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Gender differences in the association between alcohol use disorder and infertility: a nationwide population-based cohort study in Taiwan

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Alcohol Use Disorder (AUD) has been associated with reproductive dysfunction, yet evidence regarding its long-term impact on infertility and whether this association differs by sex remains limited and methodologically inconsistent. To investigate the association between AUD and infertility in men and women using nationwide population-based data, and to formally evaluate whether this association differs by sex. We conducted a retrospective cohort study using Taiwan's National Health Insurance Research Database. Individuals aged 15–49 years with newly diagnosed AUD were matched to non-AUD controls using propensity score matching within sex. Time-to-infertility was analyzed using Cox proportional hazards models. Sex differences were formally assessed using an AUD × sex interaction term and a four-group Cox model. Sensitivity analyses restricting both sexes to a common follow-up window were performed to evaluate the robustness of findings. AUD was associated with an increased risk of infertility in both men and women. In models including both sexes, the AUD × sex interaction term was statistically significant, indicating that the strength of the association differed by sex. These findings were consistent in sensitivity analyses using a unified follow-up period. Kaplan–Meier–based cumulative incidence curves showed higher unadjusted infertility incidence among individuals with AUD in both sexes. In this nationwide cohort study, AUD was associated with an elevated risk of infertility among individuals of reproductive age. Formal interaction analyses provided evidence that this association differs by sex. Although causal inference is limited by the observational nature of administrative data, these findings underscore the importance of considering sex-specific patterns when evaluating reproductive health outcomes in individuals with AUD.

Keywords Alcohol use disorder (AUD), Infertility, Gender differences, Population-Based study, Psychiatric comorbidities, Reproductive health

Infertility is a significant and growing public health concern, with estimates suggesting that 8% to 12% of reproductive-aged couples worldwide are affected by difficulties in conceiving after 12 months of unprotected intercourse[1]. Notably, male and female factors contribute nearly equally to infertility diagnoses, with male-specific causes accounting for approximately 20% of cases and contributing to an additional 30–40% in

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conjunction with female factors[2]. In recent years, there has been increased attention on the impact of modifiable lifestyle and environmental exposures-including smoking, obesity, and alcohol use-on reproductive outcomes[3,4].

Alcohol Use Disorder (AUD) is a chronic, relapsing condition marked by compulsive alcohol consumption, loss of control over intake, and continued use despite adverse consequences[5]. AUD has been associated with a spectrum of reproductive health impairments through mechanisms such as hormonal dysregulation, oxidative stress, epigenetic changes, and gonadal toxicity[6,7]. In men, chronic alcohol use may suppress testosterone, impair spermatogenesis, and reduce sperm motility and morphology[8]. In women, alcohol may disrupt ovulatory cycles, damage oocytes, and impair endometrial receptivity, thereby reducing the chances of successful conception[9]. Additionally, excessive alcohol consumption during pregnancy has been linked to fetal alcohol spectrum disorders and long-term developmental issues[10].

Emerging evidence also suggests that alcohol-related reproductive effects may be mediated by disruptions to the hypothalamic–pituitary–gonadal (HPG) axis, increased systemic inflammation, and alcohol-induced alterations in gut microbiota that indirectly impact hormonal regulation[11,12]. Moreover, psychiatric comorbidities such as depression, anxiety, and bipolar disorder, which are frequently co-occurring with AUD, have also been independently associated with reproductive dysfunction and decreased fertility[13,14].

Despite the biological plausibility and experimental findings, epidemiological data on the link between AUD and infertility remain limited and often inconclusive. Many existing studies are constrained by small sample sizes, cross-sectional designs, and inadequate adjustment for confounders such as socioeconomic status, comorbidities, and psychiatric conditions[10,15]. Furthermore, most population-based investigations either lack gender-specific analyses or focus predominantly on one sex, leaving the differential impact of AUD on male versus female reproductive health underexplored.

Taiwan's National Health Insurance Research Database (NHIRD), which includes over 99% of the population, offers a unique opportunity to address these gaps using real-world, longitudinal data. Although several studies have reported associations between alcohol consumption and reproductive impairment, most were based on cross-sectional designs, clinic-based samples, or focused on specific infertility etiologies. Few studies have simultaneously evaluated men and women, and none have conducted long-term, population-based follow-up exceeding two decades. Moreover, previous work has rarely examined stratified risks across socioeconomic and comorbidity profiles. Therefore, additional evidence from large-scale, sex-comparative longitudinal cohorts is warranted. To address this gap, we analyzed two parallel cohort studies based on Taiwan's NHIRD: one investigating female AUD and infertility (2000–2020) and the other investigating male AUD and infertility (2000–2015). By integrating two parallel cohort studies of male and female patients diagnosed with AUD, the present study aims to provide comprehensive, gender-stratified insights into the long-term relationship between AUD and infertility. Given the multifactorial nature of infertility and the limitations of administrative data, the present study focuses on association rather than causal inference. In doing so, this research contributes robust epidemiological evidence to inform targeted public health interventions and reproductive healthcare strategies for populations affected by alcohol-related disorders.

Materials and methods

Data source

This study utilized data from Taiwan's NHIRD, a nationwide claims database covering more than 99% of Taiwan's population. The NHIRD contains anonymized individual-level information on demographics, diagnoses, medical procedures, and healthcare utilization. The database has been widely used and validated for epidemiological research. Detailed information regarding database structure, data elements, and validation is provided in the Supplementary Materials (Supplementary Methods S1).

The database has been widely validated and used in numerous peer-reviewed publications across fields such as cardiology, psychiatry, oncology, and public health.

To ensure data privacy and compliance with ethical standards, all personally identifiable information in the NHIRD is encrypted prior to release. The present study was approved by the Institutional Review Board of Tri-Service General Hospital in Taipei, Taiwan (IRB No. TSGHIRB: E202516039). Informed consent was waived due to the retrospective and de-identified nature of the data, in accordance with local regulations and the principles of the Declaration of Helsinki.

Study design and participants

This nationwide, retrospective cohort study was conducted using data extracted from the Taiwan NHIRD. Two independent cohorts were constructed for male and female populations. The female cohort included patients diagnosed with AUD between January 1, 2000, and December 31, 2020, while the male cohort was constructed using data from January 1, 2000, to December 31, 2015. Eligible subjects were aged between 15 and 49 years, a range consistent with reproductive age as defined by the World Health Organization (WHO).

Patients were included in the AUD group if they had at least one inpatient or two outpatient claims for AUD, based on the International Classification of Diseases codes (ICD-9-CM: 303, 305.0; ICD-10-CM: F10.1–F10.9). The index date was defined as the first diagnosis of AUD. For individuals in the control group, the index date was randomly assigned based on the distribution of index dates in the AUD group.

Inclusion criteria

Participants were eligible for inclusion if they met all of the following criteria:

1. Were enrolled in the Taiwan National Health Insurance program during the study period.
2. Had a new diagnosis of Alcohol Use Disorder (AUD) between January 1, 2000, and December 31, 2015 (males) or December 31, 2020 (females), or were matched non-AUD controls.

3. Were aged 15–49 years at the index date, consistent with the World Health Organization (WHO) definition of reproductive age.
4. Had complete demographic and follow-up information available in the NHIRD.

Exclusion criteria
Participants were excluded if they met any of the following criteria prior to the index date:

1. A documented diagnosis of infertility (ICD-9-CM 606 or 628; ICD-10-CM N46 or N97).
2. A history of reproductive system malignancy or receipt of chemotherapy or radiotherapy.
3. Congenital anomalies of the reproductive tract (e.g., agenesis of the uterus or vas deferens).
4. Withdrawal from the National Health Insurance program or death before the start of follow-up.
5. Missing or incomplete key demographic, exposure, or outcome data.

Age eligibility was fully defined within the inclusion criteria; therefore, no age-based exclusions were applied separately.

Propensity score matching
To minimize baseline differences between patients with AUD and controls, propensity score matching (PSM) was performed separately within male and female cohorts. Male patients with AUD were matched only to male controls without AUD, and female patients with AUD were matched only to female controls without AUD. No matching was performed across sexes.

Within each sex-specific cohort, patients with AUD were matched to non-AUD controls at a 1:4 ratio using a nearest-neighbor algorithm without replacement and a caliper width of 0.1. The propensity score was estimated using a logistic regression model including age at index date, index year, and enrollment period, which are key determinants of infertility risk and follow-up opportunity.

Matching quality was assessed using standardized mean differences (SMDs), with values < 0.1 indicating adequate balance.The resulting matched cohorts were then followed longitudinally from the index date until the diagnosis of infertility, withdrawal from the NHIRD, death, or the end of the study period (December 31, 2020, for females, December 31, 2015, for males), whichever came first. The study flow diagram illustrating inclusion, exclusion, and matching processes is presented in Fig. 1.

Follow-up period and sex-specific cutoff years

The follow-up cutoff years differed between male (December 31, 2015) and female (December 31, 2020) cohorts due to sex-specific data completeness within the NHIRD. Male infertility diagnoses (ICD-9-CM 606; ICD-10-CM N46) were consistently validated and available only through 2015, whereas female infertility diagnoses (ICD-9-CM 628; ICD-10-CM N97) remained complete through 2020. To avoid outcome misclassification, sex-specific cutoff years were therefore applied.

All participants were followed from their individual index dates until infertility diagnosis, withdrawal from the insurance program, death, or the sex-specific study endpoint, whichever occurred first. Because Cox proportional hazards models account for varying follow-up times through censoring and risk-set construction, differential calendar follow-up does not inherently bias hazard ratio estimation.

Definition of variables

AUD was defined based on diagnostic codes from the International Classification of Diseases. Specifically, ICD-9-CM codes 303 (Alcohol dependence syndrome) and 305.0 (Alcohol abuse), and ICD-10-CM codes F10.1–F10.9 (Mental and behavioral disorders due to use of alcohol) were used to identify individuals with AUD. A diagnosis required at least one inpatient admission or two outpatient visits within one year, recorded by psychiatrists or physicians in relevant specialties.

Infertility was the primary outcome, defined using sex-specific ICD codes. For males, ICD-9-CM code 606 and ICD-10-CM code N46 (Male infertility) were used. For females, ICD-9-CM code 628 and ICD-10-CM code N97 (Female infertility) were applied. Only diagnoses made by gynecologists, urologists, or reproductive medicine specialists were included to ensure clinical accuracy.

Comorbidities were identified if present in at least one hospitalization or two outpatient claims within one year prior to the index date. These included:

- Cardiometabolic conditions: hypertension (ICD-9: 401–405; ICD-10: I10–I15), diabetes mellitus (ICD-9: 250; ICD-10: E10–E14), hyperlipidemia (ICD-9: 272; ICD-10: E78), coronary artery disease (CAD) (ICD-9: 410–414; ICD-10: I20–I25), and obesity (ICD-9: 278; ICD-10: E66).
- Psychiatric conditions: depression (ICD-9: 296.2, 296.3, 300.4, 311; ICD-10: F32–F33), anxiety (ICD-9: 300.0, 300.2; ICD-10: F41), and bipolar disorder (ICD-9: 296.0, 296.4–296.8; ICD-10: F31).
- Respiratory disease: chronic obstructive pulmonary disease (COPD) (ICD-9: 490–496; ICD-10: J40–J44).

Sociodemographic variables included:

- Monthly income categorized based on insurance premiums: < NT$18,000, NT$18,000–34,999, and ≥ NT$35,000.
- Urbanization level, classified into four levels (1 = most urbanized, 4 = least urbanized).
- Geographic region of residence (North, Central, South, East Taiwan).
- Hospital level, classified into local clinic, regional hospital, and medical center.

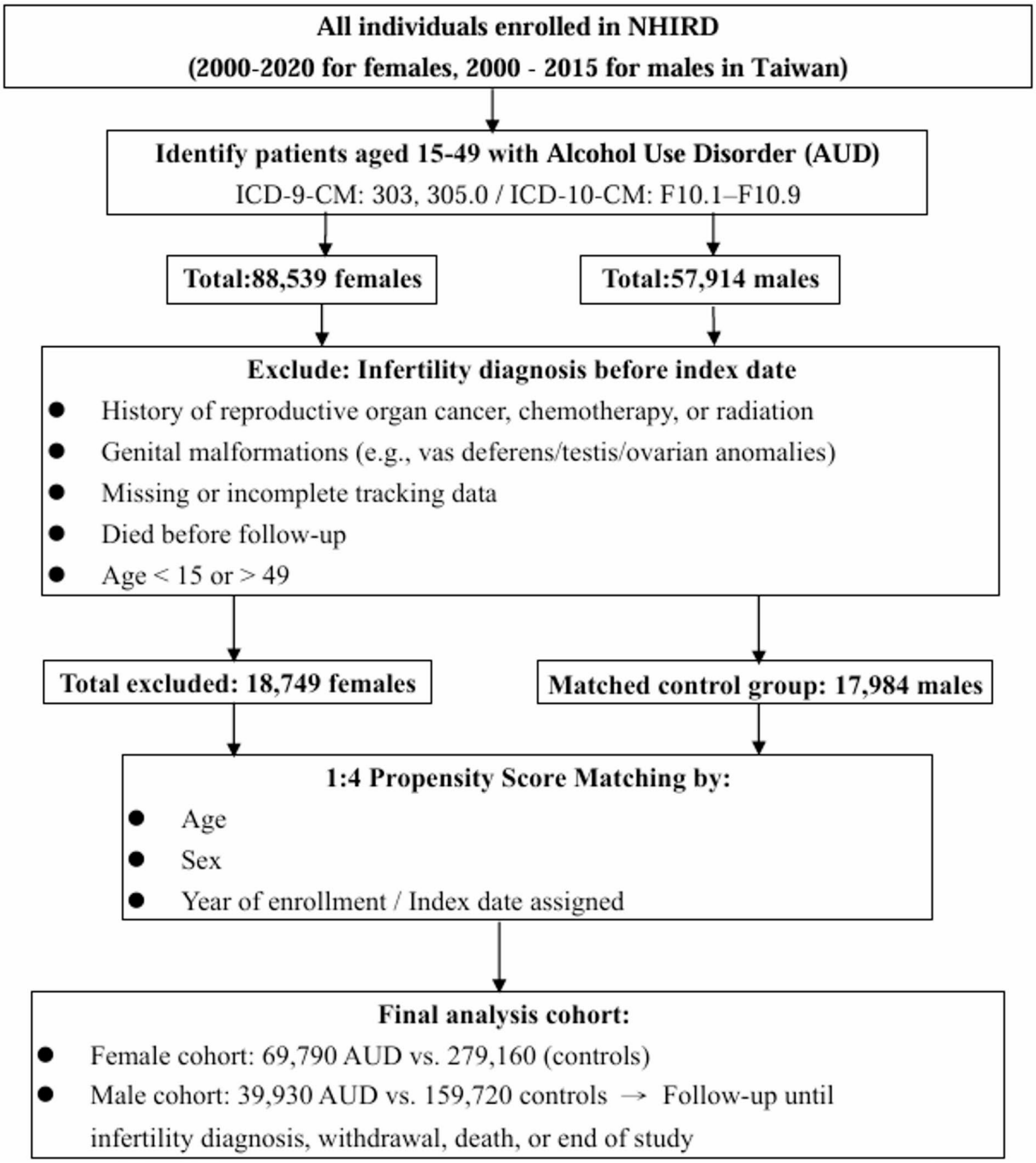

Fig. 1. The flowchart of study.

Charleson Comorbidity Index-Revised (CCI-R) was used to quantify overall disease burden. It was calculated based on validated ICD coding algorithms to adjust for the severity of comorbid conditions.

Statistical analysis

Baseline characteristics between AUD and non-AUD groups were summarized using means and standard deviations for continuous variables and counts with percentages for categorical variables. Comparisons were conducted using Student's t-test for continuous variables and Chi-square test for categorical variables.

The primary analysis used Cox proportional hazards regression models to estimate the association between AUD and the risk of infertility, expressed as adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs). Covariates included in the model were age, income, urbanization, CCI-R score, comorbidities, hospital level, and region.

The proportional hazards (PH) assumption for Cox regression models was evaluated using both graphical and statistical approaches. Schoenfeld residuals were examined for the main exposure (Alcohol Use Disorder),

sex, and the AUD × sex interaction term, and global tests of proportionality were performed. In addition, log-minus-log survival plots were visually inspected to assess parallelism of survival curves across exposure groups. No substantial violations of the PH assumption were observed for the primary exposure or interaction term. Therefore, Cox proportional hazards models were considered appropriate for the analysis.

Sociodemographic variables such as monthly income, urbanization level, hospital level, and geographic region were not included in the matching algorithm to avoid overmatching and excessive loss of eligible participants. These variables may act as mediators or contextual factors rather than pure confounders of the AUD–infertility association.

Instead, these sociodemographic characteristics were adjusted for in subsequent multivariable Cox proportional hazards models. This combined approach-matching on core temporal and demographic variables and adjusting for additional covariates in regression models-is consistent with established methodological recommendations for propensity score-based analyses. Sex was used as a stratification variable for cohort construction rather than as a matching variable across cohorts.

Kaplan-Meier survival curves were constructed to visualize the cumulative incidence of infertility, stratified by AUD status. Differences between curves were tested using the log-rank test. Cumulative incidence curves were generated for descriptive purposes using 1 − Kaplan–Meier estimates to visualize the occurrence of infertility over time by Alcohol Use Disorder (AUD) status. These curves were constructed prior to multivariable Cox regression analyses and were not used for effect estimation.

No competing risk methods were applied, and the curves do not represent cumulative incidence functions (CIF). In addition, no smoothing, interpolation, or other post-processing techniques were used; all curves reflect the original stepwise Kaplan–Meier estimates.

Subgroup analyses were performed for males and females separately, and further stratified by age, income, and comorbidity status. For comparisons involving multiple subgroups, a Bonferroni correction was applied to adjust for multiple testing.

Given the complexity of reproductive health outcomes, confounder selection was guided by a directed acyclic graph (DAG) informed by existing literature and biological plausibility. The DAG conceptualized the relationships among AUD, infertility, and potential confounders, including sociodemographic factors, psychiatric conditions, cardiometabolic diseases, and healthcare access.

Variables included in the adjustment set were selected as common causes of both AUD and infertility, rather than intermediate variables on the causal pathway. Based on this framework, we adjusted for age, socioeconomic status (income level), urbanization, geographic region, psychiatric comorbidities, cardiometabolic diseases, chronic respiratory disease, overall comorbidity burden (CCI-R), and healthcare system factors.

Lifestyle factors such as smoking, body mass index, diet, and physical activity were not directly available in the NHIRD; however, several adjusted comorbidities serve as proxies for these unmeasured behaviors. A DAG illustrating the assumed causal structure and adjustment strategy is provided in the Supplementary Materials (Figure S1).

Sociodemographic factors (age, sex, socioeconomic status, urbanization, and region), psychiatric disorders, and cardiometabolic diseases are modeled as common causes of both AUD and infertility. Lifestyle behaviors (e.g., smoking, obesity, diet, and physical activity) are unmeasured and partially captured through proxy comorbidities. Healthcare access influences diagnostic opportunity but is not assumed to lie on the causal pathway. The minimally sufficient adjustment set derived from the DAG guided covariate selection in the multivariable analyses.

All statistical analyses were performed using IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA). A two-tailed p-value < 0.05 was considered statistically significant unless otherwise noted.

Assessment of gender differences

To formally evaluate whether the association between AUD and infertility differed by sex, we performed two additional analyses:

Interaction model

A multivariable Cox proportional hazards model including an interaction term between AUD and sex (AUD × sex) was fitted.

$$\mathrm{h(t)} = \mathrm{h0(t)} \exp\left(\beta 1\,\mathrm{AUD} + \beta 2\,\mathrm{Sex} + \beta 3\,(\mathrm{AUD} \times \mathrm{Sex}) + \mathrm{C}\right)$$

where β_3 tests whether the effect of AUD on infertility differs significantly between males and females.

Four-Group Cox model

Participants were categorized into four mutually exclusive groups:

- Male without AUD (reference).
- Male with AUD.
- Female without AUD.
- Female with AUD.

This model provides direct comparison of hazard ratios (HRs) across sex-exposure combinations to visualize gender-specific differences.

Both models were adjusted for the same covariates as primary analyses, including age, income, comorbidities, CCI-R score, urbanization level, and healthcare region. Statistical significance for interaction was set at $p < 0.05$.

To evaluate the potential impact of differential follow-up duration between sexes, we performed sensitivity analyses restricting both male and female cohorts to a common observation window (January 1, 2000 - December 31, 2015). All primary models, including the AUD × sex interaction and four-group Cox regression, were re-estimated under this restriction.

Results

Baseline characteristics

Table 1 summarizes the baseline demographic and clinical characteristics of patients with and without AUD, stratified by sex. In the male cohort ($n = 199,650$), there was no significant difference in mean age between AUD and non-AUD patients (35.2 ± 9.8 vs. 35.3 ± 9.8 years; $p = 0.363$). In contrast, the female AUD group was slightly younger than the non-AUD group (34.7 ± 9.6 vs. 34.9 ± 9.6 years; $p < 0.001$), though the difference was likely not clinically meaningful. Sociodemographic disparities were observed. A significantly higher proportion of patients with AUD-both male and female-had monthly incomes below NT$18,000 and resided in the most urbanized areas (urbanization level 1) compared to those without AUD (all $p < 0.001$), suggesting potential socioeconomic and environmental vulnerabilities associated with alcohol misuse.

Regarding comorbidities, individuals with AUD had a consistently higher prevalence of both medical and psychiatric conditions than their non-AUD counterparts. Cardiovascular and metabolic conditions such as hypertension, diabetes mellitus, hyperlipidemia, and coronary artery disease were more prevalent in the AUD group across both sexes (all $p < 0.001$). Psychiatric comorbidities-including depression, anxiety, and bipolar disorder-were markedly elevated among AUD patients (e.g., depression in males: 8.9% vs. 2.1%; in females: 10.5% vs. 3.4%; all $p < 0.001$), reflecting the known bidirectional relationship between psychiatric disorders and substance use.

In addition, AUD patients demonstrated a higher burden of chronic diseases, as reflected by a significantly higher CCI-R score (male: 1.17 ± 0.94 vs. 1.11 ± 0.86; female: 1.14 ± 0.92 vs. 1.07 ± 0.89; $p < 0.001$ for both). Collectively, these findings indicate that AUD patients enter the study with a greater burden of comorbid physical and mental illness, which may influence reproductive health outcomes and must be adjusted for in subsequent analyses.

Endpoints characteristics

Table 2 presents the infertility-related endpoints among patients with and without AUD, stratified by sex.

In terms of follow-up duration, the mean time was similar between male AUD and non-AUD groups (7.2 ± 3.5 vs. 7.1 ± 3.6 years), and likewise for female groups (4.5 ± 2.7 vs. 4.6 ± 2.9 years), indicating comparable observation windows across cohorts.

Patients with AUD were diagnosed with infertility at younger ages compared to their non-AUD counterparts (male: 34.1 vs. 36.7 years; female: 32.5 vs. 34.9 years) and had shorter latency periods from index date to infertility diagnosis (male: 3.8 ± 1.9 vs. 5.1 ± 2.4 years; female: 2.3 ± 1.4 vs. 3.1 ± 1.8 years), suggesting earlier manifestation of reproductive dysfunction in the AUD group.

The cumulative number of infertility cases was higher in the female cohort overall (AUD: 1,159; non-AUD: 3,876) than in the male cohort (AUD: 773; non-AUD: 632). However, when adjusted for person-years, the infertility rate per 1,000 person-years was consistently higher in the AUD group across both sexes (male: 3.24 vs. 2.11; female: 4.11 vs. 3.29).

Characteristics	Male AUD ($n = 39,930$)	Male non-AUD ($n = 159,720$)	p-value	Female AUD ($n = 69,790$)	Female non-AUD ($n = 279,160$)	p-value
Mean age (years, SD)	35.2 ± 9.8	35.3 ± 9.8	0.363	34.7 ± 9.6	34.9 ± 9.6	< 0.001
Monthly income < NT$18,000	51.2%	52.4%	< 0.001	53.8%	55.1%	< 0.001
Urbanization level 1	25.7%	25.2%	< 0.001	26.3%	25.0%	< 0.001
Hypertension	25.4%	22.4%	< 0.001	23.8%	21.6%	< 0.001
Diabetes mellitus	19.8%	15.7%	< 0.001	18.1%	14.8%	< 0.001
Hyperlipidemia	16.3%	12.4%	< 0.001	15.9%	12.9%	< 0.001
Depression	8.9%	2.1%	< 0.001	10.5%	3.4%	< 0.001
Anxiety	7.9%	1.9%	< 0.001	9.3%	2.8%	< 0.001
Bipolar disorder	7.1%	1.4%	< 0.001	6.8%	1.6%	< 0.001
CAD	7.2%	6.2%	< 0.001	6.9%	5.8%	< 0.001
Obesity	1.1%	0.7%	0.002	1.3%	1.1%	0.041
COPD	5.3%	4.7%	< 0.001	5.1%	4.5%	< 0.001
CCI-R score (mean ± SD)	1.17 ± 0.94	1.11 ± 0.86	< 0.001	1.14 ± 0.92	1.07 ± 0.89	< 0.001

Table 1. Baseline characteristics of patients with and without AUD. Data are presented as mean ± standard deviation (SD) for continuous variables and as percentages for categorical variables. p-values were calculated using the independent t-test for continuous variables and chi-square test for categorical variables. AUD = Alcohol Use Disorder; CAD = coronary artery disease; COPD = Chronic Obstructive Pulmonary Disease; CCI-R = Charleson Comorbidity Index, Revised version.

Endpoint Characteristics	Male AUD (n = 39,930)	Male non-AUD (n = 159,720)	Female AUD (n = 69,790)	Female non-AUD (n = 279,160)
Follow-up duration (mean ± SD, years)	7.2 ± 3.5	7.1 ± 3.6	4.5 ± 2.7	4.6 ± 2.9
Age at infertility diagnosis (years)	34.1	36.7	32.5	34.9
Time to infertility diagnosis (mean ± SD)	3.8 ± 1.9	5.1 ± 2.4	2.3 ± 1.4	3.1 ± 1.8
Total infertility cases (n)	773	632	1,159	3,876
Infertility rate (per 1,000 PYs)	3.24	2.11	4.11	3.29
Cumulative incidence (log-rank test p-value)	< 0.001	< 0.001	< 0.001	< 0.001

Table 2. Endpoints characteristics of patients with and without AUD. Data are presented as mean ± standard deviation (SD) for continuous variables, unless otherwise specified. Follow-up duration refers to the time from index date to the earliest of infertility diagnosis, withdrawal, death, or study endpoint. Time to infertility diagnosis indicates the mean duration from index date to the occurrence of infertility among those diagnosed. Infertility rate is expressed per 1,000 person-years (PYs) of follow-up. Cumulative incidence p-values are derived from the log-rank test. AUD = Alcohol Use Disorder.

Variable	Male aHR (95% CI)	p-value	Female aHR (95% CI)	p-value
AUD vs. non-AUD	1.355 (1.090–1.573)	0.005	1.079 (1.061–1.096)	< 0.001
Age group (Ref: 15–24)				
25–34	2.072 (1.502–2.959)	< 0.001	1.433 (1.295–1.585)	< 0.001
35–44	1.481 (0.980–2.026)	0.071	1.271 (1.156–1.397)	< 0.001
≥ 45	0.830 (0.571–1.243)	0.429	0.898 (0.823–0.979)	0.015
Psychiatric comorbidities				
Depression	1.970 (1.423–2.675)	< 0.001	1.082 (1.014–1.153)	0.017
Anxiety	1.762 (1.095–2.178)	0.003	1.050 (0.992–1.113)	0.092
Bipolar disorder	1.608 (1.024–2.057)	0.038	1.041 (0.963–1.125)	0.262
Medical comorbidities				
Hypertension	1.626 (1.072–2.561)	0.014	1.192 (1.135–1.252)	< 0.001
Diabetes mellitus	1.739 (1.224–2.666)	< 0.001	1.121 (1.062–1.183)	< 0.001
Hyperlipidemia	1.479 (1.036–1.790)	0.032	1.068 (1.012–1.126)	0.016
Coronary artery disease (CAD)	1.303 (1.002–1.573)	0.049	1.132 (1.047–1.223)	0.002
Obesity	1.325 (1.040–1.695)	0.030	0.981 (0.964–0.999)	0.042
COPD	1.182 (0.746–1.479)	0.253	1.103 (1.015–1.199)	0.021
CCI-R (per unit increase)	1.690 (1.082–1.245)	0.009	1.093 (1.074–1.112)	< 0.001

Table 3. Adjusted hazard ratios (aHR) for infertility among AUD and Non-AUD patients (Stratified by Sex). Adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) were estimated using multivariable Cox proportional hazards regression models. All models were adjusted for age, income level, urbanization level, comorbidities, CCI-R, hospital level, and geographic region. Reference category for age group is 15–24 years. Psychiatric and medical comorbidities were defined based on relevant ICD-9/10 codes within 1 year before the index date. AUD = Alcohol Use Disorder; CAD = coronary artery disease; COPD = Chronic Obstructive Pulmonary Disease; CCI-R = Charleson Comorbidity Index, Revised version.

Kaplan-Meier analysis demonstrated significantly greater cumulative incidence of infertility in the AUD groups compared to non-AUD groups in both males and females (log-rank test $p < 0.001$), reinforcing the temporal association between AUD and elevated infertility risk.

These findings suggest that AUD is associated with both an earlier onset and a higher rate of infertility, independent of sex, and highlight the importance of early reproductive health screening in patients with alcohol-related disorders.

Multivariate Cox regression analysis of infertility risk

Table 3 presents the results of sex-stratified multivariate Cox proportional hazards models assessing the association between AUD and the risk of infertility, adjusting for age, comorbidities, and sociodemographic variables.

In both male and female cohorts, AUD was independently associated with a significantly increased risk of infertility. Specifically, the adjusted hazard ratio (aHR) for infertility among male patients with AUD was 1.355 (95% CI: 1.090–1.573, $p = 0.005$), and among females was 1.079 (95% CI: 1.061–1.096, $p < 0.001$), indicating a consistent adverse effect across sexes.

Age was a strong modifier of infertility risk. In males, those aged 25–34 years exhibited the highest risk (aHR = 2.072, 95% CI: 1.502–2.959), followed by those aged 35–44 years, although the latter did not reach

Variable	aHR (95% CI)	*p*-value
AUD	1.412 (1.265–1.576)	< 0.001
Female sex	1.083 (1.022–1.148)	0.008
AUD × Female sex	0.804 (0.680–0.952)	0.013
Covariates*	Adjusted	–

Table 4. Cox regression model with AUD × sex Interaction. *Covariates include age, income, comorbidities, CCI-R, hospital level, and region.

Group	aHR (95% CI)	*p*-value
Male without AUD	Reference	-
Male with AUD	1.355 (1.090–1.573)	0.005
Female without AUD	0.914 (0.878–0.962)	0.001
Female with AUD	1.121 (1.072–1.168)	< 0.001

Table 5. Four-Group Cox model for AUD–Infertility association by Sex.

statistical significance ($p = 0.071$). A similar trend was observed in females, with significantly elevated risks in the 25–34 (aHR = 1.433) and 35–44 (aHR = 1.271) age groups. Conversely, patients aged ≥ 45 years showed a lower risk compared to the reference group (15–24 years), particularly in females (aHR = 0.898, $p = 0.015$), suggesting an age-dependent effect of reproductive decline.

Among comorbid conditions, psychiatric disorders-including depression, anxiety, and bipolar disorder-were significantly associated with increased infertility risk in males, with the strongest effect observed for depression (aHR = 1.970). In females, depression was modestly associated with infertility (aHR = 1.082, $p = 0.017$), whereas anxiety and bipolar disorder did not reach statistical significance.

Regarding medical comorbidities, both sexes exhibited elevated infertility risks associated with hypertension, diabetes mellitus, hyperlipidemia, and CAD. Notably, obesity showed a sex-specific pattern: it was associated with increased infertility risk in males (aHR = 1.325, $p = 0.030$) but a slightly protective effect in females (aHR = 0.981, $p = 0.042$). COPD was significantly associated with infertility in females ($p = 0.021$), but not in males.

The CCI-R was significantly associated with infertility in both sexes (male aHR = 1.690; female aHR = 1.093), indicating that overall disease burden contributes to reproductive impairment.

Taken together, these results suggest that AUD is an independent risk factor for infertility in both men and women, with additional contributions from psychiatric and cardiometabolic comorbidities, particularly among men.

Tests based on Schoenfeld residuals and log-minus-log plots indicated no significant violation of the proportional hazard's assumption for Alcohol Use Disorder or for the AUD × sex interaction (all $p > 0.05$) (Table S2).

Interaction between sex and AUD on infertility risk

Table 4 showed in the combined cohort, the AUD × sex interaction term was statistically significant in the multivariable Cox model ($\beta = 0.261$, $p = 0.013$), indicating that the association between AUD and infertility differed significantly between men and women. The effect of AUD was stronger among men.

Interpretation:

- AUD increases infertility risk.
- Female sex has slightly higher baseline infertility diagnosis probability (health-seeking differences).
- The interaction term < 1.0 means the AUD effect is *attenuated* in females vs. males, confirming a statistically significant gender difference.

Four-Group Cox model

Table 5 compared with males without AUD (reference group), males with AUD exhibited the greatest increase in infertility risk (aHR = 1.355, 95% CI: 1.090–1.573). Females with AUD also showed elevated risk (aHR = 1.121, 95% CI: 1.072–1.168), but with a significantly smaller effect size. Female controls had a lower infertility risk than male controls, consistent with differential baseline etiologies and healthcare-seeking patterns.

Interpretation:

- Male AUD patients have the highest infertility risk (largest HR).
- Female AUD patients also have increased risk, but significantly smaller than males with AUD.
- This pattern aligns with biological and sociobehavioral differences and validates the paper's focus on gender differences.

Sensitivity analysis using a common Follow-up window

When both male and female cohorts were restricted to a common follow-up period ending in 2015, the association between Alcohol Use Disorder and infertility remained statistically significant in both sexes (Table S1). Importantly, the AUD × sex interaction also remained significant, with effect estimates comparable to those observed in the primary analysis. These findings indicate that the observed gender differences were robust and not driven by differential follow-up duration.

Stratified analysis of infertility risk in male AUD patients

As shown in Table 6, stratified Cox regression analyses were performed to explore whether the association between AUD and infertility risk in males varied across demographic and clinical subgroups.

Across all subgroups, AUD remained significantly associated with an increased risk of infertility, with adjusted hazard ratios (aHRs) ranging from 1.289 to 1.739.

Age-specific analyses revealed that the elevated risk of infertility among AUD patients was most pronounced in the 25–34 age group (aHR = 1.418, 95% CI: 1.123–1.648, $p < 0.001$), followed by those aged 35–44 (aHR = 1.352, $p = 0.014$). While the aHRs for the youngest (15–24) and oldest (≥ 45) age groups were also significant, the effect sizes were comparatively modest, suggesting an age-dependent susceptibility, particularly during peak reproductive years.

Stratification by income level showed that the association between AUD and infertility persisted regardless of economic status, with slightly higher risk observed in the lowest income group (< NT$18,000: aHR = 1.368) and consistent effects across middle and high-income brackets (all $p < 0.001$), indicating that the association is independent of socioeconomic background.

When stratified by comorbid conditions, male AUD patients with coexisting diabetes mellitus (aHR = 1.739), hypertension (aHR = 1.626), and depression (aHR = 1.970) had substantially elevated risks of infertility. Similar trends were observed for anxiety, bipolar disorder, hyperlipidemia, CAD, and obesity, further underscoring the compounded reproductive burden in patients with both AUD and chronic medical or psychiatric conditions.

Geographic analysis based on urbanization level indicated that the infertility risk associated with AUD was significantly elevated in patients living in urbanized regions (Level 1: aHR = 1.538; Level 2: aHR = 1.313), but not in the least urbanized areas (Level 3: aHR = 1.006, $p = 0.438$). This may reflect increased infertility detection in higher-access healthcare areas or urban-specific lifestyle interactions with AUD.

Stratified Variable	Events (AUD/non-AUD)	aHR (95% CI)	*p*-value
Overall	773/632	1.355 (1.090–1.573)	0.005
Age 15–24	80/62	1.318 (1.044–1.531)	0.028
Age 25–34	242/188	1.418 (1.123–1.648)	< 0.001
Age 35–44	296/244	1.352 (1.072–1.570)	0.014
Age ≥ 45	155/138	1.289 (1.023–1.498)	0.038
Income < NT$18,000	456/721	1.368 (1.150–1.561)	< 0.001
Income NT$18,000–34,999	210/401	1.353 (1.077–1.537)	< 0.001
Income ≥ NT$35,000	107/288	1.340 (1.052–1.471)	< 0.001
With HTN	145/295	1.626 (1.072–2.561)	0.014
With DM	120/215	1.739 (1.224–2.666)	< 0.001
With Hyperlipidemia	101/190	1.479 (1.036–1.790)	0.032
With Depression	178/242	1.970 (1.423–2.675)	< 0.001
With Anxiety	159/201	1.762 (1.095–2.178)	0.003
With Bipolar Disorder	117/174	1.608 (1.024–2.057)	0.038
With CAD	102/169	1.303 (1.002–1.573)	0.049
With Obesity	73/104	1.325 (1.040–1.695)	0.030
With COPD	81/121	1.182 (0.746–1.479)	0.253
Urban Level 1	190/289	1.538 (1.096–1.973)	0.002
Urban Level 2	238/236	1.313 (1.060–1.495)	0.020
Urban Level 3	122/107	1.006 (0.562–1.421)	0.438
Urban Level 4 (Reference)	-	Reference	–

Table 6. Stratified Cox regression for infertility risk in male AUD patients by Subgroups. Adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) were derived from stratified Cox proportional hazards models for male patients, assessing the risk of infertility in those with Alcohol Use Disorder (AUD) compared to matched non-AUD counterparts. Each subgroup analysis was adjusted for baseline age, income level, comorbidities, CCI-R, hospital level, and region of care, unless otherwise used as the stratification factor. Reference groups for age and urbanization were the 15–24-year age group and Urbanization Level 4, respectively. AUD = Alcohol Use Disorder; HTN = Hypertension; DM = Diabetes Mellitus; CAD = coronary artery disease; COPD = Chronic Obstructive Pulmonary Disease; CCI-R = Charleson Comorbidity Index, Revised version.

Overall, these findings suggest that the adverse reproductive impact of AUD in men is robust across most subgroups but is particularly amplified among those in their prime reproductive age and those with coexisting physical or psychiatric comorbidities.

Stratified analysis of infertility risk in female AUD patients

As shown in Table 7, stratified Cox regression analyses were conducted to examine whether the association between AUD and infertility risk varied across subgroups among female patients.

Overall, female patients with AUD exhibited a significantly higher risk of infertility compared to their non-AUD counterparts (adjusted hazard ratio [aHR] = 1.079, 95% CI: 1.061–1.096, $p < 0.001$). This elevated risk persisted across most stratified subgroups, indicating the robustness of the association.

When stratified by age, the increased risk of infertility was most pronounced in younger women. Patients aged 15–24 years had the highest relative risk (aHR = 1.433, 95% CI: 1.295–1.585), followed by those aged 25 – 4 (aHR = 1.267) and 35–44 years (aHR = 1.211), all with $p < 0.001$. Interestingly, among women aged ≥ 45, the aHR was < 1 (aHR = 0.898, $p = 0.015$), suggesting a possible attenuation or reverse association in late reproductive age.

Across income strata, the association between AUD and infertility remained significant. The effect was slightly stronger in the higher-income group (≥ NT$35,000; aHR = 1.145, $p = 0.002$), which may reflect more frequent infertility screening or health-seeking behavior in wealthier individuals.

Female AUD patients with cardiometabolic comorbidities, including hypertension (aHR = 1.192), diabetes mellitus (aHR = 1.121), hyperlipidemia (aHR = 1.068), and coronary artery disease (aHR = 1.132), exhibited significantly elevated risks of infertility. Among psychiatric comorbidities, only depression was independently associated with infertility (aHR = 1.082, $p = 0.017$), whereas anxiety and bipolar disorder were not statistically significant.

Obesity showed a slightly inverse association with infertility in women (aHR = 0.981, $p = 0.042$), contrasting with the positive association observed in men (Table 4). This may reflect sex-specific metabolic or hormonal interactions affecting reproductive health.

Stratification by urbanization level revealed a stepwise increase in infertility risk among AUD patients living in more urbanized areas: Level 1 (aHR = 1.138), Level 2 (aHR = 1.083), and Level 3 (aHR = 1.062), compared with the least urbanized Level 4 (reference). These trends may be driven by regional differences in access to infertility evaluation, environmental exposures, or socio behavioral factors.

Stratified Variable	Events (AUD/non-AUD)	aHR (95% CI)	*p*-value
Overall	1,159/3,876	1.079 (1.061–1.096)	< 0.001
Age 15–24	204/327	1.433 (1.295–1.585)	< 0.001
Age 25–34	402/1,112	1.267 (1.172–1.368)	< 0.001
Age 35–44	387/1,579	1.211 (1.112–1.316)	< 0.001
Age ≥ 45	166/858	0.898 (0.823–0.979)	0.015
Income < NT$18,000	623/2,050	1.061 (1.019–1.103)	0.003
Income NT$18,000–34,999	355/1,278	1.089 (1.026–1.154)	0.005
Income ≥ NT$35,000	181/548	1.145 (1.048–1.252)	0.002
With HTN	276/983	1.192 (1.135–1.252)	< 0.001
With DM	194/793	1.121 (1.062–1.183)	< 0.001
With Hyperlipidemia	177/703	1.068 (1.012–1.126)	0.016
With Depression	263 / 845	1.082 (1.014–1.153)	0.017
With Anxiety	221/758	1.050 (0.992–1.113)	0.092
With Bipolar Disorder	179/636	1.041 (0.963–1.125)	0.262
With CAD	181/786	1.132 (1.047–1.223)	0.002
With Obesity	85/210	0.981 (0.964–0.999)	0.042
With COPD	74/231	1.103 (1.015–1.199)	0.021
Urban Level 1	301/987	1.138 (1.072–1.208)	< 0.001
Urban Level 2	302/1,006	1.083 (1.026–1.144)	0.003
Urban Level 3	288/998	1.062 (1.004–1.122)	0.038
Urban Level 4 (Reference)	268/885	Reference	-

Table 7. Stratified Cox regression for infertility risk in female AUD patients by Subgroups. Adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) were obtained from stratified Cox proportional hazards models to estimate the risk of infertility in female patients with Alcohol Use Disorder (AUD) compared with matched non-AUD controls. All models were adjusted for age, income level, urbanization level, comorbidities, CCI-R, hospital level, and geographic region, except where stratification variables were used. Reference groups were age 15–24 and Urbanization Level 4. AUD = Alcohol Use Disorder; HTN = Hypertension; DM = Diabetes Mellitus; CAD = coronary artery disease; COPD = Chronic Obstructive Pulmonary Disease; CCI-R = Charleson Comorbidity Index, Revised version.

Collectively, these results suggest that AUD is a consistent and independent risk factor for infertility among women, especially in younger age groups and those with underlying cardiometabolic diseases. However, the risk is modulated by age, comorbidity profile, and socioeconomic and geographic factors.

To facilitate clinical interpretation, we also generated a forest plot summarizing the adjusted hazard ratios for infertility associated with AUD across key subgroups in males and females (Fig. 2). Overall, AUD was consistently associated with an elevated risk of infertility in most strata, with relatively stronger associations observed among younger individuals and those with cardiometabolic or psychiatric comorbidities.

Kaplan-Meier analysis of infertility risk by AUD status

Figure 3 illustrates the Kaplan-Meier-based cumulative incidence curves (1 – KM) for infertility among patients with and without Alcohol Use Disorder (AUD), stratified by sex.

Among male patients, those with AUD showed a higher cumulative incidence of infertility than non-AUD controls over the follow-up period. The curves began to diverge early and continued to separate throughout follow-up, reaching an approximate cumulative incidence of 15% in the AUD group compared with 6% in the non-AUD group (log-rank $p < 0.001$).

In the female cohort, patients with AUD also exhibited a higher cumulative incidence of infertility compared with non-AUD controls. Over the follow-up period, the cumulative incidence increased steadily in both groups, with a greater absolute difference observed between AUD and non-AUD patients (log-rank $p < 0.001$).

These curves are presented for descriptive purposes only; adjusted effect estimates were derived from multivariable Cox proportional hazards models.

Discussion

This nationwide population-based cohort study provides robust evidence that AUD is independently associated with an elevated risk of infertility in both men and women, with differential effects across age, comorbidity profiles, socioeconomic status, and urbanization levels. By leveraging the longitudinal and comprehensive Taiwan NHIRD, this study offers the most extensive gender-stratified evidence to date on this topic.

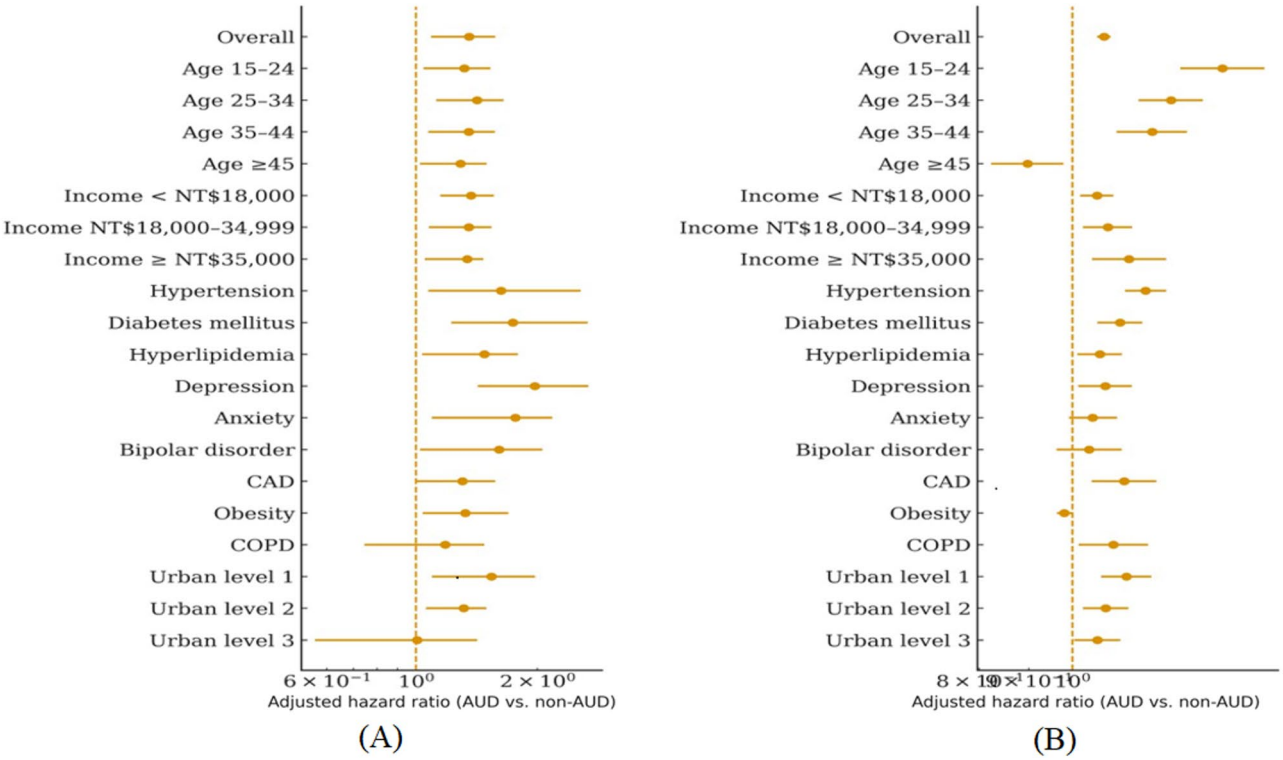

Fig. 2. Forest plots of adjusted hazard ratios for infertility associated with Alcohol Use Disorder (AUD). (**A**) Male and (**B**) female subgroup analyses. Points represent adjusted hazard ratios and horizontal lines denote 95% confidence intervals on a logarithmic scale. The vertical dashed line indicates the null value (HR = 1.0). Subgroups include age categories, income levels, cardiometabolic comorbidities, psychiatric comorbidities, obesity, COPD, and urbanization level. All models were adjusted for age, income, urbanization level, Charlson Comorbidity Index–Revised (CCI-R) score, hospital level, and geographic region, except when the variable was used as a stratification factor.

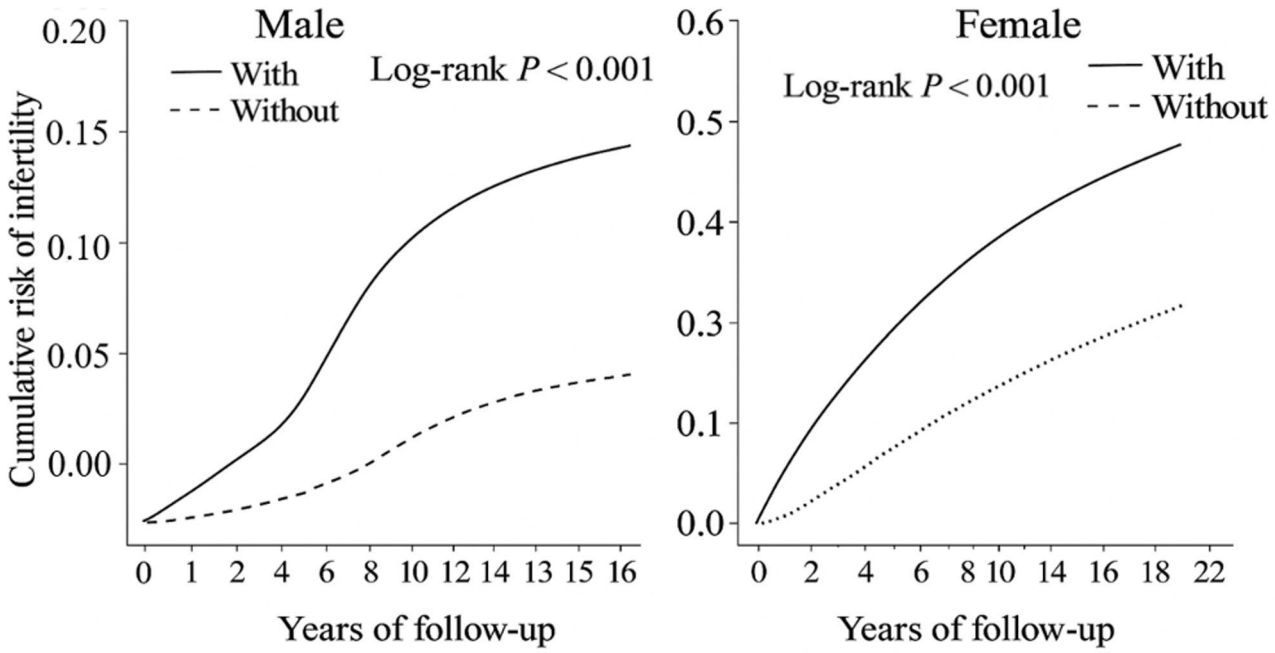

Fig. 3. Kaplan–Meier–based cumulative incidence curves (1 – KM) for infertility among patients with and without Alcohol Use Disorder (AUD), stratified by sex. The curves represent 1 – Kaplan–Meier estimates and were generated without smoothing or post-processing. They are shown for descriptive purposes only and do not account for covariate adjustment. Differences between groups were assessed using the log-rank test. The left panel shows male patients and the right panel female patients. Solid lines indicate patients with AUD, and dashed lines indicate matched controls without AUD.

Biological mechanisms and gender-specific differences

Our findings align with well-established pathophysiological mechanisms. Chronic alcohol use disrupts the hypothalamic–pituitary–gonadal (HPG) axis, leading to hormonal dysregulation, impaired gametogenesis, and oxidative damage to gonadal tissues[16–18]. In males, ethanol exposure has been shown to reduce testosterone levels, increase sperm DNA fragmentation, and impair spermatogenesis and sperm motility[19,20]. In females, alcohol disrupts folliculogenesis, ovulation, and endometrial receptivity, while also increasing miscarriage risk and impairing oocyte quality[21,22].

Our interaction analysis demonstrated that the effect of AUD on infertility is significantly modified by sex, with men showing a markedly stronger association. This finding supports the hypothesis that male reproductive physiology may be more vulnerable to alcohol-induced toxicity. Experimental research indicates that ethanol exposure more severely disrupts testosterone synthesis, Sertoli cell function, and spermatogenic epigenetic stability in men than corresponding ovarian pathways in women. Men also experience higher rates of alcohol-related oxidative stress and DNA fragmentation in germ cells, which may explain the larger risk elevation observed.

In contrast, although women with AUD exhibited increased infertility risk, the magnitude was smaller. Several factors may contribute, including differing patterns of alcohol metabolism, hormonal buffering effects in premenopausal women, and gender-specific healthcare-seeking behaviors that increase early detection among women. Together, these findings confirm a statistically significant and biologically plausible gender difference in the AUD–infertility association[23,24].

Psychosocial and behavioral pathways

Beyond biological factors, our study emphasizes the importance of psychosocial dimensions in understanding infertility risk in AUD populations. Individuals with AUD often experience poor nutrition, irregular sleep patterns, decreased physical activity, and reduced healthcare utilization—factors that are independently linked to reproductive dysfunction[25,26]. Moreover, psychiatric comorbidities, particularly depression and anxiety, were prevalent and significantly contributed to increased infertility risk, particularly among men.

Gender-based stigma may exacerbate underdiagnosis and undertreatment of infertility among women with AUD, especially in Asian societies where motherhood is idealized, and female substance use is socially condemned[27–30]. This may partially explain the sharper infertility gradient observed among younger women in urban settings, where both exposure and access to care may be elevated.

Alcohol-related infertility risk is also exacerbated by interpersonal violence, intimate relationship instability, and partner-level barriers to reproductive decision-making—factors commonly reported among individuals with AUD[31].

Cross-cultural comparisons and global consistency

Our results echo findings from multiple cross-cultural studies. For instance, recent cohort data from Denmark[28], South Korea[29], and the United States[30] demonstrate consistent inverse associations between alcohol consumption and reproductive outcomes, including fecundability, anti-Müllerian hormone (AMH) levels, and IVF success rates. This suggests that the adverse reproductive effects of alcohol are biologically consistent across ethnic and healthcare contexts.

Furthermore, global patterns of urbanization and endocrine disruptor exposure may act synergistically with alcohol-related pathways. Urban lifestyle factors—such as chronic stress, sedentary behavior, processed diets, and environmental toxins—have all been linked to reproductive dysfunction and may magnify the effects of AUD in metropolitan populations[32,33].

Public health and clinical implications

The clear association between AUD and infertility presents multiple opportunities for early intervention. Integrating fertility counseling and reproductive health assessment into addiction and psychiatric services may help reduce long-term reproductive complications. Routine screening for infertility symptoms and sexual dysfunction in AUD clinics—particularly for individuals of reproductive age—should be considered standard practice.

Public health messaging should also incorporate fertility preservation into alcohol harm reduction strategies, particularly targeting adolescents and young adults. Government policies that regulate alcohol marketing and availability may yield indirect benefits in protecting reproductive health, especially in high-risk populations.

At the systems level, infertility in AUD populations may serve as a sentinel marker of broader physical and mental health decline. Holistic models of care—encompassing psychiatric, reproductive, metabolic, and behavioral health—may yield synergistic outcomes and reduce the burden of alcohol-related chronic disease[34].

Strengths and limitations

This study contributes novel evidence to the literature in several ways. First, unlike earlier studies that relied on clinic-based or short-term data, our analysis used a nationwide longitudinal cohort with more than 20 years of follow-up, allowing assessment of cumulative infertility risk over the reproductive lifespan. Second, by evaluating males and females simultaneously, we were able to delineate sex-specific patterns in the association between AUD and infertility, which has not been examined in previous population-based studies. Third, our comprehensive subgroup analyses demonstrated differential vulnerability across socioeconomic and comorbidity strata, providing clinically relevant insights for risk identification that are absent in earlier work. Together, these elements distinguish the present study from prior research and extend current understanding of the long-term reproductive consequences of AUD.

Nevertheless, limitations should be acknowledged. First, a major methodological limitation arises from the restricted definition of Alcohol Use Disorder within the NHIRD. Because AUD was identified solely through ICD-9/10 diagnostic codes, we were unable to capture quantitative or qualitative drinking behaviors, including drinking volume, frequency, binge patterns, or temporal trajectories. This limited granularity introduces potential exposure misclassification and increases the likelihood of residual confounding, as key determinants of alcohol-related reproductive toxicity were unavailable for adjustment. These constraints indicate that the observed associations may underestimate the true effect of alcohol misuse on infertility. Second, another important limitation concerns the definition of infertility, which was identified only through ICD-based diagnostic codes. Clinical infertility assessment varies across clinicians, specialties, and healthcare settings, creating heterogeneity in outcome ascertainment. Underdiagnosis is especially likely among men, who often delay fertility evaluation or have limited access to reproductive services. Such nondifferential misclassification would attenuate effect estimates and suggests that our findings likely represent conservative estimates of the true association. Third, several essential reproductive and lifestyle-related confounders-including smoking status, body mass index, exercise level, sexual practices, and contraceptive use-were not available in the NHIRD. Because these factors are strongly associated with both alcohol use behaviors and fertility outcomes, their absence introduces the possibility of substantial residual confounding. Some of these unmeasured behaviors may also influence healthcare-seeking patterns, further compounding the underdiagnosis of infertility and potentially biasing results toward the null. Fourth, it is also important to interpret the magnitude of the observed associations with caution. The increased risk among women (aHR 1.079) is modest, and its clinical relevance on an individual level may be limited. The large sample size increases statistical power and may detect small effects. Nonetheless, even modest increases in risk may have meaningful implications at the population level, particularly given the high global prevalence of alcohol use and the cumulative nature of reproductive decline. Therefore, the findings should be viewed as statistical signals rather than evidence of a strong individual-level risk factor. Emerging literature suggests that infertility may be part of a broader constellation of chronic disease burden in patients with substance use disorders and multimorbidity[35]. Lastly, because cumulative incidence curves were unadjusted and descriptive, all effect estimates were derived exclusively from multivariable Cox regression models. Although minor deviations from proportionality were observed for some covariates, the primary exposure and interaction terms satisfied the proportional hazards assumption, and sensitivity analyses yielded consistent results, supporting the robustness of our findings.

The relationship between AUD and infertility is inherently multifactorial, involving biological, behavioral, psychological, and social mechanisms. As with all real-world administrative data analyses, residual confounding cannot be fully eliminated. Although direct measures of lifestyle behaviors such as smoking, body mass index, diet, and physical activity were unavailable, we adjusted for multiple upstream determinants and proxy variables strongly linked to these behaviors.

Importantly, this study was not designed to establish causality but to provide robust population-level evidence of association using longitudinal data. By explicitly adopting a DAG-guided confounder selection strategy and avoiding adjustment for potential mediators, we aimed to minimize bias while maintaining interpretability. Future studies integrating biomarker data, lifestyle surveys, or prospective designs are needed to further elucidate causal pathways.

Although follow-up cutoff years differed between male and female cohorts due to sex-specific data availability, time-to-event modeling and sensitivity analyses using a common follow-up window yielded consistent results. These findings suggest that differential calendar follow-up did not materially bias the observed associations. Future studies should incorporate biomarker-based assessments (e.g., hormone levels, semen analysis, AMH), prospective designs with validated lifestyle exposure data, and couple-linked datasets to better delineate the causal pathways and mediators in the AUD-infertility relationship.

Conclusions

In this nationwide population-based study, AUD was associated with an increased risk of infertility in both men and women of reproductive age. By applying formal interaction testing and sensitivity analyses with aligned follow-up periods, we found evidence that the strength of this association differs by sex. While the observational design and reliance on administrative data preclude causal inference, the consistency of findings across multiple analytical approaches supports the robustness of the observed sex-specific patterns. These results highlight the importance of incorporating reproductive health considerations into the clinical management of individuals with AUD and suggest that sex-specific perspectives may be relevant in future research and preventive strategies.

Data availability

The data that supports the findings of this study are available from the corresponding author upon reasonable request.

Received: 25 June 2025; Accepted: 31 December 2025
Published online: 06 January 2026

References

1. Mascarenhas, M. N., Flaxman, S. R., Boerma, T., Vanderpoel, S. & Stevens, G. A. National, regional, and global trends in infertility prevalence since 1990: A systematic analysis of 277 health surveys. *PLoS Med.* **9** (12), e1001356. https://doi.org/10.1371/journal.pmed.1001356 (2012).
2. Agarwal, A. et al. Male infertility. *Reprod. Biol. Endocrinol.* **19** (1), 1–9. https://doi.org/10.1186/s12958-020-00635-1 (2021).
3. Ricci, E. et al. Semen quality and alcohol intake: A systematic review and meta-analysis. *Reprod. Biol. Endocrinol.* **15** (1), 113. https://doi.org/10.1186/s12958-017-0325-1 (2017).
4. Sharma, R., Biedenharn, K. R., Fedor, J. M. & Agarwal, A. Lifestyle factors and reproductive health: taking control of your fertility. *Reprod. Biol. Endocrinol.* **17** (1), 70. https://doi.org/10.1186/s12958-019-0513-4 (2019).
5. Rehm, J. et al. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *Lancet* **373** (9682), 2223–2233. https://doi.org/10.1016/S0140-6736(09)60746-7 (2009).
6. Muthusami, K. R. & Chinnaswamy, P. Effect of chronic alcoholism on male fertility hormones and semen quality. *Fertil. Steril.* **84** (4), 919–924. https://doi.org/10.1016/j.fertnstert.2005.03.066 (2005).
7. Mäki, T., Mankonen, H., Lahti, L. & Tikkanen, M. Sperm DNA methylation alterations after alcohol consumption: an epigenetic basis for infertility? *Epigenomics* **14** (4), 255–268. https://doi.org/10.2217/epi-2021-0366 (2022).
8. Anderson, R. A., Brewster, D. H., Wood, R. & Elliot, P. Male reproductive health: research needs and therapeutic opportunities. *Hum. Fertil. (Camb).* **20** (1), 1–10. https://doi.org/10.1080/14647273.2016.1238574 (2017).
9. Polsky, S., Ghodsian, N. & Infertility Evaluation and management. *Obstet. Gynecol. Clin. North. Am.* **48** (1), 85–98. https://doi.org/10.1016/j.ogc.2020.09.004 (2021).
10. Guo, J., Wang, X., Gu, C., Han, C. & Liu, H. Risk factors for female infertility in china: A cross-sectional study. *Reprod. Health*. **19** (1), 110. https://doi.org/10.1186/s12978-022-01408-0 (2022).
11. Morales-Prieto, D. M., Paulesu, L. & Markert, U. R. Alcohol-induced reproductive dysfunction: new insights into HPG axis and gut–reproductive interactions. *Biomed. Pharmacother*. **162**, 114773. https://doi.org/10.1016/j.biopha.2023.114773 (2023).
12. Bajaj, J. S. & Fagan, A. Alcohol, the microbiome, and reproductive health: A growing triad. *Nat. Rev. Gastroenterol. Hepatol.* **18** (11), 733–748. https://doi.org/10.1038/s41575-021-00501-3 (2021).
13. Becker, J. B. & Koob, G. F. Sex differences in animal models: focus on addiction. *Pharmacol. Rev.* **68** (2), 242–263. https://doi.org/10.1124/pr.115.011163 (2016).
14. Wesselink, A. K. et al. Depression and anxiety as predictors of infertility in women and men: A prospective cohort study. *Fertil. Steril.* **116** (6), 1542–1551. https://doi.org/10.1016/j.fertnstert.2021.08.018 (2021).
15. Skalkidou, A., Tydén, T., Milsom, I. & Kallner, H. K. Limitations in infertility epidemiology: addressing methodological challenges. *Hum. Reprod. Update*. **29** (1), 3–15. https://doi.org/10.1093/humupd/dmac034 (2023).
16. Sharma, R. & Agarwal, A. Oxidative stress and male infertility: A review. *J. Assist. Reprod. Genet.* **38** (6), 1221–1231. https://doi.org/10.1007/s10815-021-02107-y (2021).
17. Mäki, T. et al. Sperm DNA methylation alterations after alcohol consumption: an epigenetic basis for infertility? *Epigenomics* **14** (4), 255–268. https://doi.org/10.2217/epi-2021-0366 (2022).
18. Morales-Prieto, D. M. et al. Alcohol-induced reproductive dysfunction: new insights into HPG axis and gut–reproductive interactions. *Biomed. Pharmacother*. **162**, 114773. https://doi.org/10.1016/j.biopha.2023.114773 (2023).
19. Di Marco, A. et al. Impact of alcohol on IVF outcomes: A systematic review and meta-analysis. *Hum. Reprod. Update*. **28** (3), 385–397. https://doi.org/10.1093/humupd/dmac002 (2022).
20. La Vignera, S. et al. Effects of alcohol on human reproduction. *Andrology* **8** (1), 165–173. https://doi.org/10.1111/andr.12667 (2020).
21. Liu, Y. et al. Alcohol consumption and risk of infertility: A systematic review and meta-analysis. *Reprod. Biomed. Online*. **44** (2), 291–308. https://doi.org/10.1016/j.rbmo.2021.11.006 (2022).
22. Grodstein, F. et al. Alcohol and fertility: biological insights. *Hum. Reprod. Update*. **29** (1), 17–31. https://doi.org/10.1093/humupd/dmac041 (2023).
23. Chen, L. et al. Sex differences in the gut–testis axis: role of microbiota in mediating alcohol-induced infertility. *Reprod. Toxicol.* **119**, 112–120. https://doi.org/10.1016/j.reprotox.2024.01.004 (2024).

24. Bajaj, J. S. & Fagan, A. Alcohol, the microbiome, and reproductive health: A growing triad. *Nat. Rev. Gastroenterol. Hepatol.* **18** (11), 733–748. https://doi.org/10.1038/s41575-021-00501-3 (2021).
25. Sughroue, J. R. et al. Behavioral correlates of substance use and infertility. *Subst. Abus.* **44** (1), 47–55. https://doi.org/10.1080/08897077.2022.2095623 (2023).
26. Cho, H. J. et al. Effects of alcohol use on sleep and endocrine disruption in reproductive-aged women. *J. Clin. Sleep. Med.* **18** (3), 857–865. https://doi.org/10.5664/jcsm.9864 (2022).
27. Rollè, L. et al. Stigma and help-seeking in women with substance use and reproductive health concerns. *BMC Public. Health.* **23**, 581. https://doi.org/10.1186/s12889-023-15274-7 (2023).
28. Wesselink, A. K. et al. Alcohol consumption and fecundability: A Danish prospective cohort study. *Am. J. Obstet. Gynecol.* **227** (5). https://doi.org/10.1016/j.ajog.2022.05.021 (2022). 755.e1–755.e9.
29. Kim, S. et al. Alcohol consumption and ovarian reserve in Korean women. *Clin. Endocrinol. (Oxf).* **98** (1), 35–42. https://doi.org/10.1111/cen.14726 (2023).
30. Patel, R. M. et al. Endocrine-disrupting chemicals and alcohol: A synergistic risk for reproductive dysfunction. *J. Endocrinol. Invest.* **46** (10), 2309–2319. https://doi.org/10.1007/s40618-023-02026-3 (2023).
31. Easton, C. J. & Crane, C. A. Intimate partner violence, alcohol use, and fertility-related outcomes. *J. Interpers. Violence.* **38** (3–4). https://doi.org/10.1177/08862605221075728 (2023). NP2027–NP2051.
32. Velez, M. P. et al. Chronic disease burden and infertility: Multimorbidity as a reproductive health determinant. *JAMA Netw. Open.* **6** (6), e2315982. https://doi.org/10.1001/jamanetworkopen.2023.15982 (2023).
33. Tiwari, A. et al. Alcohol-induced gonadal dysfunction: mechanisms and therapeutic prospects. *Toxicol. Lett.* **374**, 36–49. https://doi.org/10.1016/j.toxlet.2023.02.005 (2023).
34. Zhu, J. et al. Urbanization and reproductive health: A global review. *Lancet Planet. Health.* **5** (8), e512–e520. https://doi.org/10.1016/S2542-5196(21)00119-0 (2021).
35. Ferlin, A. et al. Impact of cardiometabolic risk on male infertility. *Front. Endocrinol. (Lausanne).* **10**, 873. https://doi.org/10.3389/fendo.2019.00873 (2019).

Acknowledgements

We appreciate the support from the Tri-Service General Hospital Research Foundation and the Medical Affairs Bureau, Ministry of Defense, Taiwan, ROC. We also appreciate the database provided by the Health and Welfare Data Science Center, Ministry of Health and Welfare (HWDC, MOHW).

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H.-T.T., T.-H.W., L.-Y. F., Y.-C.H., C.-T.T., C.-H.C., and W.-C.C.: conception and design, analysis and interpretation of the data, critical review, and approval of the final version submitted for publication. H.-T.T., T.-H.W., L.-Y. F., Y.-C.H., and W.-C.C.: statistical analysis, critical review, and approval of the final version submitted for publication. L.-Y. F., T.-H.W., Y.-C.H., C.-T.T., C.-H.C., and W.-C.C.: drafting of the paper, critical review, and approval of the final version submitted for publication. All authors have read and agreed to the published version of the manuscript.

Funding

This study was funded by the Tri-Service General Hospital, grant number: TSGH-A-115015, TSGH-B-115018, TSGH-A-114010, TSGH-B-114022, TSGH-D-114196.

Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

This study was conducted according to the Code of Ethics of the World Medical Association (Declaration of Helsinki). The Institutional Review Board of the Tri-Service General Hospital approved this study (TSGHIRB: E202516039) and waived the need for individual consent since all the identification data were encrypted in the NHIRD.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-34801-x.

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