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Association between Alcohol Abuse and Autoimmune Connective Tissue Diseases: Evidence from a National Cohort

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Abstract

Alcohol abuse is associated with dysregulated immune and inflammatory pathways, which may elevate the susceptibility to autoimmune connective tissue diseases (ACTDs). Nevertheless, evidence in Asian populations remains scarce. The present study was designed to explore this association and fill the existing research void. Data were obtained from Taiwan's National Health Insurance Research Database to identify all individuals diagnosed with alcohol abuse from 2000 to 2017. A comparison group without alcohol abuse was selected, matched by age, sex, and index date in a 3:1 ratio. Baseline comorbidities commonly linked to ACTD were recorded for adjustment. Follow-up continued in both groups until ACTD diagnosis or December 31, 2018.

The study enrolled 57,154 individuals with alcohol abuse and 171,462 without. Age and sex distributions were comparable, with males comprising 89.8% overall. Following adjustment for comorbidities, alcohol abuse was linked to an elevated ACTD risk [adjusted hazard ratio (AHR): 1.12, 95% confidence interval (CI): 1.01–1.25]. Subgroup analysis showed this association was confined to males. Furthermore, liver disease, renal disease, coronary artery disease, and chronic obstructive pulmonary disease emerged as independent risk factors for ACTD, in addition to alcohol abuse. Our findings indicate that alcohol abuse heightens the likelihood of ACTD development in Asians, especially in men. Consequently, promoting alcohol abstinence is particularly advisable for those with liver disease, renal disease, coronary artery disease, or chronic obstructive pulmonary disease.

Keywords: Alcohol abuse, Asian, Autoimmune connective tissue disease, Male, Taiwan

Introduction

Autoimmune connective tissue diseases (ACTDs) represent a heterogeneous collection of persistent inflammatory disorders that target multiple organ systems [1]. These conditions occur worldwide and impact all ethnic groups [2]. Peak incidence often falls in adolescence and young adulthood [2]. For mixed connective tissue disease, a particular subtype, annual rates generally range between 0.21 and 1.9 per 100,000 adults across nations [2]. ACTDs show marked female predominance [2], with reported female-to-male ratios varying from 3.3:1 to as high as 16:1 [2]. Their pathogenesis involves complex interactions among genetic predisposition, environmental triggers, and immune dysregulation [3]. Excessive alcohol intake has been proposed as one possible environmental contributor to ACTD onset [3].

Alcohol abuse constitutes a major global health burden, responsible for approximately 3.3 million deaths due to its detrimental effects in 2016 alone [4]. Beyond its established impact on hepatic, cardiovascular, and neurologic function, chronic heavy drinking disrupts

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immunity through changes in cytokine production and compromised immune cell activity [5, 6]. Such immune alterations have prompted questions about a potential role in autoimmune conditions.

Although growing research suggests a connection between alcohol use and autoimmune diseases, including ACTDs, results are inconsistent, and data specific to Asian cohorts are particularly limited. To bridge this gap, we performed a large-scale, population-based cohort study in Taiwan to assess ACTD risk in patients with alcohol abuse. This investigation seeks to clarify the relationship between alcohol abuse and ACTDs while providing insights into possible mechanistic pathways.

Materials and Methods

Data source

Information was drawn from Taiwan's National Health Insurance Research Database (NHIRD), which originates from the nation's mandatory single-payer health insurance system and encompasses nearly 99% of the country's 23 million residents [7]. The database includes records of inpatient and outpatient encounters, diagnostic codes, costs, and medication prescriptions [7]. Individual records are connected via encrypted personal identification numbers, enabling comprehensive tracking of healthcare utilization for each insured person [7].

Study design, setting, and participants

In Taiwan, alcohol abuse is classified as a disorder when it induces neurological alterations and leads to substantial physical and psychological consequences [8]. Such effects can manifest as hepatic disorders, cardiovascular conditions, neurological deficits, and mental health disturbances [8]. The severity of alcohol abuse among individuals presenting at medical facilities in Taiwan, similar to other areas, differs considerably based on the extent of the drinking problem, concurrent medical conditions, and overall life disruption [8]. In this investigation, alcohol abuse was defined using specific diagnostic codes from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) (291, 305.0, 303.0, 303.9, 357.5, 425.5, 535.3, 571.0–571.3, 655.4, or 760.71) or ICD-10 (F10.3–F10.9, F10.0, F10.1, F10.2, G62.1, G31.2, G72.1, I42.6, K29.2, K70–K70.4, K70.9, Q86.0, P04.3, O35.4, or K86.0). Individuals were categorized as having alcohol abuse if they were older than 20 years and had received at least one relevant ICD code during an inpatient admission. The exposed group included all adults over 20 years fulfilling these alcohol abuse criteria **(Figure 1)**. The index date was set as the initial diagnosis date of alcohol abuse. Using this index date, a non-exposed comparison group was formed by matching on age and sex in a 1:3 ratio. Participants with preexisting ACTD (ICD-9-CM 710, 714 or ICD-10 M30–M36) prior to the index date were removed from both groups.

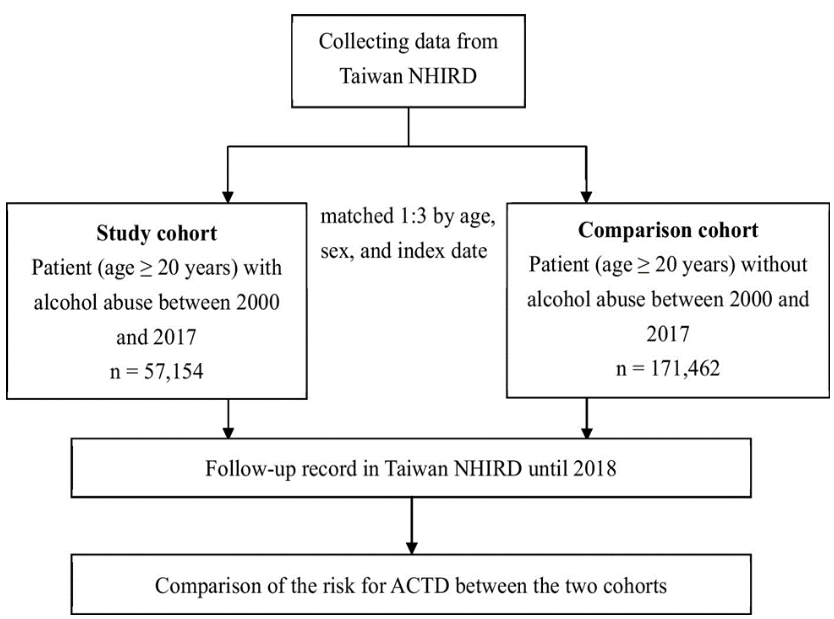

Figure 1. Flowchart of this study. NHIRD, National Health Insurance Research Database; ACTD, autoimmune connective tissue disease.

Definitions of variables

Participants were divided into four age categories: 20–34, 35–49, 50–64, and ≥65 years [9]. Baseline comorbidities were ascertained using the following codes: smoking (ICD-9-CM 305.1; ICD-10 Z72.0), diabetes (ICD-9-CM: 250; ICD-10 E08–E13), herpes zoster (ICD-9-CM: 053; ICD-10: B02), hepatitis (ICD-9-CM: 070; ICD-10: B15–B19), HIV infection (ICD-9-CM: 042, 079.53; ICD-10: B20–B24), liver disease (ICD-9-CM: 570–576; ICD-10: K70–K77), renal disease (ICD-9-CM: 580–593; ICD-10: N17–N19), malignancy (ICD-9-CM: 140–208; ICD-10: C00–C96, D00–D09), hypertension (ICD-9-CM: 401–405; ICD-10: I10–I16), hyperlipidemia (ICD-9-CM: 272; ICD-10: E78.5), coronary artery disease (CAD; ICD-9-CM: 410–414; ICD-10: I20–I25), congestive heart failure (CHF; ICD-9-CM: 428; ICD-10: I50), and chronic obstructive pulmonary disease (COPD; ICD-9-CM: 496; ICD-10: J44). Comorbidities were confirmed if diagnosed during at least one inpatient stay or across three ambulatory visits.

Outcome measures

The main endpoint was the occurrence of ACTD throughout the observation period. ACTD was confirmed via ICD-9-CM codes 710 or 714 or ICD-10-CM codes M30–M36 accompanied by at least one hospitalization. Follow-up for all subjects extended from the index date until ACTD onset, death, or December 31, 2018.

Ethical statements

This research adhered to the principles of the World Medical Association Declaration of Helsinki. Approval was granted by the Institutional Review Board of Chi-Mei Medical Center. Since NHIRD data are anonymized, the requirement for individual informed consent was exempted.

Statistical analyses

Differences in categorical and continuous variables between groups were evaluated using the Pearson chi-square test and independent t-test, respectively. To account for time-to-event data, univariate and multivariate Cox proportional hazards models were applied to determine ACTD risk in the alcohol abuse group versus the comparison group. Subgroup analyses stratified by age, sex, and comorbidities were conducted to assess possible interactions. Additional Cox regression models across the entire sample identified independent risk factors for ACTD. Analyses were carried out with SAS 9.4 for Windows (SAS Institute, Cary, NC, United States). Statistical significance was set at a two-tailed $p < 0.05$.

Results and Discussion

Patient characteristics

This investigation encompassed 57,154 cases with documented alcohol abuse alongside 171,462 cases free from such issues **(Table 1)**. The groups displayed comparable patterns in age and gender composition. The most common age bracket was 35–49 years (43.2%), then 50–64 years (34.6%), followed by 20–34 years (11.7%), and ≥65 years (10.5%). Males formed the bulk of participants in each group, making up 89.8% altogether. Individuals with alcohol abuse showed greater frequencies of smoking, hepatitis, and hepatic disorders compared to the control group. On the other hand, they presented lower occurrences of herpes zoster, HIV, kidney disorders, cancers, CAD, and COPD.

Table 1. Comparison of demographic characteristics and underlying comorbidities between alcohol abuse and non-alcohol abuse cohorts through univariate analysis.

Characteristic	No Alcohol Abuse (n = 171,462)	Alcohol Abuse (n = 57,154)	*p* value
Age group (years)			
20–34	19,983 (11.7%)	6,661 (11.7%)	>0.999
35–49	74,022 (43.2%)	24,674 (43.2%)	
50–64	59,385 (34.6%)	19,795 (34.6%)	
≥65	18,072 (10.5%)	6,024 (10.5%)	
Sex			
Women	17,439 (10.2%)	5,813 (10.2%)	>0.999
Men	154,023 (89.8%)	51,341 (89.8%)	
Baseline comorbid conditions			

Smoking	941 (0.6%)	367 (0.6%)	0.010
Diabetes mellitus	20,187 (11.8%)	6,729 (11.8%)	>0.999
Herpes zoster	958 (0.6%)	166 (0.3%)	<0.001
Hepatitis	6,855 (4.0%)	3,805 (6.7%)	<0.001
HIV infection	535 (0.3%)	85 (0.2%)	<0.001
Liver disease	14,606 (8.5%)	14,061 (24.6%)	<0.001
Renal disease	14,151 (8.3%)	2,948 (5.2%)	<0.001
Malignancy	13,705 (8.0%)	3,166 (5.5%)	<0.001
Hypertension	30,807 (18.0%)	10,269 (18.0%)	>0.999
Hyperlipidemia	12,315 (7.2%)	4,105 (7.2%)	>0.999
Coronary artery disease (CAD)	9,526 (5.6%)	1,862 (3.3%)	<0.001
Congestive heart failure (CHF)	2,759 (1.6%)	930 (1.6%)	0.766
Chronic obstructive pulmonary disease (COPD)	2,213 (1.3%)	562 (1.0%)	<0.001

Data are expressed as means ± SD or n (%). SD, standard deviation; HIV, human immunodeficiency virus; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; ACTD, autoimmune connective tissue disease.

Comparison of two cohorts: overall analysis and stratified analyses by age, sex, and underlying comorbidity

In the comprehensive evaluation, those affected by alcohol abuse demonstrated an amplified probability of ACTD emergence relative to the unaffected group, persisting after controlling for elements that varied markedly in initial assessments [adjusted hazard ratio (AHR): 1.12; 95% confidence interval (CI): 1.01–1.25, p = 0.037; **(Table 2)**]. Further breakdowns highlighted that the augmented ACTD probability tied to alcohol abuse appeared exclusively among males (AHR: 1.17; 95% CI: 1.03–1.32, p = 0.016). No noteworthy effects surfaced in alternative categories, encompassing females or subjects carrying the specified comorbid states.

Table 2. Comparison of ACTD risk between alcohol abuse and non-alcohol abuse cohorts: Cox proportional hazard regression analysis and stratified analyses by age, sex, and underlying comorbidity.

Variable	**Non–Alcohol Abuse**		**Alcohol Abuse**		**Adjusted HR† (95% CI)**	***p* value**	**Crude HR (95% CI)**	***p* value**
	Patients, n	ACTD, n (%)	Patients, n	ACTD, n (%)				
Overall population	171,462	1,538 (0.9)	57,154	506 (0.9)	1.12 (1.01–1.25)	0.037	1.14 (1.03–1.26)	0.012
Stratified analyses								
Age group (years)								
20–34	19,983	121 (0.6)	6,661	37 (0.6)	1.02 (0.69–1.51)	0.910	1.10 (0.76–1.61)	0.611
35–49	74,022	569 (0.8)	24,674	205 (0.8)	1.19 (1.00–1.41)	0.052	1.23 (1.04–1.45)	0.014
50–64	59,385	633 (1.1)	19,795	202 (1.0)	1.11 (0.94–1.32)	0.234	1.14 (0.97–1.35)	0.114
≥65	18,072	215 (1.2)	6,024	62 (1.0)	1.05 (0.76–1.45)	0.771	1.00 (0.74–1.35)	0.990
Sex								
Female	17,439	333 (1.9)	5,813	100 (1.7)	0.98 (0.77–1.25)	0.886	1.05 (0.84–1.32)	0.670

Male	154,023	1,205 (0.8)	51,341	406 (0.8)	1.16 (1.03–1.31)	0.016	1.18 (1.05–1.33)	0.005
Baseline comorbidities								
Smoking	941	9 (1.0)	367	6 (1.6)	–		–	
Diabetes mellitus	20,187	191 (1.0)	6,729	65 (1.0)	1.27 (0.93–1.74)	0.138	1.29 (0.95–1.74)	0.102
Herpes zoster	958	10 (1.0)	166	3 (1.8)	–		–	
Hepatitis	6,855	66 (1.0)	3,805	42 (1.1)	–		–	
HIV infection	535	4 (0.8)	85	0 (0.0)	–		–	
Liver disease	14,606	177 (1.2)	14,061	126 (0.9)	1.21 (0.73–2.00)	0.464	1.07 (0.67–1.72)	0.778
Renal disease	14,151	158 (1.1)	2,948	24 (0.8)	0.87 (0.27–2.84)	0.819	0.91 (0.33–2.53)	0.863
Malignancy	13,705	109 (0.8)	3,166	28 (0.9)	4.14 (0.17–103.37)	0.387	4.70 (0.52–42.78)	0.170
Hypertension	30,807	344 (1.1)	10,269	127 (1.2)	1.18 (0.94–1.48)	0.165	1.26 (1.02–1.56)	0.035
Hyperlipidemia	12,315	132 (1.1)	4,105	54 (1.3)	1.31 (0.92–1.86)	0.130	1.36 (0.98–1.88)	0.066
Coronary artery disease (CAD)	9,526	130 (1.4)	1,862	25 (1.3)	0.70 (0.22–2.18)	0.533	1.05 (0.45–2.46)	0.913
Congestive heart failure (CHF)	2,759	14 (0.5)	930	11 (1.2)	–		–	
Chronic obstructive pulmonary disease (COPD)	2,213	34 (1.5)	562	9 (1.6)	–		–	

ACTD, autoimmune connective tissue disease; HR, hazard ratio; CI, confidence interval; HIV, human immunodeficiency virus; AHR, adjusted hazard ratio; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease. *Adjusted for variables with a significant difference in the crude analysis.

Independent predictors of ACTD in all participants

Apart from alcohol abuse, distinct elements that autonomously forecasted heightened ACTD vulnerability involved hepatic disorders (AHR: 1.32; 95% CI: 1.12–1.56, p = 0.001), kidney disorders (AHR: 1.21; 95% CI: 1.00–1.47), CAD (AHR: 1.30; 95% CI: 1.04–1.62, p = 0.020), and COPD (AHR: 1.64; 95% CI: 1.08–2.49, p = 0.022; **(Table 3)**).

Table 3. Independent predictors of ACTD in all participants by a Cox proportional hazard regression analysis.

Variable	Total Patients, n	ACTD Cases, n (%)	Adjusted HR† (95% CI)	*p* value	Crude HR (95% CI)	*p* value	Variable	Total Patients, n
Study cohort							**Study cohort**	
Alcohol abuse	57,154	506 (0.9)	1.12 (1.01–1.25)	0.037	1.14 (1.03–1.26)	0.012	Alcohol abuse	57,154
No alcohol abuse	171,462	1,538 (0.9)	1.00 (reference)		1.00 (reference)		No alcohol abuse	171,462

Baseline comorbid conditions							Baseline comorbid conditions	
Smoking	1,308	15 (1.2)	–		1.37 (0.83–2.28)	0.221	Smoking	1,308
Herpes zoster	1,124	13 (1.2)	0.89 (0.46–1.71)	0.717	1.49 (0.86–2.56)	0.154	Herpes zoster	1,124
Hepatitis	10,660	108 (1.0)	1.20 (0.93–1.55)	0.165	1.46 (1.20–1.77)	<0.001	Hepatitis	10,660
HIV infection	620	4 (0.7)	–		0.79 (0.30–2.11)	0.643	HIV infection	620
Liver disease	28,667	303 (1.1)	1.32 (1.12–1.56)	0.001	1.53 (1.35–1.73)	<0.001	Liver disease	28,667
Renal disease	17,099	182 (1.1)	1.21 (1.00–1.47)	0.050	1.35 (1.16–1.57)	<0.001	Renal disease	17,099
Malignancy	16,871	137 (0.8)	1.12 (0.90–1.40)	0.297	1.47 (1.23–1.75)	<0.001	Malignancy	16,871
Coronary artery disease (CAD)	11,388	155 (1.4)	1.30 (1.04–1.62)	0.020	1.68 (1.43–1.98)	<0.001	Coronary artery disease (CAD)	11,388
Congestive heart failure (CHF)	3,689	25 (0.7)	–		1.01 (0.68–1.50)	0.950	Congestive heart failure (CHF)	3,689
Chronic obstructive pulmonary disease (COPD)	2,775	43 (1.6)	1.64 (1.08–2.49)	0.022	2.40 (1.78–3.25)	<0.001	Chronic obstructive pulmonary disease (COPD)	2,775

ACTD, autoimmune connective tissue disease; HR, hazard ratio; CI, confidence interval; HIV, human immunodeficiency virus; AHR, adjusted hazard ratio; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease. *Adjusted for variables with a significant difference in the crude analysis.

Our investigation revealed that individuals suffering from alcohol abuse faced a heightened likelihood of ACTD onset compared to those without, with this effect most pronounced in males. Moreover, independent risk factors for ACTD besides alcohol abuse encompassed hepatic disorders, kidney disorders, coronary artery disease, and chronic obstructive pulmonary disease.

Remarkably, the group with alcohol abuse initially showed reduced rates of several conditions—such as herpes zoster, HIV, kidney disorders, cancers, coronary artery disease, and chronic obstructive pulmonary disease—relative to the group without alcohol abuse **(Table 1)**. Examining prior research drawing on the NHIRD, Chen *et al*. recruited subjects with alcohol use disorder to assess mesenteric ischemia risk [10]. In their alcohol use disorder group, lower rates emerged for hyperlipidemia, stroke, ischemic heart disease, congestive heart failure, peripheral artery disease, and chronic obstructive pulmonary disease versus the control group [10]. Alcohol intake might influence treatment compliance for certain ongoing illnesses [11]. Here, we applied a stricter criterion (one inpatient admission or three ambulatory encounters with relevant ICD codes). As a result, inconsistent outpatient monitoring could contribute to underreporting of some conditions.

These outcomes align plausibly with alcohol's concentration-related influence on ACTD. Certain investigations link alcohol use to elevated autoimmune disease probability, whereas others indicate potential benefits from minimal consumption [12, 13]. A contemporary Danish analysis found greater ACTD incidence among those with alcoholic liver cirrhosis [adjusted incidence rate ratio (aIRR): 1.84; 95% CI: 1.60–2.12] [14]. Intriguingly, data point to alcohol's possible safeguarding role against disorders like autoimmune thyroiditis, systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis in both clinical and experimental settings [12, 15–17]. Nonetheless, alcohol exerts varied, organ-targeted, and gender-specific immunomodulatory impacts depending on intake levels [3]. It alters adaptive immunity based on dosage: sustained moderate drinking promotes T- and B-cell growth and activity, while prolonged excessive intake causes lymphocyte reduction, cell death, and elevated antibody levels [5, 18]. Heavy drinking also compromises intestinal integrity, fostering microbial imbalance that permits toxins, immunogens, and pathogens to enter circulation [19]. Such leakage could ignite or advance autoimmunity [20].

Gender disparities mark alcohol habits [21]. Cross-national data confirm males consume more, drink more often, and engage in riskier patterns than females [21]. In Taiwan specifically, regular drinking rates reach about 15.1% in men versus 2.6% in women [22]. Our analysis uncovered a distinctive pattern: the link between alcohol abuse and raised ACTD probability appeared solely in males, absent in females. This finding likely stems from gender variations in immunity, tissue susceptibility, reproductive factors, hormonal profiles, heredity, parental transmission, and epigenetic mechanisms [23]. Testosterone, for example, correlates with dampened immune responses and higher autoimmunity thresholds [5]. Chronic alcohol misuse lowers testosterone [24], potentially elevating male ACTD vulnerability. Males might also possess fewer baseline ACTD risks than females, rendering alcohol a more prominent trigger. Yet, evidence shows females experience stronger alcohol-induced shifts in inflammation and immunity [5], possibly due to differences in absorption, metabolism, and neural responsiveness [5]. Gender-specific ties between alcohol and ACTD demand additional scrutiny.

Key advantages of this work include its country-wide scope and substantial participant numbers. Limitations merit mention, however. Primarily, NHIRD lacks specifics on alcohol volume or patterns, risking unmeasured bias in results. Secondly, accurate socioeconomic details prove elusive; proxies like insurance category or premiums offer unreliable income indicators [25]. Thirdly, while linkage exists between alcohol abuse and ACTD, causality remains unproven amid intricate comorbid interplay. Fourthly, results may lack broad applicability owing to ethnic, cultural, healthcare, and genetic variations in alcohol effects across populations. Fifthly, reported smoking in the alcohol abuse group was minimal (0.6%), likely due to rigorous coding (one inpatient or three outpatient diagnoses via ICD-9-CM 305.1 or ICD-10 Z72.0), often capturing only cessation seekers. This could yield underestimation and non-differential bias across groups, though unlikely to alter core conclusions. Validation through multinational research is thus recommended.

Conclusion

This nationwide cohort analysis in Taiwan uncovered a significant connection between alcohol abuse and elevated ACTD probability within an Asian cohort, predominantly affecting males. Plausible explanations involve alcohol's dosage-sensitive immunomodulation. Results highlight the need for targeted abstinence initiatives, community health strategies, and behavioral changes to curb ACTD, particularly among those with hepatic, renal, coronary artery, or pulmonary obstructive conditions. The precise basis for greater male susceptibility remains elusive. Upcoming research should incorporate granular drinking data, cross-population confirmation, and deeper gender analyses to reinforce and extend these observations.

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