Gender difference in metabolic syndrome and incident colorectal adenoma
A prospective observational study (KCIS No.42)
Mei-Sheng Ku, MSca, Sherry Yueh-Hsia Chiu, PhDb,c, Kuo-Liong Chien, PhDd,e,f, Yi-Chia Lee, PhDd,e,f,g, Sam Li-Sheng Chen, PhDh,i, Chih-Dao Chen, PhDh,i
Taipei, j Department of Family Medicine, Far Eastern Memorial Hospital, New Taipei City, Taiwan.
and Policy Center for Population Health and Sustainable Environment, College of Public Health, National Taiwan University,g Department of Medical Research, National
http://dx.doi.org/10.1097/MD.00000000000026121
Received: 12 June 2020 / Received in final form: 18 April 2021 / Accepted: 10 May 2021
How to cite this article: Ku MS, Chiu SY, Chien KL, Lee YC, Chen SL, Chen CD. Gender difference in metabolic syndrome and incident colorectal adenoma: A prospective observational study (KCIS No.42). Medicine 2021;100:22(e26121).

Abstract
This community-based study aimed to elucidate whether there is a gender difference in the effect of metabolic syndrome (MetS) and its individual components on an elevated risk for incident colorectal adenoma.

A prospective cohort study was conducted by enrolling 59,767 subjects aged 40 years or older between 2001 and 2009 in Keelung, Taiwan, to test this hypothesis, excluding those with a prior history of colorectal cancer and those with colorectal cancer diagnosed at the first screening. Cox proportional hazards regression models were used to assess the effect of MetS in terms of a dichotomous classification, each individual component and the number of components for males and females.

Colorectal adenoma was present in 2.7% (n = 652) of male participants and 1.1% (n = 403) of female participants. The prevalence rate of MetS was 26.7% and 23.3% for males and females, respectively. The effect of MetS on colorectal adenoma was statistically significant and similar for the 2 genders, with an adjusted hazard ratio (aHR) of 1.33 (95% CI: 1.13–1.58) in males and 1.33 (95% CI: 1.09–1.66) in females after adjustment for confounders. However, MetS led to higher risk of advanced colorectal adenoma in men than in women. Regarding the effect of each component of MetS on colorectal adenoma, abnormal waist circumference and hypertriglyceridemia led to an elevated risk of colorectal adenoma in both genders. A rising risk of colorectal adenoma among females was noted in those with a moderately higher level of glycemia (100–125 mg/dL, aHR = 1.44, 95% CI: 1.12–1.85). Hypertriglyceridemia and high blood pressure were associated with an increased risk of advance colorectal adenoma in males.

Both male and female subjects with MetS had a higher risk of colorectal adenoma. The contributions from individual components of MetS varied by gender. These findings suggest that the possible risk reduction of colorectal adenoma through metabolic syndrome-based lifestyle modifications may differ between genders.

Abbreviations: CRC = colorectal cancer, HDL = high-density lipoprotein, HR = hazard ratio, MetS = metabolic syndrome.

Keywords: cohort studies, colorectal adenoma, metabolic syndrome

1. Introduction
An emerging body of evidence on the association between metabolic syndrome (MetS) and the risk of colorectal adenoma has been demonstrated, particularly emphasizing obesity, diabetes and insulin resistance.[1–9] However, most studies were based on the assessment of the association with a cross-sectional design, which renders the temporal relationship between MetS and colorectal adenoma elusive. Recent studies from Korea have demonstrated the impact of fasting glucose on incident colorectal cancer (CRC) based on a prospective cohort study.[10,11] Several systematic reviews involving prospective cohort studies also demonstrated that obesity and waist circumference have


2. Subjects and methods

2.1. Study population and design

A total of 59,767 subjects aged 40 years or older participating in the Keelung community-based integrated screening (hereafter abbreviated as KCIS) program between 2001 and 2009 in Keelung, Taiwan were recruited. Patients with CRC diagnosed prior to or at first screen were excluded. The KCIS used the existing pap smear screening program as the basis for integrating other disease screening activities to create a unified platform. Five neoplastic diseases (cervical neoplasia, breast cancer, colorectal neoplasia, liver cancer, and oral neoplasia) and 3 nonneoplastic chronic diseases (type 2 diabetes, hypertension, and hyperlipidemia) were screened for in this program. Due to the integration of health checkups for 3 chronic diseases, biochemical variables pertaining to the 3 nonneoplastic chronic diseases as well as blood pressure and anthropometric measures allowed us to define MetS in accordance with National Cholesterol Education Program’s Adult Treatment Panel III (NCEP-ATPIII: Asia modified diagnostic criteria) criteria. Collecting both information regarding fecal hemoglobin (f-Hb) concentration from FIT and medical treatment and metabolic control of previous cases of diabetes mellitus or hypertension obtained via self-administered questionnaires were taken into account for the criteria for impaired serum glucose and elevated blood pressure. Other characteristics such as cigarette smoking, alcohol consumption, physical activity, meat and vegetable intake, and family history of CRC were also inquired about in the questionnaire.

2.2. Ascertainment of colorectal adenoma

We used a two-stage screening design for CRC. Participants aged 40 years or older were provided with a fecal immunochemical test (FIT) kit (OC-Sensor). Those with a fecal hemoglobin concentration 100ng/mL or above were referred for a colonoscopic examination. After completing the follow-up colonoscopies, pathologically confirmed colorectal adenomas were identified, including villous, tubular adenomas, and tubulovillous adenomas. Tubulovillous adenomas, villous adenomas, or those with size larger than 1cm were defined as advanced adenomas. Details of the Keelung colorectal cancer screening program were given elsewhere. The number of criteria in the abnormal range for each subject was defined as metabolic score. Those having a metabolic score larger than or equal to 3 were defined as having MetS. Note that information regarding fecal hemoglobin (f-Hb) concentration from FIT and medical treatment and metabolic control of previous cases of diabetes mellitus or hypertension obtained via self-administered questionnaires were taken into account for the criteria for impaired serum glucose and elevated blood pressure. Other characteristics such as cigarette smoking, alcohol consumption, physical activity, meat and vegetable intake, and family history of CRC were also inquired about in the questionnaire.

2.3. MetS and other characteristics

The information collected in the KCIS program included each diagnostic component of MetS. This enabled us to identify the criteria for MetS according to the following 5 items: central obesity (defined using the adjustment for Oriental countries as men with a waist circumference greater than 90cm or women with a waist circumference greater than 80cm), triglycerides ≥150mg/dL, high-density lipoprotein (HDL) <40mg/dL for men and HDL <50mg/dL for women, systolic blood pressure ≥130mm Hg or diastolic blood pressure ≥85mm Hg, and fasting glucose ≥100mg/dL. In the light of NCEP ATP III, the number of criteria in the abnormal range for each subject was defined as metabolic score. Those having a metabolic score larger than or equal to 3 were defined as having MetS. Note that information regarding fecal hemoglobin (f-Hb) concentration from FIT and medical treatment and metabolic control of previous cases of diabetes mellitus or hypertension obtained via self-administered questionnaires were taken into account for the criteria for impaired serum glucose and elevated blood pressure. Other characteristics such as cigarette smoking, alcohol consumption, physical activity, meat and vegetable intake, and family history of CRC were also inquired about in the questionnaire.

2.4. Statistical analyses

Cox proportional regression models were used to assess the effect size of the association between baseline MetS and the risks of colorectal adenoma and advanced adenoma with adjustment for age, gender, smoking habits, betel nut chewing, alcohol consumption, physical activity, vegetable intake, meat consumption, family history of CRC, and f-Hb concentration. The outcomes of interest included adenoma and advanced adenoma. Those in the absence of an event until the end of the follow-up period were considered censored cases. The date at the end of the follow-up period was December 31, 2009. In addition to MetS, the risk of developing adenoma and advanced adenoma according to each component of MetS as defined above was also examined. The statistically significant variables in the univariate analysis were selected for the multivariate analysis. The interaction effects between gender and MetS or its individual components were tested. A subgroup analysis by gender was...
conducted to examine whether the effects of the components of MetS vary across gender. A P value less than .05 was considered statistically significant. All statistical analyses were performed with SAS version 9.4.

3. Results

In this study, 59,767 subjects (23,849 [39.9%] men aged 57.2 (±12.4) years and 35,918 [60.1%] women aged 54.2 (±11.2) years) were enrolled. The demographic characteristics and prevalence rate of an abnormal waist circumference, hypertriglyceridemia, low- and high-density lipoprotein cholesterol, high blood pressure, fasting hyperglycemia and a family history of CRC are shown in Table 1. The mean follow-up time for our study cohort was 5.8 (±2.4) years (5.7 (±2.5) years for men and 5.9 (±2.4) years for women). Colorectal adenoma was presented in 1055 (1.8%) subjects (652 [2.7%] men and 403 [1.1%] women). Among them, 342 (0.6%) cases were advanced adenoma (231 [1.0%] in males and 111 [0.3%] in females). MetS was present in 14,717 (24.6%) subjects (6362 [26.7%] males and 8355 [23.3%] females). Hypertriglyceridemia, elevated blood pressure, and higher glycemia were more frequent in men, while more women had an abnormal waist circumference and low HDL cholesterol.

The effect of MetS on colorectal adenoma was statistically significant, with a crude HR of 1.47 (95% CI: 1.29–1.68) (Table 2). MetS status elevated the risk of colorectal adenoma after considering other significant confounding factors, including age, sex, smoking status, betel quid chewing, alcohol consumption and f-Hb concentration, with an HR of 1.32

| Table 1 | Demographic characteristics of the study population by gender. |
|---------|-------------------|-------------------|-------------------|
|         | Men (n = 23849)   | Women (n = 35918) | Total (n = 59767) |
| Age group | N   | %     | N   | %     | N   | %     |
| 40–49   | 8103 | 34.0  | 14676 | 40.9 | 22779 | 38.1 |
| 50–59   | 5929 | 24.9  | 10290 | 28.6 | 16219 | 27.1 |
| 60–69   | 4975 | 20.9  | 6938  | 19.3 | 11913 | 19.9 |
| ≥70     | 4842 | 20.3  | 4014  | 11.2 | 8856  | 14.8 |
| Smoking |       |       |       |       |       |       |
| Yes     | 13117 | 55.5 | 2441  | 6.9  | 15558 | 26.3 |
| No      | 10498 | 44.5 | 33052 | 93.1 | 43850 | 73.7 |
| Unknown | 234   | 425   | 69    | 69   |
| Betel quid chewing |       |       |       |       |       |       |
| Yes     | 2909  | 12.4 | 226   | 0.6  | 3135  | 5.3  |
| No      | 20610 | 87.6 | 35215 | 99.4 | 55825 | 94.7 |
| Unknown | 330   | 477   | 807   | 807  |
| Drinking |       |       |       |       |       |       |
| Yes     | 10720 | 45.7 | 2876  | 8.1  | 13596 | 23.1 |
| No      | 12746 | 54.3 | 32450 | 91.9 | 45196 | 76.9 |
| Unknown | 383   | 592   | 975   | 975  |
| Physical activity |       |       |       |       |       |       |
| Frequent | 6794  | 29.2 | 12871 | 36.8 | 19665 | 33.7 |
| Infrequent | 16512 | 70.8 | 22090 | 63.2 | 38602 | 66.3 |
| Unknown | 543   | 957   | 1500  | 1500 |
| Meat Intake |       |       |       |       |       |       |
| Frequent | 5274  | 22.9 | 5530  | 16.1 | 10804 | 18.8 |
| Infrequent | 17759 | 77.1 | 28848 | 83.9 | 46607 | 81.2 |
| Unknown | 816   | 1540  | 2356  | 2356 |
| Vegetable Intake |       |       |       |       |       |       |
| Frequent | 5848  | 25.3 | 10106 | 29.2 | 15954 | 27.7 |
| Infrequent | 17260 | 74.7 | 24464 | 70.8 | 41724 | 72.3 |
| Unknown | 741   | 1348  | 2089  | 2089 |
| Family history of CRC |       |       |       |       |       |       |
| undetected | 9772  | 41.0 | 14854 | 41.4 | 24626 | 41.2 |
| 1–19 ng/mL | 7542  | 31.6 | 12048 | 33.5 | 19990 | 32.8 |
| 20–39 ng/mL | 3077  | 12.9 | 4682  | 13.0 | 7759  | 13.0 |
| 40–59 ng/mL | 1140  | 4.8  | 1543  | 4.3  | 2683  | 4.5  |
| 60–89 ng/mL | 746   | 3.1  | 990   | 2.8  | 1736  | 2.9  |
| 99–100 ng/mL | 135   | 0.6  | 182   | 0.5  | 317   | 0.5  |
| ≥100 ng/mL | 1437  | 6.0  | 1619  | 4.5  | 3056  | 5.1  |
| MetS |       |       |       |       |       |       |
| Yes | 6362 | 26.7 | 8355 | 23.3 | 14717 | 24.6 |
| No | 17483 | 73.3 | 27562 | 76.7 | 45045 | 75.4 |
| Unknown | 4     | 1     | 5     | 5     |

(continued)
All individual components of MetS except for hyperglycemia were associated with an increased risk of colorectal adenoma (Table 2). The significant impacts of an abnormal waist circumference, hypertriglyceridemia and moderately higher level of glycemia (100–125 mg/dL) held after considering other significant confounders. There was no interaction between gender and MetS or its individual components, except for the HDL cholesterol component ($P=0.035$).

### Table 1 (continued)

|                | Men (n=23849) | Women (n=35918) | Total (n=59767) |
|----------------|---------------|-----------------|-----------------|
|                | N  | %     | N  | %     | N  | %     |
| Normal         | 15677 | 66.4 | 22685 | 63.8 | 38362 | 64.8 |
| Abnormal       | 7938 | 33.6 | 12895 | 36.2 | 20833 | 35.2 |
| Unknown        | 234  |     | 338  |     | 572  |     |
| Triglyceride   |     |     |     |     |     |     |
| <150 mg/dL     | 15111 | 63.9 | 26839 | 75.1 | 41950 | 70.6 |
| ≥150 mg/dL     | 8555  | 36.1 | 8878  | 24.9 | 17433 | 29.4 |
| Unknown        | 183   |     | 201   |     | 384   |     |
| HDL            |     |     |     |     |     |     |
| ≥40 mg/dL (M); ≥50 mg/dL (F) | 19549 | 82.6 | 27344 | 76.6 | 46893 | 79.0 |
| <40 mg/dL (M); <50 mg/dL (F) | 4117  | 17.4 | 8373  | 23.4 | 12490 | 21.0 |
| Unknown        | 183   |     | 201   |     | 384   |     |
| Blood pressure |     |     |     |     |     |     |
| <130/85 mmHg   | 9746  | 41.1 | 20481 | 57.4 | 30227 | 50.9 |
| ≥130/85 mmHg   | 13961 | 58.9 | 15200 | 42.6 | 29161 | 49.1 |
| Unknown        | 142   |     | 237   |     | 379   |     |
| Glycemia       |     |     |     |     |     |     |
| <100 mg/dL     | 17172 | 72.56 | 27287 | 76.40 | 44459 | 74.87 |
| 100–125 mg/dL  | 4342  | 18.35 | 5775  | 16.17 | 10117 | 17.04 |
| ≥126 mg/dL     | 2152  | 9.09  | 2656  | 7.44  | 4808  | 8.10  |
| Unknown        | 183   |     | 200   |     | 383   |     |
| Adenoma        |     |     |     |     |     |     |
| Normal         | 652   | 2.7   | 403   | 1.1   | 1055  | 1.8   |
| Abnormal       | 231   | 1.0   | 111   | 0.3   | 342   | 0.6   |
| Advanced adenoma | 5.7  | 2.5   | 5.9   | 2.4   | 5.8   | 2.4   |

| Follow-up time (Yr) | 4.7 | 2.5 | 4.9 | 2.4 |

* Data are presented as the mean and sd.

† Abnormal waist circumference, >90 cm in men and >80 cm in women.

f-Hb = fecal hemoglobin, HDL = high-density lipoprotein, MetS = metabolic syndrome.

### Table 2

|                | HR  | 95% CI       | aHR | 95% CI       |
|----------------|-----|--------------|-----|--------------|
| Age            | 1.03 | (1.02, 1.03) | 1.01 | (1.00, 1.01) |
| Sex            | 2.46 | (2.17, 2.80) | 1.91 | (1.64, 2.24) |
| Smoking        | 1.97 | (1.74, 2.24) | 1.17 | (1.00, 1.37) |
| Betel quid chewing | 1.53 | (1.21, 1.93) | 0.98 | (0.76, 1.27) |
| Drinking       | 1.83 | (1.60, 2.08) | 1.19 | (1.02, 1.39) |
| Physical activity | 0.92 | (0.80, 1.05) |     |              |
| Meat intake    | 0.99 | (0.85, 1.16) |     |              |
| Vegetable intake | 1.20 | (0.99, 1.17) |     |              |
| Family history of CRC | 1.19 | (0.81, 1.74) |     |              |
| f-Hb concentration | 1.80 | (1.76, 1.85) | 1.78 | (1.73, 1.83) |
| MetS           | 1.47 | (1.29, 1.68) | 1.32 | (1.15, 1.51) |
| Abnormal WC†   | 1.37 | (1.09, 1.74) | 1.28 | (1.13, 1.46) |
| Hypertriglyceridemia‡ | 1.58 | (1.24, 2.01) | 1.34 | (1.17, 1.52) |
| Low HDL§       | 0.90 | (0.66, 1.23) | 1.05 | (0.89, 1.23) |
| High Blood Pressurejj | 1.73 | (1.36, 2.21) | 1.12 | (0.99, 1.28) |
| Glycemia       |     |     |     |     |
| 100-125 mg/dL  | 1.39 | (1.04, 1.85) | 1.27 | (1.08, 1.48) |
| ≥126           | 1.00 | (0.65, 1.56) | 0.93 | (0.75, 1.04) |

f-Hb = fecal hemoglobin, HDL = high-density lipoprotein, HR = hazard ratio, MetS = metabolic syndrome, WC = waist circumference.

* The results of the individual components of MetS in the multivariable analysis are from another model in which MetS was not included.

† Abnormal waist circumference, >90 cm in men and >80 cm in women.

‡ Hypertriglyceridemia, ≥150 mg/dL.

§ Low HDL, <40 mg/dL (1 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women.

jj High blood pressure, ≥130/85 mmHg.
The effect of MetS on colorectal adenoma was statistically significant in both genders (Table 3). In males, the crude HR was 1.39 (95% CI: 1.17–1.64), and the adjusted hazard ratio (aHR) was 1.33 (95% CI: 1.13–1.58) after adjustment for age, smoking, alcohol consumption and f-Hb concentration. The corresponding figures for females were 1.50 (95% CI: 1.21–1.87) and 1.33 (95% CI: 1.06–1.66) after adjustment for age and f-Hb concentration.

The effect of each component of MetS on colorectal adenoma varied with gender (Table 3). For males, an abnormal waist circumference (aHR = 1.25 95% CI: 1.06–1.47) and hypertriglyceridemia (≥150mg/dL; aHR = 1.36; 95% CI: 1.16–1.60) led to a significant increase in colorectal adenoma after adjustment for confounding factors. However, an abnormal waist circumference (aHR = 1.38 95% CI: 1.12–1.71), hypertriglyceridemia (≥150mg/dL; aHR = 1.31; 95% CI: 1.05–1.62) and a moderately higher level of glycemia (100–125mg/dL, aHR = 1.44, 95% CI: 1.12–1.85) contributed to a higher risk of colorectal adenoma in females.

Furthermore, we found that the effect of MetS on colorectal advanced adenoma was also statistically significant, with an increased risk of 50% (95% CI: 17%–92%), compared to those without MetS (Table 4). MetS status was associated with an elevated risk of advanced adenoma after considering other significant confounding factors, including age, sex, smoking status, alcohol consumption and f-Hb concentration, with an HR of 1.34 (95% CI: 1.04–1.72). All individual components of MetS except for low HDL cholesterol increased the risk of colorectal advanced adenoma. Hypertriglyceridemia (aHR = 1.32; 95% CI: 1.04–1.69) and high blood pressure (aHR = 1.35; 95% CI: 1.05–1.73) were associated with a risk of advanced adenoma.

Table 5 shows the impact of MetS on advanced adenoma by gender. The results show that MetS increased the risk of advanced adenoma in men in terms of dichotomous type (aHR =

### Table 3

|                | HR     | 95% CI  | aHR   | 95% CI  |
|----------------|--------|---------|-------|---------|
| Male           |        |         |       |         |
| Age            | 1.02   | (1.02, 1.03) | 1.01  | (1.00, 1.02) |
| Smoking        | 1.33   | (1.13, 1.56) | 1.22  | (1.03, 1.46) |
| Betel quid chewing | 1.04  | (0.82, 1.32) |       |         |
| Drinking       | 1.32   | (1.12, 1.54) | 1.25  | (1.06, 1.48) |
| Physical activity | 0.89 | (0.74, 1.06) |       |         |
| Meat intake    | 0.89   | (0.74, 1.08) |       |         |
| Vegetable intake | 1.01  | (0.85, 1.20) |       |         |
| Family history of CRC | 1.17 | (0.72, 1.89) |       |         |
| f-Hb concentration | 1.84 | (1.78, 1.90) | 1.82  | (1.76, 1.89) |
| MetS           | 1.39   | (1.17, 1.64) | 1.33  | (1.13, 1.58) |
| Abnormal WC†   | 1.25   | (1.06, 1.47) | 1.25  | (1.06, 1.47) |
| Hypertriglyceridemia‡ | 1.36  | (1.16, 1.60) |       |         |
| Low HDLx       | 0.94   | (0.75, 1.17) | 1.17  | (0.99, 1.38) |
| High Blood Pressurejj |       |         |       |         |
| Glycemia       |        |         |       |         |
| 100–125        | 1.15   | (0.95, 1.40) | 0.87  | (0.66, 1.16) |
| ≥126           | 0.87   | (0.66, 1.16) |       |         |
| Female         |        |         |       |         |
| Age            | 1.02   | (1.01, 1.03) | 1.00  | (0.99, 1.01) |
| Smoking        | 0.95   | (0.63, 1.44) |       |         |
| Drinking       | 0.88   | (0.60, 1.31) |       |         |
| Physical activity | 1.15  | (0.94, 1.41) |       |         |
| Meat intake    | 0.92   | (0.70, 1.20) |       |         |
| Vegetable intake | 0.94  | (0.76, 1.16) |       |         |
| Family history of CRC | 1.18 | (0.63, 2.21) |       |         |
| f-Hb concentration | 1.71 | (1.64, 1.79) | 1.71  | (1.63, 1.78) |
| MetS           | 1.50   | (1.21, 1.87) | 1.33  | (1.06, 1.66) |
| Abnormal WC†   | 1.38   | (1.12, 1.71) | 1.38  | (1.12, 1.71) |
| Hypertriglyceridemia‡ | 1.31  | (1.05, 1.62) |       |         |
| Low HDLx       | 1.19   | (0.95, 1.50) | 1.07  | (0.87, 1.32) |
| High Blood Pressurejj |       |         |       |         |
| Glycemia       |        |         |       |         |
| 100–125        | 1.44   | (1.12, 1.85) | 1.05  | (0.74, 1.51) |
| ≥126           | 1.05   | (0.74, 1.51) |       |         |

f-Hb = fecal hemoglobin, HDL = high-density lipoprotein, HR = hazard ratio, MetS = metabolic syndrome, WC = waist circumference.

* The results of individual components of MetS in the multivariable analysis are from another model in which MetS was not included.

† Abnormal waist circumference, >90 cm in men and >80 cm in women.

‡ Hypertriglyceridemia, ≥150mg/dL.

x Low HDL, <40mg/dL (1 mmol/L) in men and <50mg/dL (1.3 mmol/L) in women.

jj High blood pressure, ≥130/85 mmHg.
Table 4
Hazard ratio (95% CI) of metabolic syndrome and other risk factors for advanced colorectal adenoma.

|                        | HR     | 95% CI        | aHR   | 95% CI      |
|------------------------|--------|---------------|-------|-------------|
| Age                    | 1.03   | (1.02, 1.04)  | 1.00  | (0.99, 1.01) |
| Sex                    | 3.08   | (2.41, 3.95)  | 2.20  | (1.63, 2.97) |
| Smoking                | 2.43   | (1.92, 3.06)  | 1.28  | (0.96, 1.70) |
| Betel quid chewing     | 1.26   | (0.78, 2.03)  |       |             |
| Drinking               | 2.14   | (1.68, 2.71)  | 1.22  | (0.92, 1.61) |
| Physical activity      | 0.78   | (0.60, 1.01)  |       |             |
| Meat intake            | 0.91   | (0.68, 1.23)  |       |             |
| Vegetable intake       | 1.12   | (0.87, 1.45)  |       |             |
| Family history of CRC  | 1.41   | (0.73, 2.73)  |       |             |
| f-Hb concentration     | 1.88   | (1.78, 1.98)  | 1.84  | (1.75, 1.94) |
| MetS                   | 1.50   | (1.17, 1.92)  | 1.34  | (1.04, 1.72) |
| Abnormal WC‡           | 1.37   | (1.09, 1.74)  | 1.26  | (0.99, 1.61) |
| Hypertriglyceridemia§  | 1.58   | (1.24, 2.01)  | 1.32  | (1.04, 1.69) |
| Low HDL§               | 0.90   | (0.66, 1.23)  | 0.98  | (0.72, 1.33) |
| High Blood Pressure^   | 1.73   | (1.36, 2.21)  | 1.35  | (1.05, 1.73) |
| Glyceria               |        |               | 1.22  | (0.91, 1.62) |
| 100–125                | 1.39   | (1.04, 1.85)  |       |             |
| ≥126                   | 1.00   | (0.65, 1.56)  | 0.79  | (0.51, 1.23) |

f-Hb = fecal hemoglobin, HDL = high-density, HR = hazard ratio, MetS = metabolic syndrome, WC = waist circumference.
* The results of individual components of MetS in the multivariable analysis are from another model in which MetS was not included.
† Abnormal waist circumference, >90 cm in men and >80 cm in women.
‡ Hypertriglyceridemia, ≥150 mg/dL.
§ Low HDL, <40 mg/dL (1 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women.
^ High blood pressure, ≥130/85 mmHg.

1.36, 95% CI: 1.01–1.83). For females, the corresponding effect was marginally statistically significant for MetS (aHR = 1.20, 95% CI: 0.75–1.90). Hypertriglyceridemia remained statistically significantly associated with a higher risk of advanced adenoma in males (aHR = 1.42, 95% CI: 1.06–1.90). Nevertheless, high blood pressure was accompanied with elevated risk of advanced adenoma in men (aHR = 1.37, 95% CI: 1.25–1.50). Hypertriglyceridemia seemed to be the most significant factor leading to colorectal adenoma in females.

4. Discussion

Although several studies have already shown an association between MetS and colorectal neoplasia,[10–13] few studies were proposed to corroborate the temporal relationship between MetS (cause) and colorectal adenoma (consequence). We conducted a large population-based cohort study to confirm the cause of MetS leading to the occurrence of colorectal adenoma to demonstrate that a temporal relationship plays an important role in the reduction of the risk of colorectal cancer with a potential lifestyle modification program for the improvement of the metabolic factor profiles composing MetS.

In addition to the clarifying the temporal relationship, the innovative part of the present study in contrast to previous studies[10–12,25] is that it showed that MetS is an independent risk factor after controlling for the most important risk factor, f-Hb concentration, for colorectal adenoma and advance adenoma,[24,26] and it identified the gender-specific relationship between incident colorectal adenoma and MetS. Our study found that the presence of MetS led to a 33% elevated risk of colorectal adenoma in both genders, but the contribution of individual components of MetS was different between males and females. Hypertriglyceridemia and an abnormal waist ratio relative to others played more important roles in males, whereas hyperglycemia seemed to be the most significant factor leading to colorectal adenoma in females.

4.1. MetS and colorectal adenoma

The finding that MetS is a risk factor for adenoma was consistent with the findings of previous studies.[1,2,18,25,27–30] In contrast to other studies that either considered only CRC or the prevalence of adenoma as the main outcome, our study first identified MetS as a risk factor for colorectal adenoma with a distinct temporal relationship. This effect was further intensified by the additional finding that a greater number of individual components led to an elevated risk of colorectal adenoma suggesting, a dose-response effect.

4.2. Individual components of MetS and colorectal adenoma

As far as the results regarding gender difference are concerned, previous studies found an association between obesity and CRC or adenoma both in men and women.[18,31,32] Abdominal obesity was also mentioned as positively associated with CRC.[33] Our results also showed a positive relationship between an abnormal waist circumference and adenoma in both genders (aOR = 1.25, 95% CI: 1.06–1.47 in men and aOR = 1.38, 95% CI: 1.12–1.71 in women). However, a higher level of glycemia as an additional risk factor associated with an increased risk of colorectal adenoma for females was noted in our study. Colorectal cancer and insulin resistance have common risk factors. By using a rat model, Koohestani[34] demonstrated the relationship between insulin resistance and colorectal cancer proposed by McKeown-Eyssen and Giovannucci,[31,35] demonstrating a biologically plausible mechanism for increased CRC risk among persons with type 2 DM.
Some animal models have also shown that colonocytes under the circumstances of insulin resistance over prolonged periods lead to hyperinsulinemia, hyperglycemia, and elevated levels of triglycerides, nonesterified fatty acids, and insulin-like growth factor-1 (IGF-1). Thus, the positive association between hypertriglyceridemia and colorectal adenoma in both genders found in current study could also be explained. Such exposure could affect the growth, development, and homeostasis of colonic cells.\[31,35\] In this context, it is interesting to note that insulin promotes the growth of aberrant crypt foci (ACF) at 100 days after initiation in animals.\[36,37\] In an in vivo study,\[38\] intravenous infusion of insulin to rats further increased the proliferation of 5-bromo-2-deoxyuridine labeling of replicating DNA in colorectal epithelial cells. Many studies show that adult-onset DM is associated with a higher risk of CRC.\[39–42\] Some studies found that man with DM had a statistically increased risk of CRC after adjusting for potential confounders in a cohort of Swedish men.\[41,43\] For the premalignant state of CRC, the risk of a moderate level of blood glucose (prediabetes status, 100–126 mg/dL) was significant in women (OR = 1.78, 95% CI: 1.16–2.75).\[44\] The result may be due to an early promoting effect of abnormal glucose to the adenoma-adenocarcinoma sequence under the insulin resistance-colorectal cancer hypothesis. A prospective study found a cluster of 3 IRS-related conditions with a significantly increased risk of CRC (HR = 1.40, 95% CI: 1.12–1.74).\[45\] The IOWA Women’s Health Study confirmed that type 2 DM leads to an elevated risk of CRC. However, we found a null association between DM and colorectal adenoma in both men and women, whereas a significant association of pre-DM in women was found. Menopause status may be linked to insulin-mediated growth regulation pathways and thus could have affected colorectal carcinogenesis.\[46\]

Hyperinsulinemia is a possible link between diabetes and CRC. Some studies have shown that insulin is an important growth factor for colonic mucosal cells and stimulates colonic tumor cells.\[47,48\] Plasma concentrations of insulin-like growth factor (IGF-I) and IGF binding protein-3 (IGFBP-3) have been shown to influence the risk of CRC in a prospective follow-up study.\[47\] In their study, they found that subjects with values of IGF-I in the highest quintile were 2.5-fold more likely to develop colorectal cancer (CRC) than those with values in the lowest quintile. In contrast, increased plasma concentrations of IGFBP-3 were protective.

### Table 5

|                      | Male | Female |
|----------------------|------|--------|
|                      | HR   | 95% CI | aHR  | 95% CI |
| **Age**              | 1.02 (1.01, 1.03) | 1.00 (0.98, 1.02) |
| **Smoking**          | 1.52 (1.13, 2.05) | 0.98 (0.43, 2.24) |
| **Betel quid chewing** | 0.77 (0.48, 1.26) | 0.39 (0.12, 1.23) |
| **Drinking**         | 1.54 (1.15, 2.04) | 1.13 (0.75, 1.71) |
| **Physical activity** | 0.72 (0.51, 1.01) | 0.61 (0.33, 1.15) |
| **Meat intake**      | 0.89 (0.63, 1.25) | 1.20 (0.77, 1.86) |
| **Vegetable intake** | 1.00 (0.73, 1.37) | 2.50 (1.01, 6.14) |
| **Family history of CRC** | 0.89 (0.33, 2.40) | 1.69 (1.54, 1.84) |
| **f-Hb concentration** | 1.95 (1.82, 2.08) | 1.34 (0.86, 2.09) |
| **MetS**             | 1.49 (1.10, 2.00) | 1.50 (1.01, 1.90) |
| **Abnormal WC**†     | 1.23 (0.92, 1.64) | 1.15 (0.73, 1.82) |
| **Hypertriglyceridemia**‡ | 1.42 (1.06, 1.90) | 1.15 (0.73, 1.82) |
| **Low HDL**‡         | 0.71 (0.45, 1.10) | 1.54 (1.05, 2.17) |
| **High Blood Pressure**‡ | 1.54 (1.05, 2.17) | 1.54 (1.05, 2.17) |
| **Glycemia**         |      |        |      |        |
| 100-125              | 1.17 (0.83, 1.66) | 0.82 (0.49, 1.38) |
| ≥126                 | 1.00 (0.98, 1.02) | 0.98 (0.43, 2.24) |

|                      | Male | Female |
|----------------------|------|--------|
|                      | HR   | 95% CI | aHR  | 95% CI |
| **Age**              | 1.02 (1.00, 1.03) | 1.00 (0.98, 1.02) |
| **Smoking**          | 0.98 (0.43, 2.24) | 0.39 (0.12, 1.23) |
| **Drinking**         | 1.13 (0.75, 1.71) | 0.61 (0.33, 1.15) |
| **Physical activity** | 0.72 (0.51, 1.01) | 1.20 (0.77, 1.86) |
| **Meat intake**      | 0.89 (0.63, 1.25) | 2.50 (1.01, 6.14) |
| **Vegetable intake** | 1.00 (0.73, 1.37) | 1.69 (1.54, 1.84) |
| **Family history of CRC** | 0.89 (0.33, 2.40) | 1.34 (0.86, 2.09) |
| **f-Hb concentration** | 1.95 (1.82, 2.08) | 1.23 (0.92, 1.64) |
| **MetS**             | 1.49 (1.10, 2.00) | 1.15 (0.73, 1.82) |
| **Abnormal WC**†     | 1.42 (1.06, 1.90) | 1.54 (1.05, 2.17) |
| **Hypertriglyceridemia**‡ | 0.71 (0.45, 1.10) | 1.54 (1.05, 2.17) |
| **Low HDL**‡         | 1.23 (0.92, 1.64) | 1.15 (0.73, 1.82) |
| **High Blood Pressure**‡ | 1.05 (0.68, 1.61) | 1.05 (0.68, 1.61) |
| **Glycemia**         |      |        |      |        |
| 100-125              | 1.50 (1.01, 1.90) | 1.50 (1.01, 1.90) |
| ≥126                 | 1.30 (0.78, 2.19) | 0.73 (0.31, 1.69) |

*Hb = fecal hemoglobin, HDL = high-density lipoprotein, HR = hazard ratio, MetS = metabolic syndrome, WC = waist circumference.

†The results of individual components of MetS in the multivariable analysis are from another model in which MetS was not included.

‡Abnormal waist circumference, >90 cm in men and >80 cm in women.

§Hypertriglyceridemia, ≥150 mg/dL.

‖Low HDL, <40 mg/dL (1 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women.

jjHigh blood pressure, ≥130/85 mmHg.
4.3. Individual components of MetS and colorectal advance adenoma

We found that men with hypertriglyceridemia and high blood pressure were more likely to have advanced adenoma, but none of the individual components was associated with advanced adenoma in women. In addition to hypertriglyceridemia, whether high blood pressure is a possible risk factor for disease progression remains unclear. However, a cross-sectional study revealed the use of antihypertensive drugs was associated with the risk of colorectal polyps. Men are known to have higher blood pressure than women. The more frequent use of antihypertensive drugs in men could be one of the possible reasons for this.

The study limitations included that the results of our study were derived from Taiwanese individuals older than 40 years; thus, the generalization of our results to other populations should be limited, and other confounding factors, particularly individual gene information, were not collected and included in our analysis.

In conclusion, an effect of MetS on colorectal adenoma was observed in both genders in a community-based study, whereas the contribution of the individual components of MetS differed between men and women. These findings suggest that a possible risk reduction in colorectal adenoma occurs through metabolic-syndrome-based lifestyle modifications and may take sex differences into account.

Acknowledgments

The authors would like to thank the Public Health Bureau of Keelung City for their contribution and support.

Author contributions

Conceptualization: Mei-Sheng Ku, Sherry Yueh-Hsia Chiu.
Data curation: Mei-Sheng Ku, Sherry Yueh-Hsia Chiu.
Formal analysis: Mei-Sheng Ku, Sherry Yueh-Hsia Chiu.
Funding acquisition: Kuo-Liong Chien.
Investigation: Mei-Sheng Ku, Sherry Yueh-Hsia Chiu.
Methodology: Sam Li-Sheng Chen, Chih-Dao Chen.
Project administration: Sherry Yueh-Hsia Chiu, Sam Li-Sheng Chen.
Resources: Sherry Yueh-Hsia Chiu, Yi-Chia Lee, Sam Li-Sheng Chen.
Supervision: Chih-Dao Chen.
Writing – original draft: Mei-Sheng Ku, Sherry Yueh-Hsia Chiu.
Writing – review & editing: Kuo-Liong Chien, Yi-Chia Lee, Sam Li-Sheng Chen, Chih-Dao Chen.

References

[1] Chen THH, Chiu YH, Luh DL, et al. Taiwan Community-Based Integrated Screening GCommunity-based multiple screening model: design, implementation, and analysis of 42,387 participants. Cancer 2004;100:1734–43.
[2] Chiu HM, Lin JT, Shun CT, et al. Association of metabolic syndrome with proximal and synchronous colorectal neoplasm. Clin Gastroenterol Hepatol 2007;5:221–9. quiz 141.
[3] Le Marchand L, Wilkens LR, Colonel LN, et al. Associations of sedentary lifestyle, obesity, smoking, alcohol use, and diabetes with the risk of colorectal cancer. Cancer Res 1997;57:4787–94.
[4] Trevisan M, Liu J, Muri P, et al. Markers of insulin resistance and colorectal cancer mortality. Cancer Epidemiol Biomarkers Prev 2001;10:917–41.
[5] Terry PD, Miller AB, Rohan TE. Obesity and colorectal cancer risk in women. Gut 2002;51:191–4.
[31] Giovannucci E, Ascherio A, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Physical activity, obesity, and risk for colon cancer and adenoma in men. Ann Intern Med 1995;122:327–34.

[32] Liu PH, Wu K, Ng K, et al. Association of obesity with risk of early-onset colorectal cancer among women. JAMA Oncol 2019;5:37–44.

[33] Schoen RE, Tangen CM, Kuller LH, et al. Increased blood glucose and insulin, body size, and incident colorectal cancer. J Natl Cancer Inst 1999;91:1147–54.

[34] Koohestani N, Chia MC, Pham NA, et al. Aberrant crypt focus promotion and glucose intolerance: correlation in the rat across diets differing in fat, n-3 fatty acids and energy. Carcinogenesis 1998;19:1679–84.

[35] McKeown-Eyssen G. Epidemiology of colorectal cancer revisited: are serum triglycerides and/or plasma glucose associated with risk? Cancer Epidemiol Biomarkers Prev 1994;3:687–95.

[36] Bruce WR, Wolever TM, Giacca A. Mechanisms linking diet and colorectal cancer: the possible role of insulin resistance. Nutr Cancer 2000;37:19–26.

[37] Bruce WR, Giacca A, Medline A. Possible mechanisms relating diet and risk of colon cancer. Cancer Epidemiol Biomarkers Prev 2000;9:1271–9.

[38] Tran TT, Medline A, Bruce WR. Insulin promotion of colon tumors in rats. Cancer Epidemiol Biomarkers Prev 1996;5:1013–5.

[39] Marchand LL, Wilkens LR, Kolonel LN, Hankin JH, Lyu LC. Associations of sedentary lifestyle, obesity, smoking, alcohol use, and diabetes with the risk of colorectal cancer. Cancer Res 1997;57:4787–94.

[40] Will JC, Galuska DA, Vinicor F, Calle EE. Colorectal cancer: another complication of diabetes mellitus? Am J Epidemiol 1998;147:816–25.

[41] Hu FB, Manson JE, Liu S, et al. Prospective study of adult onset diabetes mellitus (Type 2) and risk of colorectal cancer in women. J Natl Cancer Inst 1999;91:542–7.

[42] Saydah SH, Platz EA, Rifai N, et al. Association of markers of insulin and glucose control with subsequent colorectal cancer risk. Cancer Epidemiol Biomarkers Prev 2003;12:412–8.

[43] Larsson SC, Giovannucci E, Wolk A. Diabetes and colorectal cancer incidence in the cohort of Swedish men. Diabetes Care 2005;28:1805–7.

[44] P Terry EG, Bergkvist L, Holmberg L, et al. Body weight and colorectal cancer risk in a cohort of Swedish women: relation varies by age and cancer site. Br J Cancer 2001;85:346–9.

[45] Bowers K, Albanes D, Limburg P, et al. A prospective study of anthropometric and clinical measurements associated with insulin resistance syndrome and colorectal cancer in male smokers. Am J Epidemiol 2006;164:652–64.

[46] Limburg PJ, Anderson KE, Johnson TW, et al. Diabetes mellitus and subsite-specific colorectal cancer risks in the Iowa Women’s Health Study. Cancer Epidemiol Biomarkers Prev 2005;14:133–7.

[47] Koenuma M, Yamori T, Tsuruo T. Insulin and insulin-like growth factor I stimulate proliferation of metastatic variants of colon carcinoma 26. Japanese J Cancer Res 1989;80:51–8.

[48] Linda F, Watkins LRLAE. Characterization of the synergistic effect of insulin and transferrin and the regulation of their receptors on a human colon carcinoma cell line. Int J Cancer 1990;45:372–5.

[49] Watanabe Y, Yamaji Y, Kobayashi Y, et al. Association between colorectal polyps and hypertension treatment. J Dig Dis 2015;16:649–55.

[50] Sandberg K, Ji H. Sex differences in primary hypertension. Biol Sex Differ 2012;3:7.