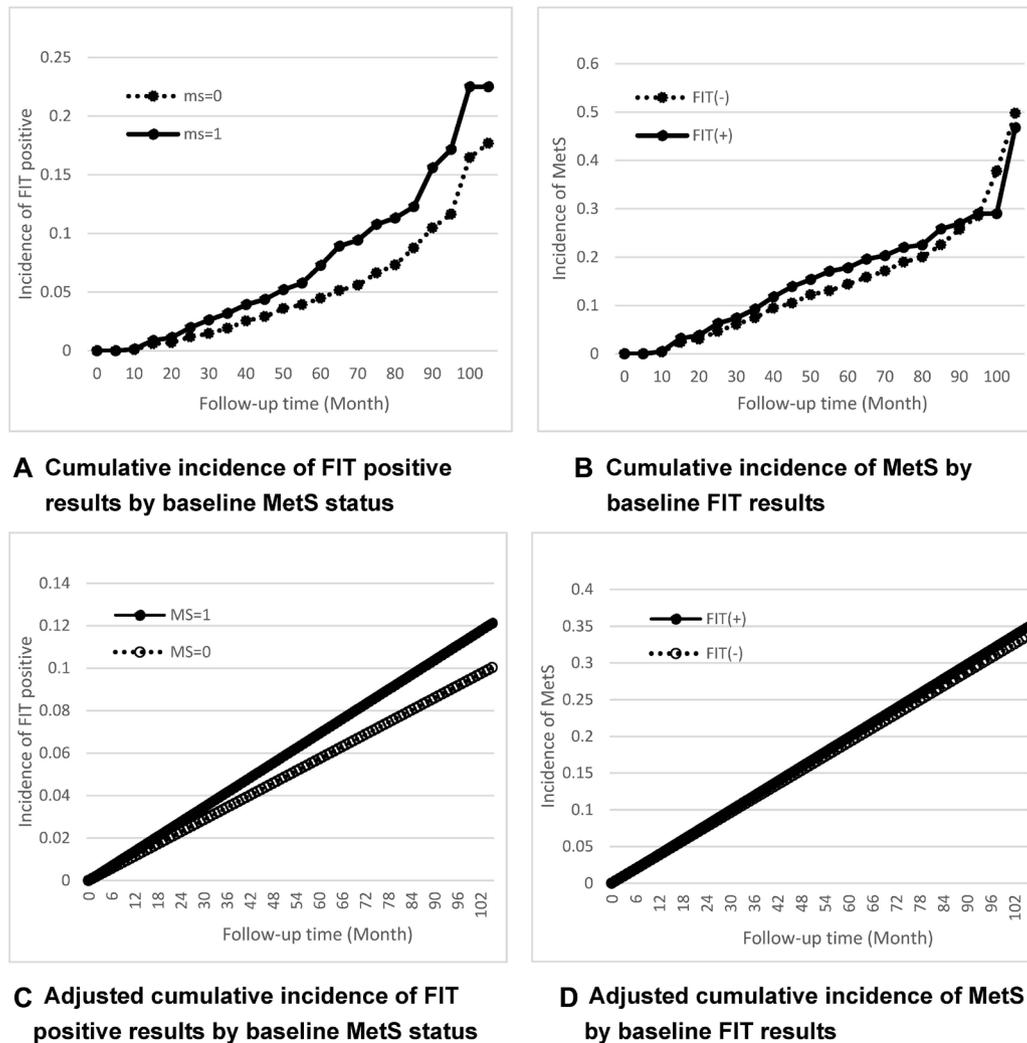
†Blood pressure: Abnormal: SBP ≥ 130 (mm Hg) or DBP ≥ 85 (mm Hg) or Hypertension history, Normal: SBP < 130 (mm Hg) and DBP < 85 (mm Hg).

‡AC Sugar (fasting plasma glucose, FPG): Abnormal: FPG ≥ 100 (mg/dL) or diabetes mellitus history, Normal: FPG < 100 (mg/dL).

§Triglycerides: Abnormal: triglycerides ≥ 150 (mg/dL), Normal: triglycerides < 150 (mg/dL).

¶HDL-C: Abnormal: < 40 (mg/dL), Normal: ≥ 40 (mg/dL).

f-Hb, faecal haemoglobin ; FIT, faecal immunisation test.



Abbreviations: MetS: metabolic syndrome; FIT: faecal immunological test

Figure 2 Observed (A, B) and predicted (C, D) cumulative incidence for FIT-positive (A, C) and MetS (B, D).

online supplementary table 2 and online supplementary figure 1b. Crude effect of baseline MetS on quartile of f-Hb measures reached statistical significance (trend test, $p < 0.0001$). After adjusting for confounding factors such as age, gender, education level, smoking and drinking status, the impact of baseline MetS on higher quartile groups of f-Hb was statistically significant (trend test, $p < 0.0001$), with the order of aOR being 0.98 (95% CI=0.88 to 1.08; $p = 0.6391$) for Q1-Q2 group, 1.06 (95% CI=0.96 to 1.17; $p = 0.2322$) for Q2-Q3 group and 1.26 (95% CI=1.14 to 1.38; $p < 0.0001$) for >Q3 group.

Effect of baseline FIT on incident metabolic status

Among 27 468 subjects free of MetS at baseline (figure 1, part III), those with FIT-positive at first screen were not statistically significantly at increased risk for incident MetS after adjusting for age, gender and other potential confounders (aHR=1.06, 95% CI=0.89, 1.25; $p = 0.5248$) although a statistically significant effect was noted in univariate analysis (HR=1.19, 95% CI=1.01 to 1.40; $p = 0.0335$) as shown in online supplementary table 3.

Figure 2A and B shows cumulative incidences of MetS and FIT-positive by follow-up time according to the baseline conditions. The adjusted cumulative incidences are also plotted in Figure 2C and D, with the covariates adjusted according to the corresponding model presented in table 2 and online supplementary table 3. We found that baseline MetS status had a higher risk of giving subsequent FIT-positive results whereas the baseline FIT result was not correlated with incident MetS.

DISCUSSION

The main rationale for envisaging this study is based on two streams of previous findings: (i) a significant association between MetS and colorectal neoplasia^{12 23-26} and (ii) also the role of f-Hb concentration as a predictor colorectal neoplasia and colorectal cancer mortality in a dose-response manner.⁵⁻⁷ By using colorectal cancer screening with FIT, colorectal cancers could be ascertained from those whose f-Hb concentrations above

100 ng Hb/mL, FIT-positive, that are further referred to undergo colonoscopy.^{4 5 7-9} It is of great interest to elucidate the temporal relationship between the emerging two markers (such as MetS and f-Hb), which has been never addressed.

The main contribution of this study is to use a bidirectional study design to elucidate the temporal sequence between MetS and f-Hb. We first demonstrated a statistically significant association between both phenotypes by information collected at baseline followed by the application of two normal incident cohort design (free of each outcome at baseline). We found the effect of MetS on FIT-positive was statistically significant but the opposite direction was not. Such findings are supported by the estimated aHR of 1.31 (95% CI=1.14 to 1.51; $p=0.0001$) and 1.06 (95% CI=0.89 to 1.25; $p=0.5248$), respectively. Furthermore, there's a significant trend effect of MetS score on FIT-positive result. This result indicates that individuals with metabolic syndrome were more likely to have an elevated risk of being FIT-positive, which further implies an increased risk for colorectal neoplasm. In addition, waist circumference (aHR=1.27, 95% CI=1.13 to 1.43; $p<0.0001$), fasting blood glucose (aHR=1.13, 95% CI 1.00 to 1.29; $p=0.0547$), and HDL-C (aHR=1.27, 95% CI=1.09 to 1.47; $p=0.0019$) were three significant individual components. These findings are consistent with those reported previous studies that noticed the recognised correlation between MetS components, namely diabetes mellitus, obesity and hypertension and elevated risk of CRC.²⁷⁻³⁰ It has been reported that chronic inflammation plays a pivotal role in complications of obesity, the core condition of MetS, mainly through the inflammatory expansion in adipose tissue.^{16 30}

The underlying biological plausibility of our finding is supported by the recent study demonstrating the correlation between glucose level and the adiponectin-adenosine monophosphate-activated protein kinase alpha signalling in the process of colorectal carcinogenesis.³¹ The hypothesised mechanism behind the potential relationship is purported to be through hyperinsulinaemia associated with insulin-like growth factor signalling^{12 32 33} or chronic inflammation.³⁴ According to Chiu *et al*, hyperinsulinaemia followed by insulin-resistance might directly activate insulin receptor, IGF-1, which are supposed to play an important role in tumorigenesis of cancers. Low HDL-C is also a characteristic feature of insulin resistance. Similar evidence was noted for the association between low HDL-C and pro-inflammatory cytokines.³⁵ Such evidence offers the underlying biological mechanisms accounting for the effect of MetS on incident FIT-positive, namely high f-Hb, which already demonstrated its predictive role for CRC in a dose–response manner. Thanks to the population-based data with incident cohort study collecting information on both of the two phenotypes, we are able to examine the temporal sequence between both.

The main limitation of this study is related to the generalisability of the results to the external population. Since our target population only included a small fraction of

Taiwanese residents aged 40–79 years and may not be fully representative of the underlying Taiwanese population, external applicability needs to be validated by other eligible population outside the KCIS programme¹¹ and even better corroborated by other ethnic groups if possible. The effect of unmeasured confounding factors such as colorectal cancer family history, aspirin intake and the amount of physical activities on the two phenotype is also a possible limitation to our study.

In conclusion, we used bidirectional incident cohort study design to disentangle the temporal relationship of both and found MetS precedes elevated f-Hb (incident FIT-positive) but the opposite temporal sequence is unlikely. Given that f-Hb have been demonstrated as the early biomarker for subsequent occurrence of colorectal neoplasm, this epidemiological finding may provide empirical evidence-based policy for adopting MetS control over lowering f-Hb concentration for the primary prevention of CRC. However, such an epidemiological association should be verified by using external data in future research.

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