ASSOCIATION BETWEEN MEOPAUSE, POSTMENOPAUSE HORMONAL THERAPY, AND PEPTIC ULCER IN TAIWANESE POPULATION

ATHORS:

Kuan-Chih Chen; Chia-Yu Kuo; Wan-Ling Tsai; Yin_jhen Wu, Jiun-Hung Geng; Chao-Hung Kuo, Szu-Chia Chen Hospital municipal Siaogang de Kaohsiung, Universidad Médica de Kaohsiung

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ABSTRACT

Menopause is associated with various health conditions such as osteoporosis, obesity, cardiovascular and psychological disorders. However, limited information is available on the relationship between perimenopause and hormone replacement therapy with the occurrence of digestive ulcers. Therefore, we conducted this population-based study of over 17,000 participants in the Taiwan Biobank to examine the association between menopause and peptic ulcer disease (PUD). In addition, we also examined associations between the types of menopause and postmenopausal hormone therapy with PUD. Menopausal status, hormone replacement therapy during menopause, and the presence of PUD were determined using self-reported questionnaires. The participants were grouped according to whether or not they had entered menopause. The participants were further categorized based on the cause of menopause: natural or surgical. Binary logistic regression was utilized for correlation analysis. Of the 17,460 individuals enrolled for analysis, 9620 (55%) were classi ed into the postmenopausal group and 7840 (45%) into the premenopausal group. After adjusting for various factors, the postmenopausal group had a 1.19 times higher risk of developing PUD compared to the premenopausal group (odds ratio [OR]: 1.19, 95% con dence interval [CI]: 1.03 to 1.38, p = 0.022). Moreover, surgical menopause was signi cantly associated with PUD (OR, 1.38; 95% CI, 1.16 to 1.63; p < 0.001), but natural menopause was not (OR, 1.128; 95% CI, 0.96 to 1.30; p = 0.153). In addition, the women with natural menopause who received postmenopausal hormone therapy had a signi cantly higher prevalence of PUD than those who did not (OR, 1.37; 95% CI, 1.11 to 1.70; p = 0.004). However, no signi cant association was found between postmenopausal hormone therapy and PUD among the women with surgical menopause (p = 0.622). Menopause was signi cantly associated with PUD. Furthermore, surgical menopause (vs. premenopause) was associated with a 1.38 times higher risk of PUD, and postmenopausal hormone therapy in women with natural menopause was associated with a 1.37 times higher risk of PUD. Further research is warranted to identify the mechanisms and potential interventions to reduce susceptibility to digestive ulcers in menopausal women.

INTRODUCTION

Peptic ulcers are a common clinical presentation associated with high medical costs (1), and peptic ulcer disease (PUD) continues to be a source of signi cant morbidity and mortality worldwide. Although approximately two-thirds of patients found to have PUD are asymptomatic (2), peptic ulcers can still cause early satiety, abdominal fullness, dyspepsia, bloating and nausea (2-4). They most commonly develop in the stomach and proximal duodenum (5), and the predominant causes in the US have traditionally been Helicobacter pylori (H. pylori) infection and nonsteroidal anti-in ammatory drug (NSAID) treatment (6). However, with the increasing use of anti-secretory drugs and decreasing prevalence of H. pylori infection in recent decades, NSAID treatment and H. pylori have gradually become less prominent causes of PUD (7,8). This trend has also been seen in Taiwan, where a prior history of PUD, low education level, high body mass index (BMI), and currently smoking have been shown to be independent risk factors for asymptomatic PUD (9).

Menopause is a normal part of aging, and accounts for the last third of a woman's lifetime after their reproductive years (10). Perimenopause is associated with many symptoms, including hot ashes, night sweats, mental illness, and neurological transition (11-13). After menopause, genitourinary symptoms including vulvovaginal atrophy and dryness predominate, along with lower urinary tract symptoms such as urinary

frequency, urgency, and nocturia, all of which can negatively affect the quality of life (14-18). Hormone treatment can address these issues, however the effects of such treatment on cardiovascular disease, cognitive dysfunction, and depression are still uncertain (19).

Recent research has focused on H. pylori eradication, proton pump inhibitor use and judicious use of NSAIDs to reduce the incidence of PUD (8,20). However, several studies suggested a correlation between sex hormones and PUD (21,22). The rst of these studies demonstrated that major male (testosterone) and female (progesterone) sex hormones had opposite effects on preexisting ulcer healing in the oral cavity and stomach (22). The second study showed that that pregnancy itself could relieve the symptoms of ulcers (21). Some research has shown that female sex has a protective effect against duodenal ulcers, and many studies have suggested that male sex may be an independent risk factor for PUD (23-25). A study conducted several decades previously reported that menstruation did not have a considerable effect on ulcer symptoms (21). These ndings may suggest that sex is not associated with peptic ulcers, however more recent research has shown a correlation between menopause and PUD. A retrospective Chinese study published in 2016 reported that late menopause may have a protective effect against chronic

PUD (26). However, little research has investigated the association between menopause status and the prevalence of PUD, and the effect of postmenopausal hormone therapy on PUD is also unclear.

Therefore, we conducted this population-based study of over 17,000 participants in the Taiwan Biobank (TWB) to examine the association between menopause and PUD. In addition, we also examined associations between the types of menopause and postmenopausal hormone therapy with PUD.

MATERIALS AND METHODS

Ethics statement

The TWB (https://www.twbiobank.org.tw) was approved by the Institutional Review Board of Biomedical Science Research at Academia Sinica and the Ethics and Governance Council of Taiwan Biobank. The current study received approval from the Research Ethics Committee of Kaohsiung Medical University Hospital (KMUHIRB-E(I)-20210058).

Study population

We obtained data from the TWB on women enrolled between 2012 and 2018. All participants in the TWB are aged 30 to 70 years without a prior cancer history, and they are all required to sign informed consent forms before data are collected through self-reported questionnaires, physical and laboratory examinations (27). Subsequently, we excluded women without data on menopausal status and obstetric history. Finally, we analyzed data from 17,460 women and divided them into premenopausal and postmenopausal groups (Figure 1).

The following data were collected at baseline: uid intake, age, BMI (kg/m2), educational status, whether the participants were current/never smokers, and whether or not they drank alcohol, lived alone, participated in regular physical activity, and were married. Data on gravidity, parity, breastfeeding, hormone therapy, etiology of menopause and whether or not they undergone an induced abortion were also recorded, along with the presence of hypertension, dyslipidemia, diabetes mellitus, gout, and chronic kidney disease (CKD). Systolic blood pressure and diastolic blood pressure measurements were also recorded. CKD was de ned as an estimated glomerular ltration rate < 60 mL/min/1.73 m2 (using the 4-variable MDRD equation 28).

Premenopausal, postmenopausal, type of menopause, postmenopausal hormone therapy, and PUD assessments

We obtained information on the presence of PUD (yes/no), premenopausal/postmenopausal status (yes/no), the type of menopause (natural/surgical/others), and postmenopausal hormone therapy (never used/ever used) based on the participants' responses on questionnaires. Postmenopausal women were de ned as those who reported no periods for more than 1 year.

Statistical Analysis

We divided the participants into two groups, premenopausal women and menopausal women. Categorical variables are shown as number and percentage, while continuous variables are shown as mean and standard deviation. The chi-square test was used to compare categorical variables between two groups, and an independent t-test was used to compare continuous variables between two groups. Association

analysis was conducted using binary logistic regression, and the results are expressed as odd ratio (OR) and 95% con dence interval (95% CI). A p value < 0.05 was considered signi cant. We used R (v3.6.2, R Foundation for Statistical Computing, Vienna, Austria) and SPSS (v20.0, IBM Inc., Armonk, NY) as the statistical tools.

RESULTS

Clinical characteristics of the study participants

Of the 17,460 included women, 7840 (44.9%) were premenopausal and 9620 (55.1%) were postmenopausal. Table 1 presents the clinical characteristics of the study participants. The postmenopausal women tended to be older and have higher rates of CKD, arrhythmia, hyperlipidemia, hypertension, diabetes, depression, Parkinson's disease, dependency, smoking, pregnancy, births, abortion, being married, and physical activity, and lower educational status than the premenopausal women. In addition, compared to the premenopausal women, the postmenopausal women had higher BMI, higher systolic and diastolic blood pressures, lower white blood cell count, lower platelet count, and higher levels of hemoglobin, fasting glucose, triglycerides, total cholesterol, low-density lipoprotein cholesterol, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase, blood urea nitrogen (BUN) and creatinine.

Association between menopause status and PUD

The postmenopausal women had a higher prevalence of PUD (16.8%) than the premenopausal women (11.5%), with an unadjusted OR of 1.55 (95% CI, 1.42 to 1.69, p < 0.001) (Table 2). After adjusting for age, postmenopausal status was still associated with PUD (OR, 1.23; 95% CI, 1.07 to 1.42; p = 0.004). Further, after multivariable adjustments for arrhythmia, hyperlipidemia, hypertension, depression, manic depression, Parkinson's disease, age, dependency, smoking status, physical activity, pregnancy, births, abortion, systolic and diastolic pressures, white blood cell count, platelet count, hemoglobin level, SGOT, BUN, ever being married, educational status, BMI, CKD and menstruation status, postmenopausal status was still signi cantly associated with PUD (OR, 1.19; 95% CI, 1.03 to 1.38; p = 0.022).

Association between the types of menopause and PUD

Both natural menopause (OR, 1.16; 95% CI 1.00 to 1.35; p = 0.049) and surgical menopause (OR, 1.42; 95% CI, 1.20 to 1.68; p < 0.001) were signi cantly associated with an increased prevalence of PUD in the age-adjusted model (Table 3). After further adjustments for multivariable analysis, we found that surgical menopause was signi cantly associated with PUD (OR, 1.38; 95% CI, 1.16 to 1.63; p < 0.001), but natural menopause was not (OR, 1.128; 95% CI, 0.96 to 1.30; p = 0.153).

Association between postmenopausal hormone therapy and PUD in the postmenopausal women

We further explored the association between postmenopausal hormone therapy and the prevalence of PUD in the women with menopause (Table 4). The results showed that the women with natural menopause who received postmenopausal hormone therapy had a signi cantly higher prevalence of PUD than those who did not receive postmenopausal hormone therapy (age-adjusted OR, 1.49; 95% CI, 1.21 to 1.83; p < 0.001, and multivariable OR, 1.37; 95% CI, 1.11 to 1.70; p = 0.004). However, no signi cant association was found between postmenopausal hormone therapy and PUD among the women with surgical menopause (age-adjusted OR, 1.18; 95% CI, 0.82 to 1.71; p = 0.369, and multivariable OR, 1.10; 95% CI, 0.75 to 1.61; p = 0.622).

TABLE 1. CLINICAL CHARACTERISTICS OF THE STUDY PARTICIPANTS

Characteristics	Premenopausal (n = 7840)	Postmenopausal (n = 9620)	p value
Age, yr	42,16 ± 6,78	58,27 ± 5,49	< 0,001
History of chronic kidney disease, n (%)	16 (0,2)	150 (1,6)	< 0,001
History of chronic kidney disease, n (%)	235 (3.0)	592 (6.2)	< 0,001
History of hyperlipidemia, n (%)	167 (2.1)	978 (10.1)	< 0,001
History of hypertension, n (%)	288 (3.7)	1553 (16.1)	< 0,001
Historial de diabetes, n (%)	107 (1.4)	647 (6,7)	< 0,001
History of depression, n (%)	270 (3,4)	405 (4.2)	0,009
History of manic depression, n (%)	40 (0,5)	59 (0,6)	0,417
History of dependency, n (%)	474 (6.0)	851 (8,8)	< 0,001
History of smoke experience, n (%)	776 (9,9)	438 (4,6)	< 0,001
History of pregnancy, n (%)	6561 (83,7)	9081 (94,4)	< 0,001
History of birth, n (%)	6324 (80,7)	8972 (93,3)	< 0,001
History of abortion, n (%)	3978 (50,7)	5966 (62,0)	< 0,001
History of getting married, n (%)	6561 (83,7)	9225 (95,9)	< 0,001
Education, n (%)			< 0,001
≤ Elementary	115 (1,5)	1465 (15.2)	
Middle to High school	3271 (41,7)	5288 (55,0)	
≥ Collage	4454 (56,8)	2867 (29,8)	
Sport habit, yes, n (%)	2239 (28,6)	5632 (58,6)	< 0,001
BMI, kg/m2	23,24 ± 3,74	23,79 ± 3,45	< 0,001
Systolic blood pressure, mm Hg	108,75 ± 15,51	121,21 ± 18,49	< 0,001
Diastolic blood pressure, mm Hg	68,15 ± 10,37	72,06 ± 10,40	< 0,001
White blood cell, 103/uL	6,04 ± 1,64	5,67 ± 1,46	< 0,001
Platelet, 103/uL	266,80 ± 61,56	236,77 ± 54,20	< 0,001

Hemoglobin, g/dL	12,68 ± 1,42	13,31 ± 1,0	< 0,001
Fasting glucose, mg/dL	90,47 ± 15,54	97,31 ± 20,14	< 0,001
Total cholesterol, mg/dL	186,02 ± 32,75	207,07 ± 35,29	< 0,001
Triglyceride, mg/dL	89,54 ± 61,05	114,47 ± 73,95	< 0,001
HDL-cholesterol, mg/dL	57,70 ± 12,80	57,73 ± 13,25	0,909
LDL-cholesterol, mg/dL	113,68 ± 29,57	127,75 ± 32,09	< 0,001
SGOT, IU/L	21,16 ± 10,23	25,86 ± 11,61	< 0,001
SGPT, IU/L	18,56 ± 17,50	23,08 ± 16,61	< 0,001
BUN, mg/dL	11.38 ± 2.97	13.89 ± 3.63	< 0,001
History of Parkinson, n (%)	1 (0.0)	12 (0.1)	0.009

BMI = Body mass index; HDL = High-Density Lipoprotein; LDL = Low-Density Lipoprotein; BUN = Blood Urea Nitrogen; SGOT = Serum Glutamic Oxaloacetic Transaminase; SGPT = Serum Glutamic Pyruvic Transaminase

TABLE 2. ODDS RATIOS FOR SELF-REPORTED PEPTIC ULCER DISEASE BY MENOPAUSAL STATUS

	Premenopausal (n = 7840)	Postmenopausal (n = 9620)	p value
Presence of peptic ulcer disease, n (%)	905 (11,5)	1616 (16.8)	
Unadjusted OR (95% CI)	1.0 (reference)	1,55 (1,42-1,69)	< 0,001
Age-adjusted OR (95% CI)	1.0 (reference)	1,23 (1,07-1,42)	0,004
Multivariable OR (95% CI)	1.0 (reference)	1,19 (1,03-1,38)	0,022

OR = odds ratio; CI = Con dence interval.

Multivariable analysis adjusts for arrhythmia, hyperlipidemia, hypertension, depression, manic depression, Parkinson, age, dependency, smoking experience, sport habit, pregnancy, birth, abortion, systolic and diastolic pressure, white blood cell count, platelet count, hemoglobin level, SGOT, BUN, ever married, educational status, BMI, chronic kidney disease and menstruation.

TABLE 3. ODDS RATIOS FOR SELF-REPORTED PEPTIC ULCER DISEASE BY THE TYPE OF MENOPAUSE

Type of menopause	Presence of peptic ulcer disease, n (%)	Age-adjusted OR (95% CI)	p value	Multivariable OR (95% CI)	p value
Premenopause	905 (11,5)	1.0 (reference)	-	1.0 (reference)	-
Natural menopause	1269 (16.3)	1,16 (1,00-1,35)	0,049	1,12 (0,96-1,30)	0,153
Surgical menopause	347 (18,7)	1,42 (1,20-1,68)	< 0,001	1,38 (1,16-1,63)	< 0,001

OR = odds ratio; CI = Con dence interval.
Multivariable analysis adjusts for arrhythmia, hyperlipidemia, hypertension, depression, manic depression, Parkinson, age, dependency, smoking experience, sport habit, pregnancy, birth, abortion, systolic and diastolic pressure, white blood cell count, platelet count, hemoglobin level, SGOT, BUN, ever married, educational status, BMI, chronic kidney disease and menstruation.

TABLE 4. AGE, AND MULTIVARIABLE-ADJUSTED ODDS RATIOS FOR SELF-REPORTED PEPTIC ULCER DISEASE BY POSTMENOPAUSAL HORMONE USE IN WOMEN WITH MENOPAUSE

Postmenopausal hormone use	Age-adjusted OR (95% CI)	p value	Multivariable OR (95% CI)	p value
Women with natural menopause	905 (11,5)			
Never-users	1.00 (reference)		1.00 (reference)	
Ever-users	1,49 (1,21-1,83)	< 0,001	1,37 (1,11-1,70)	0,004
Women with surgical menopause				
Never-users	1.00 (reference)		1.00 (reference)	
Ever-users	1,18 (0,82-1,71)	0,369	1,10 (0,75-1,61)	0,622

OR = odds ratio; CI = Confidence interval.
Multivariable analysis adjusts for arrhythmia, hyperlipidemia, hypertension, depression, manic depression, Parkinson, age, dependency, smoking experience, sport habit, pregnancy, birth, abortion, systolic and diastolic pressure, white blood cell count, platelet count, hemoglobin level, SGOT, BUN, ever married, educational status, BMI, chronic kidney disease and menstruation.

DISCUSION

In this study, we demonstrated that postmenopausal women were signi cantly associated with PUD compared to premenopausal women, particularly those who underwent surgical menopause. In addition, we found that in women with natural menopause, postmenopausal hormone therapy was associated with an increased rate of PUD.

Our nding that menopause was associated with PUD suggests that the relationship between menopause and PUD is multifaceted, involving hormonal uctuations, changes in immune response, and potentially even alterations in gastrointestinal function (29). Postmenopausal women are generally thought to be more prone to developing peptic ulcers, possibly due to

the dramatic changes in hormone levels during this stage of life (26). For example, Kim hypothesized that the female sex hormone estrogen increases the expression of tight junction proteins, sealing the gap between cells, reducing mucosal permeability, and stimulating the excretion of bicarbonate ions in the duodenal mucosa 30. These mechanisms are thought to enhance mucosal defense against acidic environments in the stomach and duodenum, thus preventing ulcer formation. In the absence of estrogen, particularly post-menopause, this protective mechanism may be weakened, leading to increased susceptibility to ulcers. In addition, older females have been shown to be at higher risk of mucosal injury, possibly as a consequence of menopause-induced hormonal alterations, including decreased levels of both estrogen and progesterone
(31,32). This is particularly relevant because aging is a known risk factor for gastrointestinal conditions, and menopause can exacerbate this risk due to the signi cant hormonal shifts that occur.

Immunosenescence, de ned as gradual weakening of the immune system with age, has also been implicated in this increased susceptibility (33,34). Several studies have shown that the major effects of estradiol are mediated through two receptors, namely alpha and beta estrogen receptors, both of which are expressed on a variety of cell types including immune cells, epithelial cells and muscle cells (33,35,36). These receptors help regulate immune responses, and the decline in estrogen during menopause may impair their function, leading to reduced immune defense against gastrointestinal pathogens and increased mucosal vulnerability (37,38). Moreover, estrogen has been shown to regulate many facets of the immune response such as immune cell differentiation, cytokine production, regulation of calcium ion mobilization and release of inducible nitric oxide synthase in leukocytes (39,40). These immunomodulatory effects of estrogen are thought to help protect against mucosal damage in the gastrointestinal tract, and their loss may contribute to the higher rates of PUD observed in postmenopausal women. Furthermore, previous studies have also shown that patients with persistent symptoms of ulcers often have a high rate of gastrointestinal abnormalities, such as hyperemesis and ulcer recurrence after parturition, particularly within the rst 6 months 10. This nding is intriguing because it suggests a connection between reproductive hormone levels and gastrointestinal health, supporting the hypothesis that hormonal uctuations, particularly those involving estrogen and progesterone, may play a signi cant role in ulcer pathogenesis and healing. In addition, Grossman reported that 88.2% of cases were associated with remission of ulcer symptoms during pregnancy, suggesting that hormonal changes

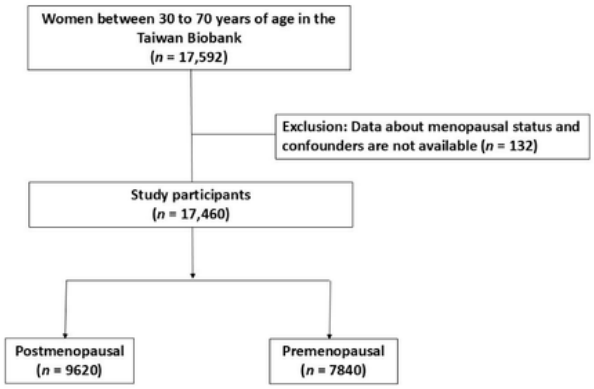

Figure 1

Flowchart of study population

may in uence PUD risk and recurrence (8,32).

These ndings support the hypothesis that hormones, particularly estrogen and progesterone, play a role in ulcer pathogenesis and healing.

Another interesting nding of this study is that the women who underwent surgical menopause were 1.38 times more likely to develop PUD compared to premenopausal women. Pillay and Manyonda reported that surgical menopause (iatrogenic menopause) occurs when both ovaries are removed before ovarian function is naturally "switched off", and that this could cause premature ovarian insu ciency leading to menopause in women before the age of 40 (41). This can then lead to a sudden and dramatic reduction in ovarian sex steroid production, particularly estrogen and progesterone (42). Natural menopause begins 4 to 6 years before the cessation of menses, and middle-aged women experience a progressive change in ovarian activity and a physiologic deterioration of hypothalamic-pituitary-ovarian axis function associated with uctuating hormone levels 43. This indicates that the abrupt loss of ovarian hormones due to surgical menopause can have wide-ranging effects on various physiological systems, including the gastrointestinal system. For example, surgical menopause has been associated with more severe and prolonged menopausal symptoms, including hot ashes, mood change, and sleep disturbance, which may

contribute to overall physiological stress and potentially in uence gastrointestinal function (44). This may further in uence other systems such as cardiovascular, neurologic, bone, and connective tissue, and affect the quality of life due to vasomotor symptoms, mood, sleep, and sexual function (45,46). The gastrointestinal system is known to be highly responsive to stress, and chronic stress has been linked to increased gastric acid secretion, reduced mucosal blood ow, and impaired mucosal healing, all of which can contribute to the development of peptic ulcers. Some studies have demonstrated surgical menopause-induced physiological and behavioral changes in relation to estradiollinked compositional changes in the intestinal microbiota (29,47-49). However, the exact mechanisms by which estrogen de ciency and hormone therapy affect the gut microbial community are not yet well understood (47). To date, no strong direct evidence has linked surgical menopause speci cally to PUD.

In this study, we also found that postmenopausal hormone therapy in the women with natural menopause was associated with an increased rate of PUD. Previous studies have reported associations between postmenopausal hormone therapy and increased rates of gastroesophageal re ux disease and PUD (31,50). In addition, postmenopausal hormone therapy has also been associated with other gastrointestinal diseases such as esophageal cancer, gastric cancer, in ammatory bowel disease, irritable bowel syndrome and colon cancer (51-53). Close et al. reported that the relationship between hormone therapy and gastrointestinal conditions appears to be multifactorial (50), involving both direct effects of hormones on the gastrointestinal tract and their systemic effects on metabolism, immune function, and in ammatory responses. Coquoz et al. performed a comprehensive literature review, and found that progesterone had dose-dependent and sex-dependent effects on gastric emptying, and that it slowed gastrointestinal motility (54). This reduced motility can lead to delayed gastric emptying, which is known to contribute to symptoms of gastroesophageal re ux disease and may also increase the risk of peptic ulcer formation by prolonging exposure of the gastric mucosa to acidic contents. In addition to its effects on gastrointestinal motility, the effects of hormone replacement therapy can vary according to the regimen used, and complications associated with hormone replacement therapy may depend on the speci c hormones administered, their dosage, and the duration of therapy (10,19). For example, studies on different animal species and humans have suggested that sex hormones in uence gastric acid secretion and contribute to the integrity of the oral and gastroduodenal mucosa (32,54). Several studies investigated female rats with intact or removed ovaries (ovariectomy) (22,36), and gastric acid secretion was determined in rats with gastric ulcers equipped with chronic gastric stula. The results showed that treatment with progesterone signi cantly accelerated ulcer healing and increased gastric blood ow at the margins of these ulcers, emphasizing that sex hormones had opposite effects on healing of preexisting ulcers in the stomach (1,22). Our study showed that postmenopausal hormone therapy was associated with an increased rate of PUD, which is contrary to the expected protective effects of hormone replacement therapy (55,56), as many previous studies have suggested such therapy should mitigate gastrointestinal issues. The contradictory ndings suggest that there may be more complex interactions between hormone replacement therapy and gastrointestinal health than previously thought (22,25). Thus, there is still no clear explanation for how menopause increases the risk of developing peptic ulcers or delays the healing process in women with preexisting ulcers.

This study is the largest population-based investigation to investigate the associations among menopausal status, type of menopause (surgical or natural), and postmenopausal hormone therapy with PUD risk in Taiwanese women. This extensive dataset offers valuable insights into the potential link between menopause and gastrointestinal health in women, providing evidence for further studies on the topic. Nevertheless, there are also several limitations. First, this was a cross-sectional study, and we did not evaluate the duration of PUD. Therefore, we could not evaluate causal relationships between these factors with PUD. Further longitudinal studies are warranted to investigate the risk of incident PUD. Second, the presence of PUD was obtained through questionnaires without endoscopic veri cation, and the type and severity of PUD could not be ascertained. Nevertheless, a previous study in Taiwan using claims records reported moderate concordance between such data and self-reported renal disease (57). Finally, participants in the TWB are of Chinese ethnicity, which may limit the broader application of our ndings to other

groups. In conclusion, the study found that menopause was signi cantly associated with PUD. Furthermore, surgical menopause (vs. pre-menopause) was associated with a 1.38 times higher risk of PUD, and that postmenopausal hormone therapy in women with natural menopause was associated with a 1.37 times higher risk of PUD. This study is the largest population-based investigation to explore the associations among menopausal status and hormone therapy with PUD in Taiwanese women. Further research should seek to identify the mechanisms and potential interventions to reduce susceptibility to peptic ulcers in menopausal women.

DECLARATIONS

Ethical Approval: The study was conducted according to the Declaration of Helsinki, and it was granted approval by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUHIRBE(I)-20210058), and the TWB was granted approval by the IRB on Biomedical Science Research, Academia Sinica, Taiwan and the Ethics applicable

Consent to Publish: Not applicable

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Resources, project administration, and funding acquisition: S-CC. Data curation: K-CC, C-YK, W-LT, Y-JW, J-HG, C-HK and S-CC. Writing—original draft preparation: K-CC and S-CC. Visualization: J-HG, C-HK and SCC. All authors and agreed to the published version of the manuscript.

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Availability of data and materials: The data underlying this study are from the Taiwan Biobank. Due to restrictions placed on the data by the Personal Information Protection Act of Taiwan, the minimal data set cannot be made publicly available. Data may be available upon request to interested researchers. Please send data requests to: Szu-Chia Chen, PhD, MD. Division of Nephrology, Department of Internal Medicine, Kaohsiung Medical University Woolf, A. & Rose, R. in StatPearls (StatPearls Publishing Copyright © 2024, StatPearls Publishing LLC., 2024).

REFERENCES

1. Woolf, A. y Rose, R. en StatPearls (StatPearls Publishing Copyright © 2024, StatPearls Publishing LLC., 2024).
2. Kavitt, RT, Lipowska, AM, Anyane-Yeboa, A. y Gralnek, IM Diagnóstico y tratamiento de la enfermedad ulcerosa péptica. Am J Med 132 , 447-456, doi:10.1016/j.amjmed.2018.12.009 (2019).
3. Kuo, CF et al. Cómo la enfermedad de úlcera péptica podría potencialmente conducir a los efectos debilitantes y de por vida del síndrome de fatiga crónica: una perspectiva. Sci Rep 11 , 7520, doi:10.1038/s41598-021-87018-z (2021).
4. Jian, C. et al. Aumento de la tasa de hospitalización por úlcera péptica grave en urgencias por enfermedades digestivas después de la pandemia. Medicine (Baltimore) 101 , e31716, doi:10.1097/md.0000000000031716 (2022).
5. Bailey, JM Afecciones gastrointestinales: enfermedad ulcerosa péptica. FP Essent 540 , 16-23 (2024). Ramakrishnan, K. y Salinas, RC Enfermedad de úlcera péptica. Médico de familia. 76 , 1005-1012 (2007).
6. Lanas, A. y Chan, FKL Enfermedad ulcerosa péptica. Lancet 390 , 613-624, doi:10.1016/s01406736(16)32404-7 (2017).
7. Wu, CY et al. Un estudio de cohorte poblacional a nivel nacional muestra una reducción de la hospitalización por enfermedad de úlcera péptica asociada con la erradicación de H. pylori y el uso de inhibidores de la bomba de protones.
8. Clin Gastroenterol Hepatol 7 , 427-431, doi:10.1016/j.cgh.2008.12.029 (2009).
9. Wang, FW et al. Prevalencia y factores de riesgo de la enfermedad ulcerosa péptica asintomática en Taiwán. World J Gastroenterol 17 , 1199-1203, doi:10.3748/wjg.v17.i9.1199 (2011).
10. Greendale, GA, Lee, NP y Arriola, ER La menopausia. Lancet 353 , 571-580, doi:10.1016/s01406736(98)05352-5 (1999).
11. Behrman, S. y Crockett, C. Enfermedad mental grave y perimenopausia. BJPsych Bull , 1-7, doi:10.1192/bjb.2023.89 (2023).
12. Brinton, RD, Yao, J., Yin, F., Mack, WJ y Cadenas, E. La perimenopausia como estado de transición neurológica. Nat Rev Endocrinol 11 , 393-405, doi:10.1038/nrendo.2015.82 (2015).
13. Delamater, L. y Santoro, N. Manejo de la perimenopausia. Clin Obstet Gynecol 61 , 419-432, doi:10.1097/grf.0000000000000389 (2018).
14. Lee, E. et al. Síntomas vasomotores de la menopausia, disfunción autonómica y enfermedad cardiovascular. Am J Physiol Heart Circ Physiol 323 , H1270-h1280, doi:10.1152/ajpheart.00477.2022 (2022).
15. Marlatt, KL et al. Composición corporal y salud cardiometabólica durante la transición a la menopausia. Obesidad (Silver Spring) 30 , 14-27, doi:10.1002/oby.23289 (2022).
16. Mosconi, L. et al. La menopausia afecta la estructura, la conectividad, el metabolismo energético y la deposición de beta amiloide del cerebro humano. Sci Rep 11 , 10867, doi:10.1038/s41598-021-90084-y (2021).
17. Opoku, AA, Abushama, M. y Konje, JC Obesidad y menopausia. Best Pract Res Clin Obstet Gynaecol 88 , 102348, doi:10.1016/j.bpobgyn.2023.102348 (2023).
18. Verdonk, P., Bendien, E. y Appelman, Y. Menopausia y trabajo: una revisión narrativa de la literatura sobre la menopausia, el trabajo y la salud. Trabajo 72 , 483-496, doi:10.3233/wor-205214 (2022).
19. Takahashi, TA y Johnson, KM Menopausia. Clínica Médica del Norte de América 99 , 521-534, doi:10.1016/j.mcna.2015.01.006 (2015).
20. Narayanan, M., Reddy, KM y Marsicano, E. Enfermedad de úlcera péptica e infección por Helicobacter pylori. Mi médico 115 , 219-224 (2018).
21. Clark, DH Úlcera péptica en mujeres. Br Med J 1 , 1254-1257, doi:10.1136/bmj.1.4822.1254 (1953).
22. Machowska, A. et al. El papel de las hormonas sexuales femeninas y masculinas en el proceso de curación de úlceras linguales y gástricas preexistentes. J Physiol Pharmacol 55 Supl 2 , 91-104 (2004).
23. Kim, YS et al. Un estudio de cohorte a nivel nacional muestra un cambio dependiente del sexo en la tendencia de la incidencia de sangrado por úlcera péptica en Corea entre 2006 y 2015. Intestino Hígado 15 , 537-545, doi:10.5009/gnl20079 (2021).
24. Duo, B. et al. Regulación estrogénica de la secreción de bicarbonato duodenal y protección específica del sexo del duodeno humano. Gastroenterología 141 , 854-863, doi:10.1053/j.gastro.2011.05.044 (2011).

25. Wu, HC et al. Prevalencia de úlcera péptica en pacientes dispépticos e influencia de la edad, el sexo y la infección por Helicobacter pylori. Dig Dis Sci 53 , 2650-2656, doi:10.1007/s10620-007-0177-7 (2008).
26. Fu, Y. et al. Edad menopáusica y enfermedades crónicas en mujeres mayores: un estudio transversal en el noreste de China. Int J Environ Res Public Health 13 , doi:10.3390/ijerph13100936 (2016).
27. Fan, CT, Hung, TH y Yeh, CK Regulación de los biobancos en Taiwán. J Law Med Ethics 43 , 816-826, doi:10.1111/jlme.12322 (2015).
28. Levey, AS et al. Un método más preciso para estimar la tasa de filtración glomerular a partir de la creatinina sérica: una nueva ecuación de predicción. Grupo de estudio de modificación de la dieta en la enfermedad renal. Ann Intern Med 130 , 461-470, doi:10.7326/0003-4819-130-6-199903160-00002 (1999).
29. Amalia, R. et al. Prevalencia, etiología y tratamiento de las úlceras y perforaciones gastroduodenales: Una revisión sistemática. J Clin Med 13 , doi:10.3390/jcm13041063 (2024).
30. Kim, N. en Medicina sexual/específica de género en las enfermedades gastrointestinales (ed. Nayoung Kim) 131-151 (Springer Nature Singapore, 2022).
31. Grishina, I., Fenton, A. y Sankaran-Walters, S. Diferencias de género, envejecimiento y estado hormonal en la lesión y reparación de la mucosa . 5 , 160-169, doi:10.14336/ad.2014.0500160 (2014).
32. Grossman, C. Posibles mecanismos subyacentes del dimorfismo sexual en la respuesta inmunitaria: hechos e hipótesis. J Steroid Biochem 34 , 241-251, doi:10.1016/0022-4731(89)90088-5 (1989).
33. Bird, MD, Karavitis, J. y Kovacs, EJ Diferencias sexuales y modulación de la respuesta inmunitaria celular por estrógenos después de una lesión. Cell Immunol 252 , 57-67, doi:10.1016/j.cellimm.2007.09.007 (2008).
34. Gomez, CR, Plackett, TP y Kovacs, EJ Envejecimiento y estrógeno: modulación de las respuestas inflamatorias después de una lesión. Exp Gerontol 42 , 451-456, doi:10.1016/j.exger.2006.11.013 (2007).
35. Buchanan, DL et al. Función de los receptores de estrógeno estromales y epiteliales en la proliferación, estratificación y cornificación del epitelio vaginal. Endocrinología 139 , 4345-4352, doi:10.1210/endo.139.10.6241 (1998).
36. Velders, M., Schleipen, B., Fritzemeier, KH, Zierau, O. & Diel, P. La activación selectiva del receptor β de estrógeno estimula el crecimiento y la regeneración del músculo esquelético. faseb j 26 , 1909-1920, doi:10.1096/fj.11-194779 (2012).
37. Angele, MK, Schwacha, MG, Ayala, A. y Chaudry, IH Efecto del género y las hormonas sexuales en las respuestas inmunitarias después del shock . 14 , 81-90, doi:10.1097/00024382-200014020-00001 (2000).
38. Kovacs, EJ, Plackett, TP y Witte, PL Reemplazo de estrógeno, envejecimiento e inmunidad celular después de una lesión. J Leukoc Biol 76 , 36-41, doi:10.1189/jlb.1103538 (2004).
39. Hildebrand, F. et al. ¿Los efectos protectores del 17 beta-estradiol sobre los macrófagos y esplenocitos esplénicos después de un traumatismo hemorrágico están mediados por el receptor de estrógeno (ER) alfa o beta? J Leukoc Biol 79 , 1173-1180, doi:10.1189/jlb.0106029 (2006).
40. Kovats, S. y Carreras, E. Regulación de la diferenciación y función de las células dendríticas por ligandos del receptor de estrógeno. Cell Immunol 252 , 81-90, doi:10.1016/j.cellimm.2007.10.008 (2008).
41. O, CP y Manyonda, I. La menopausia quirúrgica. Best Pract Res Clin Obstet Gynaecol 81 , 111-118, doi:10.1016/j.bpobgyn.2022.03.001 (2022).
42. Kurt, D. et al. Efecto de la ovariectomía y la administración de hormonas sexuales femeninas sobre la ulceración gástrica inducida por el frío y la inmovilización. Saudi Med J 28 , 1021-1027 (2007).
43. Gava, G. et al. Cognición, estado de ánimo y sueño en la transición menopáusica: el papel de la terapia hormonal para la menopausia. Medicina (Kaunas) 55 , doi:10.3390/medicina55100668 (2019).
44. Rodríguez, M. y Shoupe, D. Menopausia quirúrgica. Endocrinol Metab Clin North Am 44 , 531-542, doi:10.1016/j.ecl.2015.05.003 (2015).
45. Kingsberg, SA, Larkin, LC y Liu, JH Efectos clínicos de la menopausia temprana o quirúrgica. Obstet Gynecol 135 , 853-868, doi:10.1097/aog.0000000000003729 (2020).
46 . Stuursma, A., van Driel, CMG, Wessels, Nueva Jersey, de Bock, GH y Mourits, MJE Gravedad y duración de los síntomas menopáusicos después de una salpingooforectomía para reducir el riesgo. Maturitas 111 , 6976, doi:10.1016/j.maturitas.2018.01.012 (2018).

47. Zeibich, L. et al. La menopausia quirúrgica y la terapia con estrógenos modulan la microbiota intestinal, los marcadores de obesidad y la memoria espacial en ratas. Front Cell Infect Microbiol 11 , 702628, doi:10.3389/fcimb.2021.702628 (2021).
48. Kaliannan, K. et al. Las alteraciones del microbioma intestinal mediadas por estrógenos influyen en el dimorfismo sexual en el síndrome metabólico en ratones. Microbioma 6 , 205, doi:10.1186/s40168-018-0587-0 (2018).
49. O'Toole, PW y Jeffery, IB Microbiota intestinal y envejecimiento. Ciencia 350 , 1214-1215, doi:10.1126/science.aac8469 (2015).
50. Close, H., Mason, JM, Wilson, D. y Hungin, AP La terapia de reemplazo hormonal está asociada con la enfermedad por reflujo gastroesofágico: un estudio de cohorte retrospectivo. BMC Gastroenterol 12 , 56, doi:10.1186/1471-230x-12-56 (2012).
51. Chen, C. et al. El papel del estrógeno y de los receptores de estrógeno en las enfermedades gastrointestinales. Oncol Lett 18 , 5673-5680, doi:10.3892/ol.2019.10983 (2019).
52. Jacobson, BC, Moy, B., Colditz, GA y Fuchs, CS Uso de hormonas posmenopáusicas y síntomas de reflujo gastroesofágico. Arch Intern Med 168 , 1798-1804, doi:10.1001/archinte.168.16.1798 (2008).
53. Nilsson, M., Johnsen, R., Ye, W., Hveem, K. y Lagergren, J. La obesidad y el estrógeno como factores de riesgo de los síntomas del re ux gastroesofágico. jama 290 , 66-72, doi:10.1001/jama.290.1.66 (2003).
54. Coquoz, A., Regli, D. y Stute, P. Impacto de la progesterona en el tracto gastrointestinal: una revisión exhaustiva de la literatura. Climaterio 25 , 337-361, doi:10.1080/13697137.2022.2033203 (2022).
55. Vigneswaran, K. y Hamoda, H. Terapia de reemplazo hormonal: recomendaciones actuales. Best Pract Res Clin Obstet Gynaecol 81 , 8-21, doi:10.1016/j.bpobgyn.2021.12.001 (2022).
56. Hodis, HN y Mack, WJ Terapia de reemplazo hormonal para la menopausia y reducción de la mortalidad por todas las causas y las enfermedades cardiovasculares: es cuestión de tiempo y de oportunidad. Cancer J 28 , 208-223, doi:10.1097/ppo.0000000000000591 (2022).
57. Wu, CS, Lai, MS, Gau, SS, Wang, SC y Tsai, HJ Concordancia entre los autoinformes de los pacientes y los datos de reclamaciones sobre diagnósticos clínicos, uso de medicamentos y utilización del sistema de salud en Taiwán. PLoS One 9 , e112257, doi:10.1371/journal.pone.0112257 (2014).