

BMJ Open Gender differences in the association of non-alcoholic fatty liver disease and metabolic syndrome with erosive oesophagitis: a cross-sectional study in a Taiwanese population

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ABSTRACT

Objectives: Although metabolic syndrome correlates with erosive oesophagitis, few studies have examined the association between non-alcoholic fatty liver disease (NAFLD), associated with obesity and insulin resistance as metabolic syndrome, and erosive oesophagitis. The possible gender differences in risk factors of erosive oesophagitis should be considered. This study aimed to determine the concomitant effects of NAFLD and metabolic syndrome on erosive oesophagitis with respect to gender.

Design, setting, participants and outcome

measures: This cross-sectional study, conducted between January 2000 and August 2009, included 12 090 participants from the health examination center of a tertiary hospital. NAFLD was diagnosed according to ultrasonographic findings after excluding participants with excessive alcohol consumption or other liver diseases. Metabolic syndrome was determined using the revised National Cholesterol Education Program Adult Treatment Panel III criteria. Erosive oesophagitis was defined according to the Los Angeles classification by oesophagogastroduodenoscopy.

Results: On the basis of the oesophagogastroduodenoscopic findings, the prevalence of erosive oesophagitis was 20.1% (n=1427/7110) and 9.9% (n=477/4842) in males and females, respectively. After adjusting for other variables, metabolic syndrome (OR 1.26; 95% CI 1.09 to 1.45) but not NAFLD (OR 1.14; 95% CI 0.98 to 1.30) significantly correlated with erosive oesophagitis in males, while NAFLD (OR 1.50; 95% CI 1.21 to 1.86) but not metabolic syndrome (OR 1.24; 95% CI 0.94 to 1.63) positively correlated with erosive oesophagitis in females.

Conclusions: The detrimental effect on erosive oesophagitis is greater by metabolic syndrome than by NAFLD in males but greater by NAFLD than by metabolic syndrome in females.

Strengths and limitations of this study

- Although metabolic syndrome (MS) and non-alcoholic fatty liver disease (NAFLD) are associated with erosive oesophagitis (EO), until now there are no studies on the concomitant effects of these conditions on EO with respect to gender.
- This study reveals significant gender differences in the effects of NAFLD and MS on EO, with a greater detrimental effect on EO by MS in males and NAFLD in females.
- NAFLD positively correlates with EO in premenopausal females but not in postmenopausal females or males, suggesting that serum oestrogen levels may play an important role in EO.
- This study is cross-sectional, and thus cannot provide evidence to indicate a causal relationship between NAFLD/MS and EO with respect to gender.

INTRODUCTION

Gastro-oesophageal reflux disease involves the abnormal reflux of gastric contents into the oesophagus. Based on oesophagogastroduodenoscopic findings, the condition is classified as erosive oesophagitis (EO) or non-erosive reflux disease with or without mucosal damage. EO is a major health problem in Western countries, and epidemiological studies have demonstrated its increasing incidence.¹ It affects the quality of a patient's life and increases the risk of oesophageal ulcers, peptic stricture, Barrett's oesophagus and oesophageal adenocarcinoma.^{2 3} Contributing factors to increased risk of EO include male sex, lifestyle, obesity, hiatal hernia and *Helicobacter pylori* negativity.⁴⁻⁷

Metabolic syndrome (MS) is significantly associated with EO.^{6,8} The primary abnormalities of this condition are abdominal adiposity and insulin resistance. Fatty liver, presented as a macrovesicular fatty change of the liver, is also closely related to abdominal adiposity and insulin resistance.⁹ Park *et al*¹⁰ examined the simultaneous effects of MS and fatty liver on EO and found that conditions are associated with EO in a Korean population. However, this earlier study did not exclude the potentially confounding effects of excessive alcohol consumption, hepatitis B and hepatitis C.¹⁰ Excessive alcohol consumption, which can result in EO and fatty liver, may confound the effects of fatty liver on EO.^{10,11} Furthermore, hepatitis B may play a role in fatty liver and EO, while hepatitis C is associated with fatty liver.^{12–14} Non-alcoholic fatty liver disease (NAFLD) is defined as a subclass of fatty liver that is not caused by excessive alcohol consumption or other factors causing steatosis.¹⁵ Gender differences in NAFLD, MS and EO have been recently reported.^{5,7,16–18} Sogabe *et al*^{16,17} divided MS into visceral and subcutaneous types, with each having significantly different effects on EO; they also found that the visceral type was predominant among males, while the subcutaneous type was predominant among females. However, until now, there have been no studies regarding the concomitant effects of NAFLD and MS on EO with respect to gender. Our previous study demonstrated that NAFLD was positively correlated with EO after excluding participants with excessive alcohol drinking and hepatitis B/C¹⁹ but did not further consider the effect of gender on EO and its risk factors. This study aimed to reveal any gender differences in the association of NAFLD and MS with EO.

MATERIALS AND METHODS

Study subjects

A total of 10 876 male and 7341 female participants who underwent a health check-up were enrolled from the Health Examination Center of National Cheng Kung University Hospital, Taiwan between 1 January 2000 and 31 August 2009. Since this study was a secondary data analysis without any personal identification information, the requirement for informed consent was waived. We excluded participants with cancer (men/women, n=93/177), hepatitis B (men/women, n=1643/829), hepatitis C (men/women, n=283/268), excessive alcohol drinking (>20 g/day, men/women, n=85/6), current medications for gastrointestinal disease (men/women, n=441/312), current medication for arthritis (men/women, n=67/71), previous gastrointestinal surgery (men/women, n=7/5) and incomplete data (men/women, n=1147/831). Finally, a total of 7110 male and 4842 female participants were included for analysis.

Questionnaire

The baseline data included medical history, menopausal status (in women), medication use and lifestyle (tea

drinking, smoking, alcohol consumption and habitual exercise). As previously described in detail,¹⁹ tea drinking was defined as at least once per week for at least the previous half year; smoking was defined as at least 1 pack/month for at least the previous half year;²⁰ alcohol consumption was divided into two grades: drinker, 40–140 g/week and non-drinker, <40 g/week for at least the previous half year;⁴ and habitual exercise was defined as vigorous exercise at least 3 times/week for at least the previous half year.

Anthropometric and laboratory measurements

When standing relaxed at the end of normal expiration, waist circumference (WC) was measured midway between the lower rib border and iliac crest.²¹ Body mass index (BMI) was calculated as the weight (kg) divided by the square of the height in metres (kg/m²). Obesity was defined as BMI of ≥ 27 kg/m² according to the Nutrition and Health Survey in Taiwan.²² On the basis of the WHO Asia-Pacific criteria, central obesity was defined as WC of ≥ 90 cm in men or ≥ 80 cm in women.²³

A blood pressure monitor (Model 1846SX DINAMAP Monitor, Critikon, Florida, USA) was used to measure brachial systolic blood pressure and diastolic blood pressure in the supine position after at least 15 min of rest. According to the Seventh Report of the Joint National Committee, hypertension was defined as systolic blood pressure of ≥ 140 mm Hg or diastolic blood pressure of ≥ 90 mm Hg or participants who reported a history of hypertension or had undergone antihypertensive therapy.²⁴

Blood samples were obtained from all participants in the morning following an overnight fast of at least 10 hours. The laboratory tests were conducted using a direct method with an automatic biochemical analyser (Model 7600, Hoffmann-La Roche, New Jersey, USA) and included the following parameters: fasting plasma glucose, glycosylated haemoglobin, aspartate aminotransferase, alanine aminotransferase, creatinine, total cholesterol, triglyceride and high-density lipoprotein cholesterol (HDL-C). Estimated glomerular filtration rate (eGFR) was calculated by the Modification of Diet in Renal Disease equation.²⁵ Participants without a history of diabetes mellitus were assessed for 2 hours postload glucose level after a 75 g oral glucose tolerance test. Diabetes mellitus was determined on the basis of the American Diabetes Association diagnostic criteria: (1) a positive history of diabetes or current use of anti-diabetic therapy, (2) fasting plasma glucose level of ≥ 126 mg/dL (7.0 mmol/L), (3) 2 hours postload glucose level of ≥ 200 mg/dL (11.1 mmol/L) and (4) glycosylated haemoglobin level of $\geq 6.5\%$.²⁶ Based on the revised National Cholesterol Education Program Adult Treatment Panel III criteria for Asian populations,²⁷ MS was diagnosed when participants presented any three of the following five risk factors: (1) central obesity; (2) systolic blood pressure of ≥ 130 mm Hg,

diastolic pressure of ≥ 85 mm Hg, or current medication for hypertension; (3) low HDL-C as HDL-C level of < 40 mg/dL (1.03 mmol/L) for men or < 50 mg/dL (1.29 mmol/L) for women; (4) fasting plasma glucose level of ≥ 100 mg/dL (5.6 mmol/L) or current use of antidiabetic therapy; and (5) hypertriglyceridaemia as triglyceride level of ≥ 150 mg/dL (1.69 mmol/L).

Determination of NAFLD

Abdominal ultrasound was performed for all participants after overnight fasting by an experienced radiologist using a 3.5 MHz linear transducer and high-resolution ultrasonography (Xario SSA-660A; Toshiba, Nasu, Japan). Subcostal and intercostal regions were scanned and images were captured with participants in the supine position. NAFLD was diagnosed as echo findings of hepatorenal echo contrast, bright liver, deep (posterior beam) attenuation and vascular blurring.²⁸ The degree of NAFLD was assessed by the following rule: (1) mild NAFLD: increased liver echogenicity, slightly hepatorenal contrast and relative conservation echo pattern of the walls of the portal veins; (2) moderate NAFLD: greater hepatorenal contrast, deep attenuation of echoes, loss of echoes from the walls of the portal veins and featureless appearance of the liver; and (3) severe NAFLD: obvious increased hepatorenal contrast, significantly deep attenuation of echoes and loss of most echoes from the walls of the portal veins, including the main branches.²⁸

Upper gastrointestinal endoscopy

As previously described in detail,¹⁹ LUCERA gastroscopes (LUCERA gastroscopes; GIF-XQ260, Olympus, Tokyo, Japan) were used for oesophagogastroduodenoscopic examination, which was performed by six experienced gastroenterologists who have 15–25 years of experience to perform this examination after overnight fasting. The endoscopic classification system, as grades A, B, C and D, for EO that was proposed by the World Congress of Gastroenterology in Los Angeles was used to determine EO.²⁹ The diagnosis of hiatal hernia was determined as diaphragmatic indentation located at > 2 cm distal to the Z-line (squamocolumnar junction) and the proximal margins of the gastric mucosal folds.³⁰

Statistical analyses

The SPSS software (V.17.0; SPSS, Chicago, Illinois, USA) was used for statistical analyses. The χ^2 and Student's t-tests were used for comparing categorical and continuous variables, where appropriate, between participants with and without EO. Multivariate logistic regression analyses were used to test whether NAFLD and MS were significant correlates of EO, and the covariates were age, hiatal hernia, eGFR, alcohol consumption, tea drinking, smoking and habitual exercise in the male group. Since no members of the female group consumed alcohol, the predictor variables were the same as those in the male group excluding alcohol consumption. Finally, we tried to examine the association between the NAFLD severity

(as non, mild, moderate and severe) and the grade of EO (as A, B, and C–D). Spearman's correlation was used for univariate analysis and ordinal regression for multivariate analysis. The adjusted OR, 95% CI and p value were estimated for each variable using logistic regression analysis. A p value of < 0.05 was defined as statistically significant.

RESULTS

On the basis of oesophagogastroduodenoscopic findings, the prevalence of EO was 20.1% ($n=1427/7110$) and 9.9% ($n=477/4842$) in males and females, respectively. The prevalences of grades A, B and C–D of EO were 16.7% ($n=1187/7110$) and 2.5% ($n=177/7110$) and 0.3% ($n=18/7110$) in males, respectively. Besides, the prevalences of grades A, B and C or D of EO were 8.6% ($n=414/4842$) and 0.6% ($n=27/4842$) and 0.02% ($n=1/4842$) in females, respectively. The prevalence of MS/NAFLD was 23.8/25.9% ($n=1694/7110$; $n=1839/7110$) and 17.2/28.0% ($n=833/4842$; $n=1357/4842$) in males and females, respectively. In addition, the prevalence of hiatal hernia was 3.6% ($n=257/7110$) and 1.5% ($n=75/4842$) in males and females, respectively. The prevalence of mild, moderate and severe NAFLD was 16.0% ($n=1137/7110$) and 9.7% ($n=687/7110$) and 1.8% ($n=129/7110$) in males, respectively. Besides, the prevalence of mild, moderate and severe NAFLD was 17.2% ($n=832/4842$) and 10.7% ($n=520/4842$) and 0.8% ($n=39/4842$) in males, respectively. Comparison of the clinical characteristics between participants with and without EO is shown in [table 1](#). In the male group, compared with participants without EO, those with EO were older and exhibited higher levels of BMI, WC, systolic blood pressure, 2 hours postload glucose, glycosylated haemoglobin, and triglyceride and a higher prevalence of general obesity, central obesity, hypertriglyceridaemia, low HDL-C, diabetes mellitus, MS, NAFLD, hiatal hernia, tea drinkers, smokers and habitual exercisers, but a lower level of HDL-C. In the female group, participants with EO had higher BMI and WC and a higher prevalence of general obesity, central obesity, MS, NAFLD and hiatal hernia than those without EO. No participants in the female group consumed 40–140 g of alcohol per week.

Results of multivariate logistic regression analysis of the relationship between EO and various risk factors for male participants are shown in [table 2](#). In model 1, MS was significantly associated with EO (OR 1.25; 95% CI 1.08 to 1.44) with an adjustment for age, hiatal hernia, eGFR, alcohol consumption, tea drinking, smoking and habitual exercise. Using model 2, NAFLD, substituted for MS in model 1, was not an independent risk factor for EO (OR 1.12; 95% CI 0.98 to 1.29). When considering MS and NAFLD simultaneously in model 3 with adjustment for the same variables in model 1, MS was positively correlated with EO (OR 1.26; 95% CI 1.09 to 1.45) but not NAFLD

Table 1 Comparisons of clinical variables between participants with and without EO by gender

Clinical variables	M (n=7110)			F (n=4842)		
	EO (n=1438)	non-EO (n=5739)	p Value	EO (n=484)	non-EO (n=4429)	p Value
Age (years)	49.5±11.9	48.4±13.0	0.002	49.4±13.0	49.0±13.1	0.452
BMI (kg/m ²)	25.6±3.3	24.9±3.2	<0.001	23.9±3.9	23.3±3.7	0.004
General obesity	398 (27.9)	1325 (23.3)	<0.001	91 (19.1)	637 (14.6)	0.009
Waist circumference (cm)	89.5±8.7	87.6±8.7	<0.001	78.3±9.7	77.0±9.3	0.005
Central obesity	660 (46.3)	2222 (39.1)	<0.001	182 (38.2)	1474 (33.8)	0.055
Systolic blood pressure (mm Hg)	123.2±16.6	122.0±15.9	0.014	115.2±19.4	113.7±17.9	0.100
Diastolic blood pressure (mm Hg)	73.8±10.5	73.8±10.1	0.858	66.2±10.5	65.8±10.1	0.347
Fasting plasma glucose (mmol/L)	5.41±1.63	5.36±1.49	0.264	5.18±1.50	5.16±1.30	0.726
2-hour postload glucose (mmol/L)	7.32±3.19	6.96±3.11	<0.001	6.86±2.74	6.72±2.77	0.315
Glycated haemoglobin (%)	5.92±1.14	5.81±1.01	0.002	5.78±0.95	5.74±0.91	0.350
Aspartate aminotransferase (IU/L)	27.2±17.7	26.7±14.0	0.232	23.2±10.1	23.1±11.0	0.895
Alanine aminotransferase (IU/L)	35.8±24.4	34.8±25.3	0.161	23.6±15.4	23.1±17.7	0.659
Creatinine (µmol/L)	88.8±51.6	88.8±40.0	1.000	64.5±23.0	63.6±17.7	0.345
eGFR (mL/min/1.73 m ²)	95.9±26.1	94.2±26.0	0.035	105.5±31.1	104.0±28.4	0.310
Total cholesterol (mmol/L)	5.15±0.95	5.14±0.97	0.893	5.13±0.99	5.14±0.99	0.858
Triglyceride (mmol/L)	1.82±1.23	1.72±1.22	0.003	1.28±0.91	1.24±0.78	0.303
HDL-C (mmol/L)	1.12±0.29	1.16±0.30	<0.001	1.42±0.38	1.43±0.36	0.558
Hypertriglyceridaemia (≥1.69 mmol/L)	631 (44.2)	2093 (36.8)	<0.001	97 (20.3)	792 (18.1)	0.241
Low HDL-C (F<1.29, M<1.03 mmol/L)	609 (42.7)	2027 (35.7)	<0.001	188 (39.4)	1648 (37.8)	0.497
Diabetes mellitus	251 (17.6)	838 (14.7)	0.008	69 (14.5)	546 (12.5)	0.223
Hypertension	320 (22.4)	1241 (21.8)	0.632	95 (19.9)	725 (16.6)	0.068
Metabolic syndrome	421 (29.5)	1273 (22.4)	<0.001	99 (20.8)	734 (16.8)	0.030
NAFLD	405 (28.4)	1434 (25.2)	0.015	173 (36.3)	1184 (27.1)	<0.001
Hiatal hernia	209 (14.6)	48 (0.8)	<0.001	65 (13.6)	10 (0.2)	<0.001
Alcohol consumption	11 (0.8)	37 (0.7)	0.621			
Tea drinking	555 (38.9)	2002 (35.2)	0.010	121 (25.4)	1187 (27.2)	0.394
Smoking	268 (18.8)	918 (16.2)	0.017	9 (1.9)	85 (1.9)	0.928
Habitual exercise	155 (10.9)	504 (8.9)	0.020	26 (5.5)	245 (5.6)	0.884

Data are shown as the mean±SD or number (%).

BMI, body mass index; eGFR, estimated glomerular filtration rate; EO, erosive oesophagitis; F, female; HDL-C, high-density lipoprotein cholesterol; M, male; NAFLD, non-alcoholic fatty liver disease.

Table 2 Association of clinical variables with the risk of erosive oesophagitis in males*

Clinical variables	Model 1		Model 2		Model 3	
	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Age (years)	1.02 (1.01 to 1.02)	<0.001	1.02 (1.01 to 1.02)	<0.001	1.02 (1.01 to 1.02)	<0.001
Metabolic syndrome (yes vs no)	1.25 (1.08 to 1.44)	0.002			1.26 (1.09 to 1.45)	0.002
NAFLD (yes vs no)			1.12 (0.98 to 1.29)	0.101	1.14 (0.98 to 1.30)	0.095
Hiatal hernia (yes vs no)	19.88 (14.42 to 27.41)	<0.001	20.03 (14.53 to 27.61)	<0.001	19.75 (14.33 to 27.23)	<0.001
eGFR (mL/min/1.73 m ²)	1.01 (1.00 to 1.01)	<0.001	1.01 (1.01 to 1.01)	<0.001	1.01 (1.00 to 1.01)	<0.001
Alcohol consumption (yes vs no)	0.93 (0.43 to 1.98)	0.841	0.87 (0.41 to 1.87)	0.734	0.91 (0.42 to 1.94)	0.800
Tea drinking (yes vs no)	1.08 (0.94 to 1.23)	0.285	1.07 (0.93 to 1.22)	0.344	1.06 (0.93 to 1.22)	0.364
Smoking (yes vs no)	1.15 (0.97 to 1.35)	0.110	1.16 (0.98 to 1.37)	0.078	1.14 (0.96 to 1.35)	0.129
Habitual exercise (yes vs no)	1.26 (1.03 to 1.54)	0.027	1.23 (1.01 to 1.51)	0.043	1.25 (1.02 to 1.53)	0.034

Adjusted OR.

*Binary logistic regression analysis.

eGFR, estimated glomerular filtration rate; NAFLD, non-alcoholic fatty liver disease.

(OR 1.14; 95% CI 0.98 to 1.30). In addition, other important factors, including age, hiatal hernia, eGFR and habitual exercise, were also demonstrated to be associated with EO.

Results of multivariate logistic regression analysis of the association between EO and various risk factors for female participants are shown in [table 3](#). With adjustment for age, hiatal hernia, eGFR, tea drinking,

Table 3 Association of clinical variables with the risk of erosive oesophagitis in females*

Variables	Model 1		Model 2		Model 3	
	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Age (years)	1.00 (0.99 to 1.01)	0.652	1.00 (0.99 to 1.01)	0.792	1.00 (0.99 to 1.01)	0.872
NAFLD (yes vs no)	1.49 (1.21 to 1.85)	<0.001			1.50 (1.21 to 1.86)	<0.001
Metabolic syndrome (yes vs no)			1.22 (0.92 to 1.61)	0.161	1.24 (0.94 to 1.63)	0.128
Hiatal hernia (yes vs no)	65.74 (33.43 to 129.30)	<0.001	67.64 (34.43 to 132.88)	<0.001	65.08 (33.09 to 128.00)	<0.001
eGFR (mL/min/1.73 m ²)	1.00 (1.00 to 1.01)	0.248	1.00 (1.00 to 1.01)	0.645	1.00 (1.00 to 1.01)	0.400
Tea drinking (yes vs no)	0.91 (0.72 to 1.16)	0.441	0.92 (0.73 to 1.17)	0.496	0.91 (0.72 to 1.15)	0.423
Smoking (yes vs no)	1.13 (0.56 to 2.29)	0.734	1.15 (0.67 to 2.33)	0.697	1.12 (0.55 to 2.27)	0.756
Habitual exercise (yes vs no)	0.93 (0.59 to 1.46)	0.746	0.96 (0.61 to 1.51)	0.864	0.93 (0.59 to 1.46)	0.761

Adjusted OR.

*Binary logistic regression analysis.

eGFR, estimated glomerular filtration rate; NAFLD, non-alcoholic fatty liver disease.

smoking and habitual exercise, NAFLD was positively related to EO in model 1 (OR 1.49; 95% CI 1.21 to 1.85). Using model 2, MS did not correlate with EO (OR 1.22; 95% CI 0.92 to 1.61). When considering MS and NAFLD simultaneously in model 3, NAFLD (OR 1.50; 95% CI 1.21 to 1.86) but not MS (OR 1.24; 95% CI 0.94 to 1.63) was still associated with an increased risk of EO in the female group. Hiatal hernia was an additional important risk factor for EO. We divided females into premenopausal (n=2472, 51.1%) and postmenopausal (n=2370, 48.9%) groups. In premenopausal females, NAFLD (OR 1.93; 95% CI 1.43 to 2.59) but not MS (OR 1.20; 95% CI 0.69 to 2.08) positively correlated with EO. In contrast, neither NAFLD (OR 1.15; 95% CI 0.84 to 1.57) nor MS (OR 1.25; 95% CI 0.91 to 1.73) was an independently associated factor for EO in postmenopausal females (data not shown in the table).

Finally, we examined the association between NAFLD severity and EO severity in either gender. In univariate analysis, there was a slight positive correlation between the severity of NAFLD and the grade of EO (males: Spearman's correlation coefficient=0.028, p=0.020; females: Spearman's correlation coefficient=0.038, p=0.008). In multivariate analysis, based on ordinal regression, MS was positively associated with the grade of EO (OR=1.201, 95% CI 1.039 to 1.387, p=0.013), but the severity of NAFLD was not. In females, although mild NAFLD was related to the grade of EO (OR=1.385, 95% CI 1.069 to 1.793, p=0.013), MS, moderate and severe NAFLD were not (data not shown).

DISCUSSION

Our results indicate significant gender differences in the effects of NAFLD and MS on EO. Subgroup analysis with respect to gender demonstrated that MS is significantly associated with EO in males but not in females,

and NAFLD correlates positively with EO in females but not in males when considering NAFLD and MS simultaneously. Based on the findings from the association between NAFLD severity and EO severity, male participants with MS still exhibited a higher risk for the grade of EO, although different severity of NAFLD was not. In females, mild NAFLD was related to the grade of EO, but MS, moderate and severe NAFLD were not. The discrepancy for the effect of different NAFLD severity on the grade of EO in females can be explained by the small number of participants with grade B–D of EO or severe NAFLD resulting in an unreliable model for the association between NAFLD severity and EO severity. To the best of our knowledge, this is the first study to reveal significant gender differences in the association of NAFLD and MS with EO.

MS is known to be independently associated with EO via the effects of increased serum cytokines and the volume of visceral fat.^{6, 10} Elevated serum cytokine levels, such as interleukin 6 (IL-6) and tumour necrosis factor- α , can alter neurogenic oesophageal muscle contraction following impaired acid clearance and augmented reflux episodes.³¹ In addition, an increased volume of visceral fat positively correlates with elevated serum cytokine levels⁶ and increased mechanical gastric pressure, causing frequent relaxation of the lower oesophageal sphincter with acid reflux.³² NAFLD, known to be associated with obesity and insulin resistance as MS,³³ was demonstrated to independently correlate with EO in this study, possibly through the effects of increased serum cytokine levels, visceral fat volume and systemic oxidative stress with a diminished antioxidant capacity.^{9, 34, 35} Increased oxidative stress may lead to damage of the adherent mucus layer and oesophageal mucosa,³⁶ while decreased antioxidant capacity can decrease the ability to prevent oesophageal mucosal damage and accentuate the severity of EO.³⁶

Several factors could explain why MS is a significant risk factor for EO in males but not in females. First, the patterns of fat distribution differ between males and females. Females more often develop subcutaneous adiposity, whereas males are more prone to visceral fat deposition.³⁷ Among participants with MS, males have more visceral fat than subcutaneous fat, while the reverse was observed in females.^{16–17} Compared with females, males might suffer more detrimental effects of increased visceral fat volume on EO through elevated serum cytokine levels and mechanically raised gastric pressure.^{6–32} Moreover, greater visceral adiposity, which is observed more often in males than in females, could result in an increase in serum cytokine secretion to cause EO.³⁸ These findings are consistent with a recent study reporting that serum IL-6 and tumour necrosis factor- α levels were higher in males with MS than in females.³⁹ Thus, compared with females, males with MS have a higher visceral fat volume and more visceral adiposity, which may result in elevating serum cytokine levels, thereby causing EO. In contrast, the effect of MS on EO was not significant in females with MS, possibly because of a lower visceral fat volume and less visceral adiposity.

The observed gender differences in the relationship between NAFLD and EO may be associated with the effects of oestrogen, which plays a protective role against EO by decreasing serum proinflammatory cytokine levels⁴⁰ and oxidative stress.¹⁸ One study reported that NAFLD in females correlates with decreased serum oestrogen levels because of impaired mitochondrial and peroxisomal fatty acid β -oxidation and increased oxidative stress;¹⁸ hence, the protective effects of oestrogen on EO may be lower in females with NAFLD. Our study also demonstrated that the effect of NAFLD on EO was stronger in premenopausal females than in postmenopausal females. This observation also implied that the serum oestrogen level may play an important role on EO. Furthermore, oestrogen has been associated with less visceral fat volume and smaller visceral adiposity, resulting in lower serum proinflammatory cytokines levels and increased gastric pressure.^{6–32–38} This study found no significant increase in the prevalence of EO in females with MS, and this may be because of the effects of oestrogen on body fat distribution and adipocyte size.

This study has several limitations. First, previous studies demonstrated an association between *H. pylori* infection negativity and EO;⁴¹ however, data regarding such an infection were unavailable in this study. Second, data regarding the pattern of fat distribution, serum oestrogen and cytokine levels were also unavailable. Third, since our study participants were restricted to those undergoing self-paid health check-ups, there is a possibility of selection bias. Thus, these results may not apply to the general population. Fourth, the findings might not be generalisable to other ethnic groups because the participants were all Taiwanese. Finally, this study is cross-sectional and thus cannot provide evidence to

indicate a causal relationship between NAFLD/MS and EO with respect to gender.

CONCLUSIONS

Significant gender differences were observed in the effects of NAFLD and MS on EO. The effect of MS on EO severity might be greater than that of NAFLD in males, while the effect of NAFLD on EO severity was greater than that of MS in females. Further studies regarding gender differences in EO should focus on EO management and clarifying the relationship between serum oestrogen levels and EO.

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REFERENCES

- Goh KL. Gastroesophageal reflux disease in Asia: a historical perspective and present challenges. *J Gastroenterol Hepatol* 2011;26(Suppl 1):2–10.
- Ronkainen J, Talley NJ, Storskrubb T, *et al.* Erosive esophagitis is a risk factor for Barrett's esophagus: a community-based endoscopic follow-up study. *Am J Gastroenterol* 2011;106:1946–52.
- Parasa S, Sharma P. Complications of gastro-oesophageal reflux disease. *Best Pract Res Clin Gastroenterol* 2013;27:433–42.
- Gunji T, Sato H, Iijima K, *et al.* Risk factors for erosive esophagitis: a cross-sectional study of a large number of Japanese males. *J Gastroenterol* 2011;46:448–55.
- Ou JL, Tu CC, Hsu PI, *et al.* Prevalence and risk factors of erosive esophagitis in Taiwan. *J Chin Med Assoc* 2012;75:60–4.
- Chung SJ, Kim D, Park MJ, *et al.* Metabolic syndrome and visceral obesity as risk factors for reflux oesophagitis: a cross-sectional

- case-control study of 7078 Koreans undergoing health check-ups. *Gut* 2008;57:1360–5.
7. Park CH, Kim KO, Baek IH, *et al.* Differences in the risk factors of reflux esophagitis according to age in Korea. *Dis Esophagus* 2014;27:116–21.
 8. Wu P, Ma L, Dai GX, *et al.* The association of metabolic syndrome with reflux esophagitis: a case-control study. *Neurogastroenterol Motil* 2011;23:989–94.
 9. Jang S, Lee CH, Choi KM, *et al.* Correlation of fatty liver and abdominal fat distribution using a simple fat computed tomography protocol. *World J Gastroenterol* 2011;17:3335–41.
 10. Park JH, Park DI, Kim HJ, *et al.* Metabolic syndrome is associated with erosive esophagitis. *World J Gastroenterol* 2008;14:5442–7.
 11. Völzke H. Multicausality in fatty liver disease: is there a rationale to distinguish between alcoholic and non-alcoholic origin? *World J Gastroenterol* 2012;18:3492–501.
 12. Altıparmak E, Koklu S, Yalınkilic M, *et al.* Viral and host causes of fatty liver in chronic hepatitis B. *World J Gastroenterol* 2005;11:3056–9.
 13. Nascimento AC, Maia DR, Neto SM, *et al.* Nonalcoholic fatty liver disease in chronic hepatitis B and C patients from Western Amazon. *Int J Hepatol* 2012;2012:695950.
 14. Hsu CS, Wang CC, Wang PC, *et al.* Increased incidence of gastroesophageal reflux disease in patients with chronic hepatitis B virus infection. *Hepatology* 2010;4:585–93.
 15. Neuschwander-Tetri BA, Caldwell SH. Nonalcoholic steatohepatitis: summary of an AASLD Single Topic Conference. *Hepatology* 2003;37:1202–19.
 16. Sogabe M, Okahisa T, Kimura Y, *et al.* Visceral fat predominance is associated with erosive esophagitis in Japanese men with metabolic syndrome. *Eur J Gastroenterol Hepatol* 2012;24:910–16.
 17. Sogabe M, Okahisa T, Tsujigami K, *et al.* Visceral fat predominance is associated with non-alcoholic fatty liver disease in Japanese women with metabolic syndrome. *Hepatology* 2014;44:515–22.
 18. Gutierrez-Grobe Y, Ponciano-Rodriguez G, Ramos MH, *et al.* Prevalence of non alcoholic fatty liver disease in premenopausal, postmenopausal and polycystic ovary syndrome women. The role of estrogens. *Ann Hepatol* 2010;9:402–9.
 19. Hung WC, Wu JS, Yang YC, *et al.* Nonalcoholic fatty liver disease vs. obesity on the risk of erosive oesophagitis. *Eur J Clin Invest* 2014;44:1143–9.
 20. Husten CG. How should we define light or intermittent smoking? *Nicotine Tob Res* 2009;11:111–21.
 21. WHO. *Report of a WHO Consultation on Obesity: Prevention and Managing, the Global Epidemic.* Geneva: World Health Organization, 1999.
 22. Pan WH, Lee MS, Chuang SY, *et al.* Obesity pandemic, correlated factors and guidelines to define, screen and manage obesity in Taiwan. *Obes Rev* 2008;9(Suppl 1):22–31.
 23. WHO. *International Association for the Study of Obesity, International Obesity Task Force: the Asia-Pacific Perspective: redefining obesity and its treatment.* Sydney: Health Communications, 2000.
 24. Lenfant C, Chobanian AV, Jones DW, *et al.*, Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7): resetting the hypertension sails. *Hypertension* 2003;41:1178–9.
 25. Levey AS, Bosch JP, Lewis JB, *et al.* A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999;130:461–70.
 26. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2011;34(Suppl 1):S62–9.
 27. Grundy SM, Cleeman JI, Daniels SR, *et al.* Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005;112:2735–52.
 28. Saverymuttu SH, Joseph AE, Maxwell JD. Ultrasound scanning in the detection of hepatic fibrosis and steatosis. *BMJ* 1986;292:13–15.
 29. Armstrong D, Bennett JR, Blum AL, *et al.* The endoscopic assessment of esophagitis: a progress report on observer agreement. *Gastroenterology* 1996;111:85–92.
 30. Johnson DA, Younes Z, Hogan WJ. Endoscopic assessment of hiatal hernia repair. *Gastrointest Endosc* 2000;52:650–9.
 31. Rieder F, Biancani P, Harnett K, *et al.* Inflammatory mediators in gastroesophageal reflux disease: impact on esophageal motility, fibrosis, and carcinogenesis. *Am J Physiol Gastrointest Liver Physiol* 2010;298:G571–81.
 32. Wu JC, Mui LM, Cheung CM, *et al.* Obesity is associated with increased transient lower esophageal sphincter relaxation. *Gastroenterology* 2007;132:883–9.
 33. McCullough AJ. Pathophysiology of nonalcoholic steatohepatitis. *J Clin Gastroenterol* 2006;40(Suppl 1):S17–29.
 34. Wiecekowska A, Papouchado BG, Li Z, *et al.* Increased hepatic and circulating interleukin-6 levels in human nonalcoholic steatohepatitis. *Am J Gastroenterol* 2008;103:1372–9.
 35. Kumar R, Prakash S, Chhabra S, *et al.* Association of pro-inflammatory cytokines, adipokines & oxidative stress with insulin resistance & non-alcoholic fatty liver disease. *Indian J Med Res* 2012;136:229–36.
 36. Oh TY, Lee JS, Ahn BO, *et al.* Oxidative stress is more important than acid in the pathogenesis of reflux oesophagitis in rats. *Gut* 2001;49:364–71.
 37. Williams CM. Lipid metabolism in women. *Proc Nutr Soc* 2004;63:153–60.
 38. Pradhan AD. Sex differences in the metabolic syndrome: implications for cardiovascular health in women. *Clin Chem* 2014;60:44–52.
 39. Bălăşoiu M, Bălăşoiu AT, Stepan AE, *et al.* Proatherogenic adipocytokines levels in metabolic syndrome. *Rom J Morphol Embryol* 2014;55:29–33.
 40. Tani A, Yasui T, Matsui S, *et al.* Circulating levels of monocyte chemoattractant protein-1 and interleukin-7 in women who have undergone bilateral salpingo-oophorectomy. *J Inflamm Res* 2013;7:1–7.
 41. Koike T, Ohara S, Sekine H, *et al.* Helicobacter pylori infection prevents erosive reflux oesophagitis by decreasing gastric acid secretion. *Gut* 2001;49:330–4.