Sex-influenced association of non-alcoholic fatty liver disease with colorectal adenomatous and hyperplastic polyps

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AIM
To investigate the relationship between non-alcoholic fatty liver disease (NAFLD) and colorectal adenomatous and hyperplastic polyps.

METHODS
A retrospective cross-sectional study was conducted on 3686 individuals undergoing health checkups (2430 males and 1256 females). All subjects underwent laboratory testing, abdominal ultrasonography, colonoscopy, and an interview to ascertain the baseline characteristics and general state of health. Multinomial logistic regression analysis was performed to examine the association between NAFLD and the prevalence of colorectal adenomatous and hyperplastic polyps.
Non-alcoholic fatty liver disease (NAFLD), a metabolic disease of the liver, is well recognized as the most prevalent chronic liver disease worldwide, and its prevalence is dramatically increasing both in Asian and Western countries[12]. Patients with NAFLD present higher levels of insulin, insulin resistance status and chronic inflammation conditions[13-15]. Insulin and the insulin-like growth factor (IGF) axis play an important role in cell metabolism and growth. Insulin stimulates colorectal cell proliferation and increases bioactive IGF-1, which promotes cell cycle progression through mitogenic and antiapoptotic effects[16].

Recent studies suggested that NAFLD was associated with an increased risk for colorectal adenomas and advanced neoplasms[17-19]. Hwang et al[19] conducted an investigation of 2917 subjects divided into two groups (556 adenomatous polyps and 2361 polyp-free). They found that NAFLD was an independent risk factor for colorectal adenoma (OR = 1.28, 95%CI: 1.03-1.60, P = 0.029)[19]. However, this study ignored non-adenomas, such as hyperplastic polyps and inflammatory polyps, and investigated the association between NAFLD and non-adenomatous polyps. Limited data are available in the literature regarding the relationship between NAFLD and hyperplastic polyps. Given that insulin level was specifically associated with adenomatous and hyperplastic polyps and related to NAFLD, our aim was to explore the relationship between NAFLD and colorectal adenomatous and hyperplastic polyps.

In addition, Touzin et al[20] conducted a retrospective observational study to explore the relationship between biopsy-proven NAFLD and colorectal adenoma but failed to demonstrate that patients with biopsy-proven NAFLD had an increased incidence of colorectal adenoma. The association between NAFLD and colorectal polyps may be controversial. Furthermore, the prevalence of NAFLD (60.8% in males and 43.5% in females) and colorectal polyps (35.5% in males and 20.9% in females) was not consistent in different sex groups. Several studies demonstrated a significant association between dyslipidemia and colon adenoma in men but not in women[22,23]. Therefore, our study further explored the link between NAFLD and colorectal adenomatous and hyperplastic polyps in different sex groups.

INTRODUCTION

Colorectal adenomatous polyps and some subsets of hyperplastic polyps have been considered precursors of hereditary and sporadic colorectal cancer[1-5]. Currently, the incidence of colorectal polyps and colorectal cancer has been increasing over recent decades worldwide[6]. Identifying risk factors for colorectal cancer and performing colonoscopy and polypectomy are considered efficient surveillance programs to detect colorectal polyps and reduce malignant progression and mortality among the general population[7]. In a cross-sectional study of 343 patients who underwent colonoscopy, serum insulin levels as a metabolic factor were correlated with the prevalence of adenomatous (OR = 1.5, 95%CI: 1.1-2.0, P = 0.005) and hyperplastic polyps (OR = 1.3, 95%CI: 1.0-1.7, P = 0.075). In addition, some suggested that hyperplastic polyps could act as a marker for the future development of adenomas in the general population[8-11].

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MATERIALS AND METHODS

Subjects
Study participants consisted of individuals who had a routine health checkup and colonoscopy at the Medical and Health Care Center of the First Affiliated Hospital of Wenzhou Medical University from September 2014 to November 2016. A standard questionnaire was administered to obtain relevant information from each participant, including smoking status (yes or no), alcohol consumption and medical history.

A total of 6035 participants were screened (Figure 1). In total, 2349 subjects were excluded based on the following reasons: incomplete colonoscopy, polypectomy, inflammatory bowel disease, carcinoma, liver cirrhosis, viral hepatitis, toxic and autoimmune liver diseases and excess alcohol consumption (moderately (> 140 g/wk for men or > 70 g/wk for women)). Thus, the final study population consisted of 3686 subjects (2430 males and 1256 females). Physical examination data were collected as part of a study, and formal ethical approval was not required.

Anthrometric index and laboratory tests
Well-trained examiners measured the body weight (measured to the nearest 0.1 kg) with a balance scale and the height (measured to the nearest 0.1 cm) with a portable stadiometer of every individual dressed in light clothes and without shoes in the morning. Body mass index (BMI) was calculated by dividing weight in kilograms by the height squared. Blood pressure was measured in the right arm in a seated state after they had at least 15 min of rest with a standard automatic instrument (Omron, model 705 cp, Kyoto, Japan) and recorded as systolic blood pressure (SBP) and diastolic blood pressure (DBP).

Following an 8-h fast, blood samples were collected and analyzed from antecubital vein sampling. Biochemical markers, such as fasting plasma glucose (FPG), triglyceride (TG), total cholesterol (TC), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), alanine aminotransferase and aspartate aminotransferase, were subsequently analyzed with an automated analyzer (Abbott AxSYM, Park, IL).

Colonoscopy
Following full bowel preparation, colonoscopy (OLYMPUS, Tokyo, Japan) was performed in all participants by experienced gastroenterologists using a standard protocol identical for diagnostic colonoscopy.

Colonoscopic findings, including the type, location, size and number of polyps, were recorded. All polypectomy specimens were classified by experienced histopathologists. Based on the results of colorectal biopsies, individuals were divided into four groups: polyp-free group, adenomatous polyps group, hyperplastic polyps group and inflammatory polyps group. The location was stratified as following: (1) proximal lesions (polyps located in the cecum, ascending and transverse colon); (2) distal lesions (polyps located in the splenic flexure, descending sigmoid colon and rectum); and (3) bilateral lesions (polyps locating on both sides). The size of polyps was divided into two groups. Less than 10 mm was defined as small, whereas 10 mm or greater was defined as large. The number of polyps was also divided into two groups: single and multiple.

Diagnostic criteria
Abdominal ultrasonography was performed by professional radiologists to diagnose fatty liver. According
to the four knowledgeable ultrasound criteria (liver brightness, deep attenuation, hepatorenal echo contrast and vascular blurring), subjects who met hepatorenal contrast and liver brightness were diagnosed with fatty liver disease\textsuperscript{[29]}\textsuperscript{[29]}. NAFLD was diagnosed based on the guidelines for assessment and management of NAFLD in the Asia-Pacific region when fatty liver was present in the absence of the following: (1) viral hepatitis (hepatitis B or hepatitis C); (2) hepatic cirrhosis and liver carcinoma; (3) autoimmune liver disease or other liver disease; and (4) excess alcohol consumption (> 140 g/wk for men or > 70 g/wk for women)\textsuperscript{[29]\textsuperscript{[29]}. The definition of metabolic syndrome (MS) was based on the presence of three or more of the following China Diabetes Federation MS criteria: (1) central obesity: BMI ≥ 25 in both genders; (2) hypertension: SBP ≥ 140 mmHg or DBP ≥ 90 mmHg or previously diagnosed; (3) dyslipidemia: TG ≥ 1.7 mmol/L and/or HDL-C < 0.9 mmol/L in males and < 1.0 mmol/L in females; and (4) hyperglycemia: FPG ≥ 6.1 mmol/L or hyperglycemia previously diagnosed\textsuperscript{[29]\textsuperscript{[29]}. Statistical analysis

Statistical analyses were conducted using SPSS software (SPSS version 23.0 for Windows). Demographic data and other risk factors for colorectal polyps, adenomatous polyps and hyperplastic polyps are presented as the mean ± SD or percentages. One-way analysis of variance (ANOVA) or Kruskal-Wallis test for continuous variables and Pearson χ² tests for categorical variables were used to compare the baseline of the study population according to the

### Table 1  Demographic and clinical characteristics of the subjects according to colonoscopic findings (n (%))

| Characteristic       | Polyp-free     | Colorectal polyps | P value vs Polyp-free | Adenomatous polyps | P value vs Polyp-free | Hyperplastic polyps | P value vs Polyp-free |
|----------------------|---------------|-------------------|-----------------------|-------------------|----------------------|---------------------|----------------------|
| Male                 | 2501 (67.9)   | 1185 (32.1)       | < 0.001               | 498 (13.5)        | < 0.001              | 288 (7.8)           | < 0.001              |
| Age (yr)             | 1487 (59.5)   | 945 (79.6)        | < 0.001               | 395 (83.0)        | < 0.001              | 239 (77.9)          | < 0.001              |
| Weight (kg)          | 64.27 ± 11.29 | 68.33 ± 11.04     | < 0.001               | 67.58 ± 11.13    | < 0.001              | 69.57 ± 11.01       | < 0.001              |
| Height (cm)          | 164.64 ± 7.71 | 166.59 ± 7.26     | < 0.001               | 165.95 ± 7.47    | 0.001                | 167.46 ± 7.01       | < 0.001              |
| BMI (kg/m²)          | 23.62 ± 3.22  | 24.54 ± 3.10      | < 0.001               | 24.45 ± 3.10     | < 0.001              | 24.75 ± 3.13        | < 0.001              |
| SBP (mmHg)           | 124.43 ± 17.78| 129.99 ± 18.34    | < 0.001               | 130.57 ± 18.75   | < 0.001              | 127.72 ± 17.94      | 0.003                |
| DBP (mmHg)           | 73.48 ± 12.27 | 76.96 ± 12.11     | < 0.001               | 77.19 ± 12.13    | < 0.001              | 76.72 ± 12.26       | < 0.001              |
| FPG (mmol/L)         | 4.78 ± 1.13   | 5.01 ± 1.41       | < 0.001               | 4.99 ± 1.39      | 0.001                | 4.93 ± 1.56         | 0.032                |
| TG (mmol/L)          | 1.79 ± 1.71   | 2.01 ± 1.81       | < 0.001               | 1.98 ± 2.04      | 0.032                | 2.05 ± 1.23         | 0.013                |
| TC (mmol/L)          | 5.35 ± 1.12   | 5.44 ± 1.12       | 0.020                 | 5.44 ± 1.21      | 0.093                | 5.53 ± 1.10         | 0.009                |
| HDL-C (mmol/L)       | 1.32 ± 0.33   | 1.26 ± 0.30       | < 0.001               | 1.28 ± 0.31      | 0.003                | 1.24 ± 0.28         | < 0.001              |
| LDL-C (mmol/L)       | 3.19 ± 0.86   | 3.27 ± 0.86       | 0.011                 | 3.25 ± 0.84      | 0.154                | 3.36 ± 0.92         | 0.002                |
| ALT (IU/L)           | 29.25 ± 29.65 | 32.23 ± 27.51     | 0.004                 | 31.86 ± 22.61    | 0.065                | 32.85 ± 25.87       | 0.051                |
| AST (IU/L)           | 27.24 ± 16.19 | 28.89 ± 17.63     | 0.007                 | 28.75 ± 11.80    | 0.049                | 28.57 ± 13.43       | 0.184                |
| NAFLD                | 488 (17.9)    | 291 (24.6)        | < 0.001               | 122 (27.4)       | 0.002                | 79 (22.6)           | 0.001                |
| MS                   | 246 (10.1)    | 180 (15.6)        | < 0.001               | 73 (15.5)        | 0.005                | 44 (16.4)           | 0.016                |
| Smoking              | 662 (26.6)    | 373 (31.7)        | 0.002                 | 151 (30.5)       | 0.087                | 101 (33.2)          | 0.004                |
| Alcohol              | 854 (34.4)    | 445 (37.8)        | 0.042                 | 191 (38.6)       | 0.078                | 118 (41.3)          | 0.028                |

BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FPG: Fasting plasma glucose; TG: Triglyceride; TC: Total cholesterol; HDL-C: High density lipoprotein-cholesterol; LDL-C: Low density lipoprotein-cholesterol; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; NAFLD: Non-alcoholic fatty liver disease; MS: Metabolic syndrome.

### RESULTS

#### Subject characteristics

The demographic and clinical characteristics of eligible subjects according to colonoscopic findings are presented in Table 1. Among 3686 subjects in our study, 1185 (32.1%) were diagnosed with colorectal polyps, including 498 (13.5%) with adenomatous polyps, 288 (7.8%) with hyperplastic polyps, and 399 (10.8%) with inflammatory polyps. Of the 2430 male subjects, 1487 (61.2%) were in the normal group, and 943 (79.6%) were in the colorectal polyps group, including 498 (13.5%) with adenomatous polyps, 288 (7.8%) with hyperplastic polyps, and 399 (10.8%) with inflammatory polyps. Of the female subjects, 1227 (59.5%) were in the normal group, and 393 (16.2%) were in the colorectal polyps group, including 498 (17.9%) with adenomatous polyps and 239 (8.9%) with hyperplastic polyps (Table 2). Of the female
subjects, 1014 (80.7%) were in the normal group, and 242 (19.3%) were in the colorectal polyps group, including 105 (8.4%) with adenomatous polyps and 49 (3.9%) with hyperplastic polyps. The prevalence of NAFLD in the colorectal polyps group, adenomatous polyps group, and hyperplastic polyps group were 268 (28.4%), 116 (29.5%), and 72 (30.1%) in males and 23 (9.5%), 6 (5.7%), and 7 (14.3%) in females, respectively. Overall, subjects without colorectal polyps had younger age, higher HDL-C, and reduced weight, BMI values, SBP, DBP, FPG, TG, TC, LDL-C, MS prevalence, smoking, and alcohol use.

**NAFLD is related to the prevalence of adenomatous polyps and hyperplastic polyps**

The results of the multinomial logistic regression of risk factors for colorectal polyps, adenomatous polyps and hyperplastic polyps are presented in Table 3. In model A, compared with the polyp-free group, multinomial logistic regression demonstrated that subjects with NAFLD exhibited an increased prevalence of colorectal polyps (OR = 1.49, 95%CI: 1.26-1.76, P < 0.001), adenomatous polyps (OR = 1.49, 95%CI: 1.18-1.87, P < 0.05) and hyperplastic polyps (OR = 1.73, 95%CI: 1.31-2.29, P < 0.001) compared with subjects without NAFLD. In model C, the adjusted ORs for colorectal polyps persist after sex analysis?

Does the association between NAFLD and colorectal polyps persist after sex analysis?

Multinomial logistic regression was performed to obtain a deeper understanding of the relationship between

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**Table 2** Demographic and clinical characteristics of 2430 males and 1256 females according to colonoscopic findings a (%)  

| Characteristic of males | Polyp-free | Colorectal polyps | P value vs Polyp-free | Adenomatous polyps | P value vs Polyp-free | Hyperplastic polyps | P value vs Polyp-free |
|-------------------------|------------|-------------------|-----------------------|--------------------|----------------------|---------------------|---------------------|
| Polyp-free (61.2)       | 1487       | 943 (38.8)        | < 0.001               | 393 (16.2)         | < 0.001              | 239 (9.8)          |                     |
| Age (yr)                | 44.6 ± 9.91| 50.18 ± 9.67      | < 0.001               | 51.71 ± 9.54       | < 0.001              | 47.56 ± 8.90       | < 0.001              |
| Weight (kg)             | 69.46 ± 10.18| 70.88 ± 10.20   | 0.001                 | 70.27 ± 10.12      | 0.164                | 71.47 ± 10.74      | 0.005                |
| Height (cm)             | 169.13 ± 5.56| 168.88 ± 5.80   | 0.305                 | 168.28 ± 6.04      | 0.012                | 169.64 ± 5.72      | 0.427                |
| BMI (kg/m²)             | 24.28 ± 3.22| 24.81 ± 3.06     | < 0.001               | 24.77 ± 3.03       | 0.006                | 24.85 ± 3.22       | 0.011                |
| SBP (mmHg)              | 127.29 ± 16.24| 130.47 ± 17.83 | < 0.001               | 131.97 ± 18.29     | < 0.001              | 127.82 ± 16.88     | 0.639                |
| DBP (mmHg)              | 76.44 ± 11.75| 78.14 ± 12.03    | 0.001                 | 78.77 ± 11.93      | 0.011                | 77.57 ± 12.11      | 0.173                |
| FPG (mmol/L)            | 4.86 ± 1.26| 5.06 ± 1.49       | 0.001                 | 5.04 ± 1.46        | 0.012                | 4.96 ± 1.42        | 0.233                |
| TG (mmol/L)             | 2.14 ± 0.24| 2.15 ± 0.95       | 0.920                 | 2.16 ± 2.24        | 0.878                | 2.14 ± 2.24        | 0.987                |
| TC (mmol/L)             | 5.42 ± 1.16| 5.42 ± 1.12       | 0.954                 | 5.45 ± 1.24        | 0.866                | 5.45 ± 1.28        | 0.374                |
| HDL-C (mmol/L)          | 1.22 ± 0.28| 1.22 ± 0.29       | 0.892                 | 1.24 ± 0.30        | 0.244                | 1.21 ± 0.27        | 0.597                |
| LDL-C (mmol/L)          | 1.32 ± 0.86| 1.32 ± 0.84       | 0.829                 | 1.34 ± 0.83        | 0.632                | 1.34 ± 0.90        | 0.221                |
| ALT (IU/L)              | 34.71 ± 33.63| 35.31 ± 29.49    | 0.657                 | 35.54 ± 23.59      | 0.649                | 35.2 ± 27.84       | 0.834                |
| AST (IU/L)              | 20.00 ± 17.83| 20.32 ± 19.06    | 0.115                 | 20.37 ± 12.31      | 0.155                | 20.39 ± 13.41      | 0.796                |
| NAFLD                   | 297 (11.3) | 288 (12.4)        | < 0.001               | 297 (12.4)         | 0.018                | 297 (12.4)         | 0.038                |
| MS                      | 194 (13.3) | 156 (17.0)        | 0.076                 | 156 (17.0)         | 0.013                | 156 (17.0)         | 0.034                |
| Smoking                 | 465 (31.4)| 327 (34.9)        | 0.056                 | 327 (34.9)         | 0.071                | 327 (34.9)         | 0.045                |
| Alcohol                 | 577 (39.0) | 377 (40.3)        |                     | 377 (40.3)         |                     | 377 (40.3)         |                     |

BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FPG: Fasting plasma glucose; TG: Triglyceride; TC: Total cholesterol; HDL-C: High density lipoprotein-cholesterol; LDL-C: Low density lipoprotein-cholesterol; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; NAFLD: Non-alcoholic fatty liver disease; MS: Metabolic syndrome.

Does the association between NAFLD and colorectal polyps persist after sex analysis?
NAFLD and the prevalence of adenomatous polyps and hyperplastic polyps in males and females (Table 4). In model A, NAFLD was independently related to both adenomatous polyps (OR = 1.34, 95%CI: 1.04-1.71, P < 0.05) and hyperplastic polyps (OR = 1.38, 95%CI: 1.02-1.86, P < 0.05) in males, whereas no significant relationship was noted between NAFLD and colorectal polyps in females. After adjustment for age and smoking (model B), associations between NAFLD and adenomatous polyps (OR = 1.53, 95%CI: 1.19-1.98, P < 0.05) and hyperplastic polyps (OR = 1.44, 95%CI: 1.06-1.95, P < 0.05) were noted in males. In model C, after controlling for confounding factors, such as age, smoking, alcohol and MS, the associations between NAFLD and adenomatous polyps and hyperplastic polyps remained (OR = 1.53, 95%CI: 1.18-2.00, P < 0.05; OR = 1.42, 95%CI: 1.04-1.95, P < 0.05) statistically significant in males.

**Stratified analysis**

The stratified analysis performed according to the number, size and location of adenomatous polyps and hyperplastic polyps is presented in Table 5. In the adenomatous polyps group, compared with non-NAFLD and adjusted for age, smoking, alcohol and MS, NAFLD was associated with multiple adenomas (OR = 1.82, 95%CI: 1.29-2.55, P = 0.001), distal adenoma (OR = 1.63, 95%CI: 1.11-2.39, P = 0.013), and bilateral adenoma (OR = 1.89, 95%CI: 1.23-2.91, P = 0.004). The OR for large adenoma (OR = 2.13, 95%CI: 1.21-3.76, P = 0.009) increased by approximately 1.5-fold compared with small adenoma (OR = 1.44, 95%CI: 1.08-1.91, P = 0.013). In addition, the associations between NAFLD and the prevalence of single (OR = 1.81, 95%CI: 1.19-2.74, P = 0.005), small (OR = 1.45, 95%CI: 1.05-2.00, P = 0.023) and proximal (OR = 2.62, 95%CI: 1.32-5.17, P = 0.006) hyperplastic polyps were noticeably stronger.

**DISCUSSION**

Our study presented that individuals with NAFLD exhibited an increased prevalence of colorectal adenomatous polyps compared with individuals without NAFLD, which is consistent with previous reports[19,21]. This study also showed that NAFLD is a risk factor for the increased prevalence of hyperplastic polyps. Therefore, this is the first study performed to explore an association between ultrasound-diagnosed NAFLD and colorectal adenomatous and hyperplastic polyps.

In our study, for the entire enrolled population, NAFLD is a risk factor for the prevalence of adenomatous polyps (OR = 1.28) and hyperplastic polyps (OR = 1.35). To analyze whether sex influences the association of NAFLD with adenomatous and hyperplastic polyps, we presented data classified according to sex and demonstrated that NAFLD is a risk factor for adenomatous (OR = 1.53) and hyperplastic polyps (OR = 1.42) in males after considering confounding variables, such as age, smoking, alcohol and MS. In contrast, no association was noted between NAFLD and adenomatous and hyperplastic polyps in females. In the adenomatous polyps group, individuals with NAFLD had an increased risk of multiple, including small and large, distal and bilateral polyps. Furthermore, the association between NAFLD and hyperplastic polyps was more prominent for the risk of single, small and proximal hyperplastic polyps. Our results may explain why Touzin et al[20] failed to demonstrate that patients with biopsy-proven NAFLD had an increased incidence of colorectal adenoma, with only 233 (48% in females) patients enrolled.

The significant association between NAFLD and colorectal adenomatous polyps has been recognized by several researchers. Hwang et al[19] conducted a cross-sectional study and demonstrated that NAFLD is an independent risk factor for the prevalence of colorectal adenoma and particularly associated with an increased risk for multiple adenomas. Furthermore, Stadmayer et al[21] examined 1200 patients via screening colonoscopy and identified an increased prevalence of colorectal adenomas and early colorectal cancer in patients with NAFLD compared with those without NAFLD. This study also reported that the prevalence rate of colorectal adenomas was obviously increased in males with NAFLD compared with females with NAFLD. In addition, Wong et al[20] conducted a cross-sectional study of 433 subjects, including 135 with biopsy-proven NAFLD, and demonstrated that patients with...
NAFLD exhibited an increased prevalence of adenomas (34.7% vs 21.5%, \( P = 0.043 \)). Among biopsy-proven NAFLD patients, patients with non-alcoholic steatohepatitis exhibited an increased prevalence of adenomas (51.0% vs 25.6%, \( P = 0.005 \)).

Currently, the mechanisms responsible for the relationship between NAFLD and colorectal adenomas have not been clearly understood. The potential mechanisms for how NAFLD promotes the development of colorectal adenomas include insulin resistance and chronic inflammation[30,31]. Insulin and IGF may facilitate the development of colorectal adenoma through their antiapoptotic and proliferative effects[31]. It is generally accepted that adipocytokine metabolism, such as interleukin-6, tumor necrosis factor-alpha and adiponectin, play an important role in the development of colorectal adenomas in NAFLD patients. The levels of interleukin-6 and tumor necrosis factor-alpha, as carcinogens and growth-promoting factors, are increasing. In contrast, the levels of adiponectin, a protective factor, are reduced with NAFLD[30]. Furthermore, inflammatory cytokines, such as interleukin-6, tumor necrosis factor-alpha and adiponectin, play an important role in the development of colorectal adenomas in NAFLD patients. The levels of interleukin-6 and tumor necrosis factor-alpha, as carcinogens and growth-promoting factors, are increasing. In contrast, the levels of adiponectin, a protective factor, are reduced with NAFLD[30].

Although hyperplastic polyps have been regarded as non-neoplastic polyps lacking malignant potential, recent studies provided some evidence of the presence of molecular changes consistent with neoplasia, including ras mutations, hypomethylation of the c-myc gene and high levels of microsatellite instability[36-41]. Furthermore, Huang et al.[41] conducted a retrospective cohort study using the records of a single surgeon’s colonoscopic experience over a 20-year period and inflammatory response and the release of other cytokines[34]. Furthermore, inflammatory cytokines, such as interleukin-6, tumor necrosis factor-alpha and adiponectin, play an important role in the development of colorectal adenomas in NAFLD patients. The levels of interleukin-6 and tumor necrosis factor-alpha, as carcinogens and growth-promoting factors, are increasing. In contrast, the levels of adiponectin, a protective factor, are reduced with NAFLD[30].

### Table 4 Adjusted odds ratios and 95% CIs of clinical variables on the risk of colorectal polyps, adenomatous polyps and hyperplastic polyps according to different-sex groups based on multinomial logistic regression

| Polyps               | Male OR (95%CI) | Female OR (95%CI) | Male OR (95%CI) | Female OR (95%CI) | Male OR (95%CI) | Female OR (95%CI) |
|----------------------|----------------|------------------|----------------|------------------|----------------|------------------|
| Colorectal polyps    |                |                  |                |                  |                |                  |
| NAFLD                | 1.27 (1.05-1.52)\(^a\) | 1.04 (0.64-1.68)  | 1.41 (1.16-1.71)\(^*\) | 0.80 (0.49-1.32)  | 1.40 (1.14-1.71)\(^*\) | 0.78 (0.47-1.28)  |
| Age                  | 1.06 (1.05-1.07)\(^b\) | 1.05 (1.03-1.06)\(^b\) | 1.06 (1.05-1.07)\(^*\) | 1.05 (1.03-1.06)\(^*\) | 1.23 (1.02-1.50)\(^*\) | 0.88 (0.57-1.36) |
| Smoking              | 1.22 (1.02-1.46)\(^*\) | 0.95 (0.66-1.36)  | 0.98 (0.81-1.19)  | 1.19 (0.81-1.74)  | 1.07 (0.84-1.37)  | 1.37 (0.80-2.34)  |
| Alcohol              |                |                  |                |                  |                |                  |
| MS                   |                |                  |                |                  |                |                  |
| Adenomatous polyps   |                |                  |                |                  |                |                  |
| NAFLD                | 1.34 (1.04-1.71)\(^*\) | 0.60 (0.26-1.41)  | 1.53 (1.19-1.98)\(^*\) | 0.45 (0.19-1.07)  | 1.53 (1.18-2.00)\(^*\) | 0.44 (0.18-1.04)  |
| Age                  | 1.08 (1.06-1.09)\(^b\) | 1.05 (1.03-1.07)\(^b\) | 1.08 (1.06-1.09)\(^*\) | 1.05 (1.03-1.07)\(^*\) | 1.12 (0.85-1.46)  | 0.90 (0.50-1.61)  |
| Smoking              | 1.10 (0.86-1.40) | 1.24 (0.76-2.02)  | 0.97 (0.75-1.25)  | 1.77 (1.06-2.96)  | 0.98 (0.71-1.36)  | 1.17 (0.53-2.56)  |
| Alcohol              |                |                  |                |                  |                |                  |
| MS                   |                |                  |                |                  |                |                  |
| Hyperplastic polyps  |                |                  |                |                  |                |                  |
| NAFLD                | 1.38 (1.02-1.86)\(^*\) | 1.65 (0.72-3.78)  | 1.44 (1.06-1.95)\(^*\) | 1.30 (0.56-3.03)  | 1.42 (1.04-1.95)\(^*\) | 1.18 (0.50-2.78)  |
| Age                  | 1.04 (1.02-1.05)\(^b\) | 1.04 (1.01-1.07)\(^*\) | 1.04 (1.02-1.05)\(^*\) | 1.04 (1.01-1.07)\(^*\) | 1.38 (1.01-1.88)  | 0.71 (0.31-1.65)  |
| Smoking              | 1.38 (1.03-1.83)\(^*\) | 1.01 (0.49-2.06)  | 1.01 (0.74-1.36)  | 1.85 (0.92-3.72)  | 1.02 (0.69-1.52)  | 2.01 (0.81-4.94)  |
| Alcohol              |                |                  |                |                  |                |                  |
| MS                   |                |                  |                |                  |                |                  |

Model A is univariate analysis; Model B is adjusted for age and smoking; Model C is adjusted for age, smoking, alcohol and MS.

**NAFLD**: Non-alcoholic fatty liver disease; **MS**: Metabolic syndrome.

### Table 5 Adjusted odds ratios and 95% CIs of non-alcoholic fatty liver disease for adenomatous polyps and hyperplastic polyps of the colon and rectum by morphological characteristics in males

| Polyps       | OR (95%CI) | \( P \) value | OR (95%CI) | \( P \) value |
|--------------|------------|---------------|------------|---------------|
| Adenomatous polyps |            |               |            |               |
| Number       |            |               |            |               |
| Single       | 1.27 (0.88-1.82) | 0.205 | 1.17 (0.19-2.74) | 0.005 |
| Multiple     | 1.12 (2.92-2.55) | 0.001 | 1.13 (0.73-1.76) | 0.503 |
| Size         |            |               |            |               |
| Small (< 1 cm)| 1.44 (1.08-1.91) | 0.013 | 1.45 (1.05-2.00) | 0.023 |
| Large (≥ 1 cm)| 2.13 (1.21-3.76) | 0.009 | 1.00 (0.20-5.07) | 0.999 |
| Location     |            |               |            |               |
| Proximal lesions | 1.15 (0.73-1.80) | 0.539 | 2.62 (1.32-5.17) | 0.006 |
| Distal lesions | 1.63 (1.14-2.39) | 0.013 | 1.33 (0.91-1.95) | 0.146 |
| Bilateral lesions | 1.89 (1.23-2.91) | 0.004 | 1.05 (0.51-2.17) | 0.894 |

Odds ratios compared with non-alcoholic fatty liver disease and adjusted for age, smoking, alcohol and metabolic syndrome.
found that patients with hyperplastic polyps on initial colonoscopic examination may have twice the risk of adenomas on follow-up colonoscopy compared with those with clean initial examination. Hyman et al\textsuperscript{[42]} found that 7 (54\%) of 13 patients with hyperplastic polyposis developed colorectal cancer during their study period and suggested that patients with hyperplastic polyposis are at high risk for colorectal cancer. A cross-sectional study suggested that higher serum insulin levels were associated with an increased risk of proximal colon adenomatous and hyperplastic polyps\textsuperscript{[8]}. An experimental study reported that hyperinsulinemia was associated with high susceptibility to colonic carcinogenesis induced by DNA methylation in animals\textsuperscript{[43]}. Furthermore, the roles of insulin resistance and hyperinsulinemia in NAFLD are well recognized\textsuperscript{[44,45]}. Given the link between NAFLD and hyperinsulinemia and the link between hyperinsulinemia and hyperplastic polyps, our study clearly demonstrated that NAFLD was associated with hyperplastic polyps.

Some studies demonstrated that the association of dyslipidemia and colon adenoma existed in different sex groups. Kim et al\textsuperscript{[23]} supported that the risk of adenoma increased significantly by 2-fold when TC $\geq 150$ mg/dL or HDL-C $<40$ mg/dL in males. In contrast, no association was noted between adenoma prevalence and dyslipidemia in females. In addition, Liu et al\textsuperscript{[22]} declared that dyslipidemia and large waist, as a component of MS, exhibited an association with colon adenoma in males but not in females. As a metabolic disease, NAFLD is closely correlated with dyslipidemia. The relationship between NAFLD and colorectal polyps may not be consistent in different sex groups.

Our study had several limitations that should be acknowledged. First, potential selection bias might exist based on general health check-ups, and data, such as visceral fat, fat intake and intestinal flora, are insufficient. Second, the causality between NAFLD and the risk for colorectal adenomatous and hyperplastic polyps is difficult to infer through a cross-sectional study. Third, our study subjects were derived from a single center, and multi-centered research should be performed to further confirm the association in the next step. Fourth, although liver biopsy is a standard criterion for NAFLD diagnosis, the diagnosis of fatty liver was based on ultrasound imaging with a 94\% sensitivity and 84\% specificity\textsuperscript{[46]}.

In conclusion, our study clearly demonstrated that NAFLD is specifically associated with an increased risk of colorectal adenomatous and hyperplastic polyps in men. However, NAFLD is not a significant factor in the prevalence of colorectal polyps in women.

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P- Reviewer: Kahraman A, Rocha R  S- Editor: Ma YJ  L- Editor: Wang TQ  E- Editor: Zhang FF

Chen QF *et al*. NAFLD and colorectal polyps
