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Association between abdominal aortic aneurysms and alcohol-related diseases

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Abstract

Heterogeneous associations exist between alcohol consumption and the initial presentation of cardiovascular diseases (CVDs). Studies regarding the association between abdominal aortic aneurysms (AAAs) and alcohol consumption are still limited and controversial. We hypothesize that patients with alcohol-related diseases are susceptible to AAA formation due to the presence of overlapping epidemiological factors and molecular mechanisms. We aimed to use a nationwide population-based retrospective cohort study to evaluate the association between alcohol-related diseases and AAA.

The data were extracted from the National Health Insurance Research Database (NHIRD) in Taiwan. The study outcome assessed was the cumulative incidence of AAA in patients with alcohol-related diseases during a 14-year follow-up period.

Our study included 22,878 patients who had alcohol-related diseases; these patients with alcohol-related diseases had a significantly higher cumulative risk of developing AAA 5 years after the index date than did the 91,512 patients without alcohol-related diseases. Patients with alcohol-related diseases also exhibited a significantly increased incidence of AAA compared with the incidence among patients without alcohol-related diseases, according to Cox regression analysis and Fine & Gray's competing risk model (adjusted hazard ratio = 2.379, 95% confidence interval = 1.653 -3.424, $P < .001$). In addition, male gender, older age, and chronic kidney disease were also associated with an increased risk of developing AAA. An interaction model showed that males with alcohol-related diseases had a 10.4-fold higher risk of AAA than did females without alcohol-related diseases.

We observed an association between alcohol-related diseases and AAA even after adjusting for several comorbidities and medications in a nationwide population database.

Abbreviations: AAA = abdominal aortic aneurysm, ALDH2 = acetaldehyde dehydrogenase, CIs = confidence intervals, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, CVDs = cardiovascular diseases, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical, LHID = Longitudinal Health Insurance Database, MMPs = matrix metalloproteinases, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database.

Keywords: abdominal aortic aneurysm, alcohol, alcohol related diseases, national health insurance research database

1. Introduction

Heterogeneous associations exist between the level of alcohol consumption and the initial presentation of cardiovascular diseases (CVDs).[1] Previous studies indicated that low to moderate levels of alcohol consumption could reduce the risk of most CVDs. Studies regarding the association between abdominal aortic aneurysms (AAAs) and alcohol consumption are still limited, with controversial results. Although some studies indicated that low to moderate levels of alcohol consumption were associated with reduced mortality due to aortic disease and a smaller abdominal aortic diameter,[2,3] other studies revealed that alcohol consumption is also

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Wu-Chien Chien and Shih-Hung Tsai contributed equally to this work.

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a risk factor for the development of and mortality due to AAA.[4–6]

It could be speculated that those who have alcohol-related diseases either have been exposed to a greater amount of alcohol or are more susceptible to alcohol than are those without alcohol-related diseases. Studies regarding alcohol consumption generally rely on self-report questionnaires.[7] There are significant differences in alcohol tolerance due to different genetic backgrounds.[8] Specifically, whether alcohol-related diseases are associated with AAA remains unanswered. We hypothesize that patients who develop alcohol-related diseases are susceptible to the formation of AAA due to the presence of overlapping epidemiological factors and molecular mechanisms.

For the purpose of testing this hypothesis, we used the National Health Insurance Research Database (NHIRD) to evaluate whether associations exist between alcohol-related diseases and AAA.

2. Methods

2.1. Data source

The National Health Insurance (NHI) Program was launched in Taiwan in 1995. It includes more than 99% of the entire Taiwanese population (more than 23 million beneficiaries). The NHIRD contains encrypted patient identification numbers, birthdays, genders, dates of admission and discharge, ICD-9-CM (International Classification of Diseases, 9th Revision, Clinical Modification) diagnostic and procedure codes (up to 5 each), and outcomes. The data we used were from the Longitudinal Health Insurance Database 2005 (LHID 2005), which is a subset of the NHIRD. The LHID 2005 contains information on the medical service utilization of approximately 1 million randomly selected beneficiaries, representing approximately 5% of the population in Taiwan in 2005. Information from 2000 to 2013 was extracted from the NHIRD. The NHI Administration randomly reviews the medical records periodically to verify the accuracy of the diagnoses. The accuracy of the diagnoses of major diseases in the NHIRD, such as acute coronary syndrome, stroke, aortic aneurysm, and aortic dissection, has been validated in previous studies.[9–11] This study was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). This study was approved by the Institutional Review Board of Tri-Service General Hospital at the National Defense Medical Center in Taipei, Taiwan, which waived the need for individual consent because all the identifying data were encrypted.

2.2. Sampled patients

Study and comparison cohorts were included. Patients in the LHID 2005 database aged ≥20 years who were newly diagnosed with alcohol-related morbidities such as alcoholic psychosis (ICD-9-CM 291), alcohol abuse (ICD-9-CM 303.0, 305.0), alcohol dependence syndrome (ICD-9-CM 303.9), alcohol polyneuropathy (ICD-9-CM 357.5), alcohol cardiomyopathy (ICD-9-CM 425.5), alcoholic gastritis (ICD-9-CM 535.3), alcoholic liver disease (ICD-9-CM 571.0–571.3), fetal alcohol syndrome (ICD-9-CM 655.4, 760.71), and accidental poisoning by alcoholic beverages (ICD-9-CM E860.0) after 2005 and followed up between 2000 and 2013 were used to estimate the incidence of alcohol-related diseases as previously mentioned in the "Chronic Causes" of "Alcohol-Related ICD Codes" by the Centers for Disease Control and Prevention (https://nccd.cdc.gov/DPH_ARDI/Info/ICDCodes.aspx) and as previously described in the literature.[12,13] AAA was identified using the codes ICD-9-CM 441.3–441.7 (abdominal aortic aneurysm and thoracoabdominal aortic aneurysm, with or without rupture) during the study period. We excluded patients who had been diagnosed with alcohol-related disorders, who were aged <20 years, who had a follow-up duration of less than 6 months, and who had AAA before the index date. The date of the diagnosis of an alcohol-related disease was used as the index date. Control patients were selected from individuals in the LHID 2005. The patient and control cohorts were selected by 1:4 matching according to baseline variables, namely, age; gender; comorbidities, including cancer (ICD-9-CM 140–208), diabetes mellitus (ICD-9-CM 250), hyperlipidemia (ICD-9-CM 272.0–272.4), hypertension (ICD-9-CM 401–405), atrial fibrillation (ICD-9-CM 427.31), coronary artery disease (ICD-9-CM 410–414), heart failure (ICD-9-CM 428), intracerebral hemorrhage (ICD-9-CM 430, 431, 432.9), ischemic stroke (ICD-9-CM 433–434, 436, 437.1), chronic obstructive pulmonary disease (COPD, ICD-9-CM 490–496), chronic kidney disease (CKD, ICD-9-CM 580–589), and the number of medical visits. The outcome that was evaluated in this study was the diagnosis of AAA.

2.3. Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics 22.0 (IBM Corp., released 2013, IBM SPSS Statistics for Windows, version 22.0. Armonk, NY). The clinical characteristics of the patients enrolled in the study are expressed in numerical form. Categorical variables, which are presented as percentages, were compared using Fisher exact test and Chi-squared tests. Continuous variables are presented as the means and standard deviations and were compared using *t* tests. The primary goal of the study was to determine whether the clinical characteristics of patients were associated with the development of AAA. Fine and Gray's survival analysis and regression analysis were used to determine the risk of AAA (competing with mortality), and the results are presented as the hazard ratio (HR) with the associated 95% confidence interval (95% CI). Associations between time-to-event outcomes (prognoses) and clinical characteristics were examined using the Kaplan–Meier method and multivariate Cox regression analysis with stepwise selection. The results are presented as adjusted HRs with the corresponding 95% CI. Statistical significance was indicated by $P < .05$.

2.4. Patient involvement

This study did not involve the collection of data that could identify patients, but this research was reviewed, and access to data was approved by the Institutional Review Board of Tri-Service General Hospital at the National Defense Medical Center in Taipei, Taiwan.

3. Results

Among the total of 987,403 patients in the LHID 2005 from the NHIRD, 25,549 patients were identified as having been diagnosed with alcohol-related diseases. In total, 22,878 patients were then assigned to the study cohort, and another 91,512 age-, gender-, and comorbidity-matched patients formed the comparison cohort (Fig. 1). There were no significant differences in

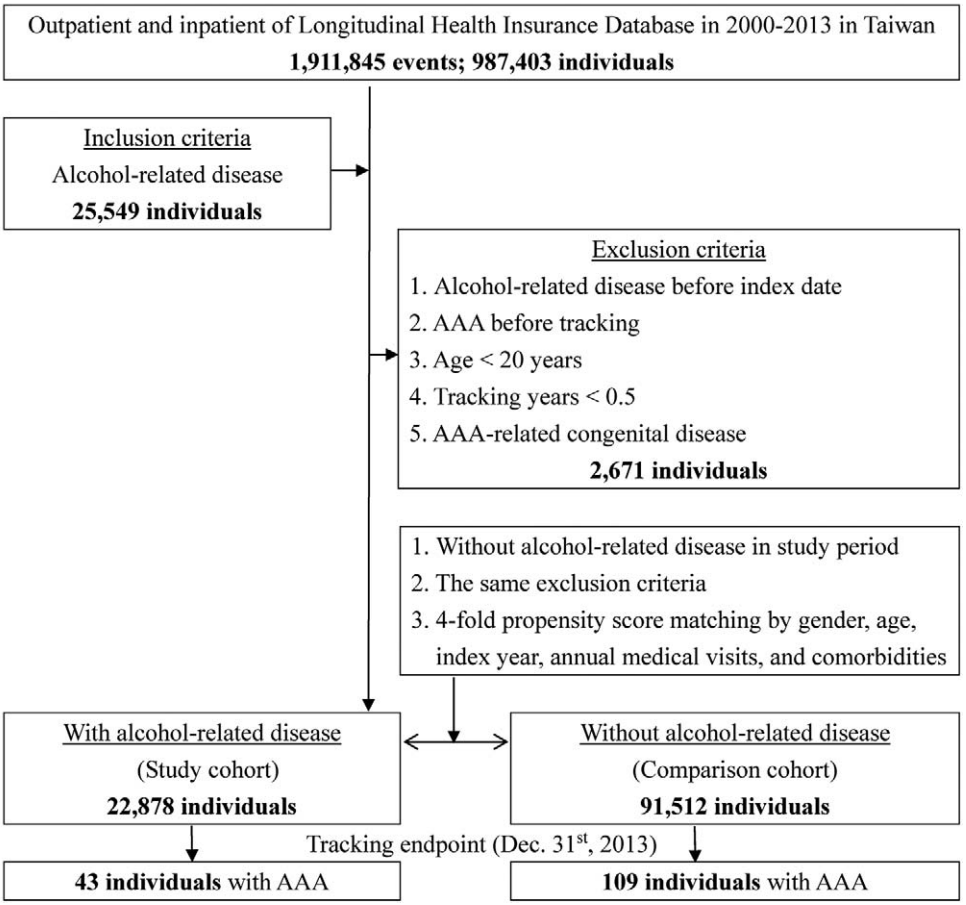

Figure 1. Patient selection flowchart.

gender, age, comorbidities, or the number of medical follow-up visits between the groups with and without alcohol-related diseases after matching (Table 1).

Compared with patients without alcohol-related diseases, patients who had alcohol-related diseases had a significantly higher cumulative risk of developing AAA 5 years after the index

Table 1

Characteristics of the study participants at the baseline.

	Total N (%)	Alcohol related diseases with N (%)	Without N (%)	*P*
Total	114,390	22,878 (20%)	91,512 (80%)	
Gender				.999
Male	105,890 (92.57%)	21,178 (92.57%)	84,712 (92.57%)	
Female	8500 (7.43%)	1700 (7.43%)	6800 (7.43%)	
Age, yr	46.01 ± 13.53	45.91 ± 12.38	46.04±13.80	.194
Hypertension	9084 (7.94%)	1819 (7.95%)	7265 (7.94%)	.224
Hyperlipidemia	6309 (5.52%)	1277 (5.58%)	5,032 (5.50%)	.623
COPD	4041 (3.53%)	809 (3.54%)	3232 (3.53%)	.974
DM	13,564 (11.86%)	2766 (12.09%)	10,798 (11.80%)	.224
Malignancy	5378 (4.70%)	1083 (4.73%)	4295 (4.69%)	.283
CKD	3345 (2.92%)	644 (2.81%)	2701 (2.95%)	.283
Ischemic stroke	1766 (1.54%)	368 (1.61%)	1398 (1.53%)	.375
Intracerebral hemorrhage	1059 (0.93%)	210 (0.92%)	849 (0.93%)	.905
CAD	3399 (2.97%)	698 (3.05%)	2701 (2.95%)	.428
AF	728 (0.64%)	130 (0.57%)	598 (0.65%)	.151
HF	1306 (1.14%)	237 (1.04%)	1069 (1.17%)	.096
Annual medical visiting	6.99±7.79	7.06±9.99	6.97±7.14	.118

P value (category variable: Chi-square/Fisher exact test; continue variable: *t* test).

AF = atrial fibrillation; CAD = coronary artery disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; HF = heart failure.

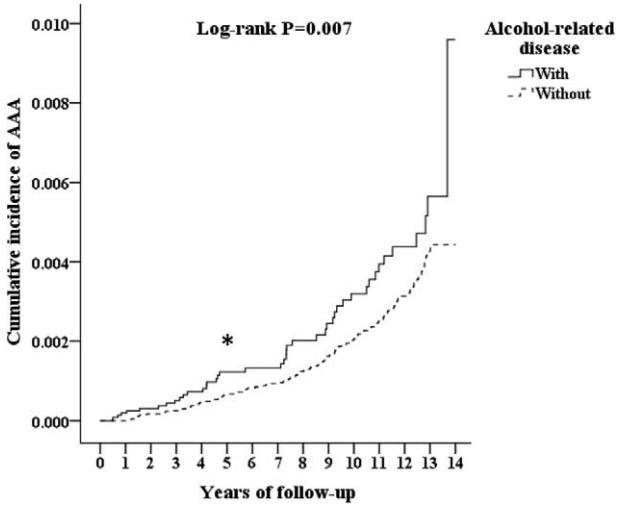

Figure 2. Kaplan–Meier curve of the cumulative risk of abdominal aortic aneurysms due to alcohol-related diseases.

date (log-rank test $P = .007$, Fig. 2). At the end of the 14-year follow-up period, significantly higher incidences of AAA (0.19% vs 0.12%, $P = .013$) and several comorbidities were observed in patients with alcohol-related diseases than in those without those diseases (Table 2). Furthermore, patients with alcohol-related diseases also exhibited a significantly increased incidence of AAA than did patients without alcohol-related diseases, according to Cox regression analysis and Fine & Gray's competing risk model (adjusted HR = 2.379, 95% CI = 1.653–3.424, $P < .001$ Table 3). In addition, male gender (adjusted HR = 5.111, 95% CI = 1.627–16.051, $P = .005$), older age (adjusted HR = 1.078, 95% CI = 1.064–1.091, $P < .001$), and CKD (adjusted HR = 2.137, 95% CI = 1.302–3.509, $P < .001$) were also associated with an increased risk of the development of AAA. Because the most prominent risk factors were male sex and alcohol-related diseases, an interaction model was employed. The results showed that males with alcohol-related diseases had a 10.4-fold increased risk of AAA compared with that of females without alcohol-related diseases (Fig. 3).

4. Discussion

In this population-based study in a nationwide dataset, we revealed that alcohol-related diseases were associated with nearly 2.4-fold increased incidence of AAA, even after adjusting for age, gender, and comorbidities.

The period of exposure to alcohol, the amount of alcohol, and the types of alcohol could have substantial effects on the development of alcohol-related diseases. It can be speculated that those with alcohol-related diseases either were exposed to a greater amount of alcohol or are more susceptible to alcohol than are those without alcohol-related diseases. The definition used for the amount of alcohol consumed could not be generalized. The self-reported amount of alcohol consumed could be significantly biased.[7,14] In addition, the susceptibility to alcohol-related disease also differs based on the individual's genetic background. A single point mutation at E487K in ALDH2 in East Asians known as ALDH2*2 intrinsically reduced the level of antioxidative stress and detoxification activity of ALDH2.[15] The presence of the inactive ALDH2*2 variant affects approximately 40% of East Asians. The rs671 polymorphism of ALDH2*2 is associated with vascular inflammation and increased incidence rates of coronary artery diseases in Han Chinese individuals.[16,17] Therefore, in this study, we specifically identified individuals with alcohol-related diseases to study the association between alcohol consumption and AAA.

There are overlapping risk factors and underlying molecular mechanisms for both alcohol-related diseases and AAA. The reported risk factors for the development of AAA are age, male gender, smoking, hypertension, body mass index, hyperlipidemia, and family history.[18][19] Alcohol consumption is usually associated with an elevated body mass index and smoking.[20] Increased alcohol consumption not only increases the risk of cirrhosis but also enhances the risk of hypertension, heart

Table 2

Incidences of abdominal aortic aneurysms and other characteristics during the 13-yr follow-up period.

	Total N (%)	Alcohol related diseases with N (%)	Without N (%)	*P*
Total	114,390	22,878 (20.00%)	91,512 (80.00%)	
AAA	152 (0.13%)	43 (0.19%)	109 (0.12%)	.013*
Gender				.999
Male	105,890 (92.57%)	21,178 (92.57%)	84,712 (92.57%)	
Female	8500 (7.43%)	1700 (7.43%)	6800 (7.43%)	
Age, yr	51.75 ± 14.78	51.74 ± 15.22	51.80 ± 12.85	.585
Hypertension	16,024 (14.01%)	2285 (9.99%)	13,739 (15.01%)	<.001*
Hyperlipidemia	3437 (3.00%)	523 (2.29%)	2914 (3.18%)	<.001*
COPD	5,531 (4.84%)	1022 (4.47%)	4509 (4.93%)	.004*
DM	14,902 (13.03%)	3945 (17.24%)	10,957 (11.97%)	<.001*
Malignancy	14,520 (12.69%)	3853 (16.84%)	10,667 (11.66%)	<.001*
CKD	6615 (5.78%)	1940 (8.48%)	4675 (5.11%)	<.001*
Ischemic stroke	2577 (2.25%)	411 (1.80%)	2166 (2.37%)	<.001*
Intracerebral hemorrhage	1633 (1.43%)	478 (2.09%)	1155 (1.26%)	<.001*
CAD	7356 (6.43%)	887 (3.88%)	6469 (7.07%)	<.001*
AF	1256 (1.10%)	208 (0.91%)	1048 (1.15%)	.002*
HF	2995 (2.62%)	516 (2.26%)	2479 (2.71%)	<.001*

AAA = abdominal aortic aneurysm; AF = atrial fibrillation; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; CKD = chronic kidney disease; CAD = coronary artery disease; HF = heart failure.
* *P* values < .05 were considered statistically significant.

Table 3

Factors associated with abdominal aortic aneurysms according to the Cox regression and Fine and Gray's competing risk model.

Variables	Crude HR	95% CI	P	Adjusted HR	95% CI	P
Alcohol-related diseases	1.262	1.08–1.990	.032	2.379	1.653–3.424	<.001*
Male	4.002	0.99–16.229	.052	5.111	1.627–16.051	.005*
Age (years)	1.081	1.07–1.097	<.001	1.078	1.064–1.091	<.001*
Hypertension	2.139	1.436–3.186	<.001	1.587	1.120–2.251	.009*
Hyperlipidemia	1.743	0.875–3.471	.114	1.078	0.526–2.210	.838
COPD	1.613	0.839–3.100	.152	0.611	0.335–1.116	.109
DM	0.597	0.338–1.045	.071	0.366	0.219–0.612	<.001*
Malignancy	0.724	0.368–1.424	.350	0.524	0.287–0.954	.035*
CKD	2.012	1.056–3.833	.034	2.137	1.302–3.509	<.001*
Ischemic stroke	2.107	0.923–4.808	.077	1.890	1.028–3.476	.040*
Intracerebral hemorrhage	0.922	0.127–6.680	.936	0.596	0.083–4.287	.607
CAD	2.241	1.373–3.658	.001	1.355	0.848–2.103	.212
AF	1.083	0.267–4.390	.912	0.924	0.372–2.294	.865
HF	1.707	0.745–3.910	.206	0.947	0.470–1.907	.878

AAA = abdominal aortic aneurysm; AF = atrial fibrillation; HF = heart failure; CAD = coronary artery disease; CKD = Chronic kidney disease; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus.

* *P* values < .05 were considered statistically significant.

diseases, and hyperlipidemia.[21,22] We controlled for certain comorbidities, such as hypertension and COPD (used as a surrogate for smoking), in the current study. The effect of alcohol on AAA may be mediated through the ability of alcohol at higher levels of consumption to raise blood pressure.[20] Inflammatory factors, oxidative stress, and matrix metalloproteinases (MMPs) are enriched in the aneurysmal vascular wall.[23,24] High levels of alcohol have been shown to upregulate MMPs in the aorta and kidneys in rats.[25,26] The associations between alcohol consumption and doses and the incidence of AAA are still controversial. A moderate level of alcohol consumption, specifically the consumption of wine and beer, is associated with a smaller aortic diameter and a reduced risk of AAA.[3,27] Low to moderate levels of alcohol consumption are also associated with reduced mortality from aortic disease among Japanese men.[2] Alcohol consumption was nonetheless a reported risk factor for the development of AAA in a meta-analysis study and in a Korean population study.[5,6] In a meta-analysis, although lower levels of alcohol consumption appeared to be associated with a lower risk of AAA, the risk of AAA appeared to increase with increasing alcohol consumption after the threshold of approximately 15 to 20 g/day was reached.[4] The consumption of liquor demonstrated the strongest positive association with AAA.[7] There was a positive association between infrarenal aortic diameters and high levels of alcohol consumption.[28] Our results were consistent with those of previous studies regarding the development of alcohol-related diseases that were associated with subsequent AAA events.

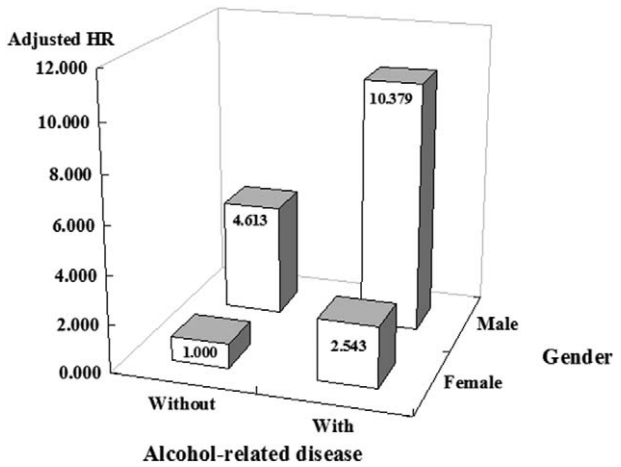

Figure 3. Interaction model of the risk of AAA due to male sex and alcohol-related diseases.

Consistent with the findings of previous studies, in this study, we found that males were more susceptible than females were to AAA once the daily level of alcohol consumption was greater than 2 units.[4] In this study, we also found that male patients with alcohol-related diseases have a 10-fold increased risk of AAA compared with that of female patients, even after adjusting for the number of medical visits. No evidence has suggested that commonly used cardiovascular medications, including calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and statins, can effectively limit the progression of AAA.[29] The usual threshold for elective AAA repair is an aortic diameter of 5.5 cm in men and 5.0 cm in women. Repair should be considered for an AAA with a growth rate exceeding 0.5 cm in diameter over a period of 6 months, regardless of its absolute size.[18,30] We therefore propose that male patients with alcohol-related disease should undergo additional screening examinations for AAA.

4.1. Limitations

Although we extensively adjusted our results by utilizing multivariate logistic regression models, there may still be residual confounders. The NHIRD registry does not provide detailed information regarding family histories, health-related lifestyle factors, and imaging and laboratory results, which may represent potential confounding factors. The estimated amount of alcohol and the types of alcoholic beverages consumed could not be verified in this NHIRD-based study. Compared with beer and liquor, wine might be associated with a lower risk of alcoholic cirrhosis.[22] The genetic background of the subjects, such as the presence of ALDH2*2, could not be obtained. Because smoking is a crucial risk factor for AAA, COPD incidence was used as a proxy variable for tobacco use to neutralize its potential

confounding effect, as previously described.[31] There are clear and distinct pathophysiological differences between thoracic aortic aneurysms and AAA,[32] and we did not evaluate other aneurysmal diseases in this study. We aware that using the ICD-9-CM codes to identify AAA and alcohol-related diseases could result in bias. Previous studies have provided varying degrees of validation with regard to the use of these codes for the diagnosis of aortic aneurysms, cirrhosis of the liver, and alcohol dependence syndrome that were relevant to the current study; however, validation is still lacking for some alcohol-related diseases.[10,33,34]

5. Conclusion

We observed an association between the development of alcohol-related diseases and AAA even after adjusting for several comorbidities and medications in a nationwide population database.

Author contributions

J-CW and S-HT conceived of and designed the study. W-CC and C-HC provided materials and analyzed the data for the study. N-ST interpreted the data and critically revised the manuscript. All of the authors collected and interpreted the data and wrote and approved the paper.

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