

# BMJ Open Risk of aortic dissection or aneurysm in patients with gallstone disease: a retrospective cohort study in Taiwan

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## ABSTRACT

**Objective** This nationwide population-based cohort study was to compare the risk of aortic dissection (AD) or aortic aneurysm (AN) between the subjects with and without gallstone disease (GD). We also compare the risk of AD/AN between the patients with GD with and without cholecystectomy.

**Setting** This nationwide population-based cohort study.

**Participants** We extracted the hospitalisation database from the National Health Insurance Research Database of Taiwan and identified a total of 343 300 patients aged  $\geq 20$  years with GD newly diagnosed between 2000 and 2010 as the study cohort, including 191 111 with cholecystectomy and 152 189 without cholecystectomy, respectively. We randomly selected those without GD as the control cohort, by 1:1 propensity score matching with the study cohort based on age, sex, comorbidities and year of the index date for GD diagnosis.

**Results** The incidence of AD/AN was 6.65/10 000 person-years for the GD cohort and 6.24/10 000 person-years for the non-GD cohort (adjusted HR (aHR)=1.11, 95% CI=1.09 to 1.13), respectively ( $p<0.001$ ). Furthermore, the incidence of AD/AN in the patients with GD was 9.93/10 000 person-years for the non-cholecystectomy patients (aHR=1.24, 95% CI=1.22 to 1.26) and 4.63/10 000 person-years for the cholecystectomy patients (aHR=0.97, 95% CI=0.95 to 0.99), respectively ( $p<0.05$ ).

**Conclusions** The GD cohort was associated with and greater risk of AD/AN than the non-GD cohort, but the risk of AD/AN in the patients with GD would decrease after cholecystectomy.

## INTRODUCTION

Aortic aneurysm (AN) is per definition a localised increase of the diameter  $>50\%$ , and the risk of dissection increases with incremental diameter to reach a mortality of 50%–80%.<sup>1</sup> The lethal aortic dissection (AD) results from bleeding within the disrupted aortic wall.<sup>2</sup> The reported prevalence of AN is lower in Asia than in Western countries.<sup>3–6</sup> However, the incidence of AN in Taiwan has steadily increased from 6.46/100 000 persons in 2005 to 8.25/100 000 persons in 2011.<sup>7</sup> Furthermore, with an average annual incidence of 5.6/100 000 persons, the incidence of AD in Taiwan has gradually increased between 2005

## Strengths and limitations of this study

- The National Health Insurance programme is a mandatory and single-payer healthcare system with a coverage of almost every resident in Taiwan (99.6%); therefore, the findings of this study with a 12-year-long follow-up provides the generalisability in Taiwan.
- Comparing the risk of aortic dissection or aneurysm between the gallstones patients with and without cholecystectomy, rather than between cholecystectomy and general population, mitigates the misclassification of asymptomatic gallstones into general population.
- This study is subject to the limited information on lifestyle and dietary habits.
- This observatory study cannot ascertain the protective mechanisms of cholecystectomy against the development of aortic dissection or aneurysm.

and 2011.<sup>8</sup> With an average annual mortality of 2/100 000 persons, the mortality of abdominal AD in Taiwan has significantly increased between 2005 and 2011.<sup>4</sup> Without gender bias in the rupture and operative rates, the reported territory-wide operative mortality rates for intact and ruptured aneurysms were 10% (4%–24%) and 70% (38%–100%), respectively. In general, the overall mortality was 17% for intact Abdominal Aortic Aneurysm (AAAs) and 78% for ruptured AAAs.<sup>4</sup> The reported incidence and mortality of AD/AN is actually expected to increase further due to increasing utilisation of CT and increasing prevalence of the elderly. AD/AN will cast a heavy burden on medical expenditures and substantial disabilities on the patients' life. Therefore, it is important to identify the associated factors and to adopt feasible strategies for preventing this life-threatening disease.

The reported prevalence of gallstone disease (GD) in Taiwan is about 5% based on our former community study.<sup>9</sup> With increasing prevalence of the elderly, sedentary lifestyle and metabolic disorders, GD is well known as one of the most common



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gastrointestinal tract disorders globally. Cholecystectomy for GD is clinically indicated for biliary complications and the reported annual complication rate of GD is only 1%–2%.<sup>10–12</sup> There are several studies on the association between GD and cardiovascular disease (CVD).<sup>13–15</sup> Cholesterol accumulation, oxidative stress, dysbiosis and genetic polymorphism for cholesterol metabolism have been shown to be the possible pathogenic mechanisms for the linkage between GD and CVD.<sup>16–20</sup>

The possible pathogenic mechanisms for AD/AN is similar to that of CVD, such as inflammation, degradation of extracellular matrix and apoptosis of vascular smooth muscle cell.<sup>21–23</sup> GD has been shown positively related to abdominopelvic atherosclerosis,<sup>24</sup> and it can be found in 5%–20% of patients with an abdominal aortic aneurysm.<sup>25</sup> In an old study, gallstones were detected in 42 of 865 patients (4.9%) with abdominal AN.<sup>26</sup> However, the effect of cholecystectomy on AD/AN has never been studied to date. In this study, we hypothesise that GD is associated with the development of AD/AN. Furthermore, we suppose that cholecystectomy will diminish the risk of AD/AN if GD per se in an independent risk factor. This nationwide population-based cohort study uses the database of one hospitalisation database of the Taiwan National Health Insurance Research Database (NHIRD), to appraise the association between GD and the subsequent development of AD/AN. Furthermore, we also compare the risk (adjusted HR (aHR)) of AD/AN between the patients with GD with and without cholecystectomy.

## METHODS

### Cohort description

Taiwan has launched the National Health Insurance (NHI) programme since 1 March 1995, and this single-payer and compulsory medicare system has provided coverage more than 99.6% of the 23 million residents in Taiwan.<sup>27 28</sup> All the information of NHI programme has been inputted into the NHIRD with the claim codes made based on 2001 International Classification of Diseases, ninth revision, Clinical Modification (ICD-9-CM).

### Recruitment criteria of the cohort

We enrolled the patients aged  $\geq 20$  years who had a new diagnosis of GD (ICD-9-CM 574) between 1 January 2000 and 31 December 2010 as the GD cohort. By 1:1 propensity score matching with the GD cohort based on index date for the diagnosis of GD, age, sex and comorbidities of hypertension, diabetes, hyperlipidaemia, coronary heart disease (CHD), heart failure, chronic obstructive pulmonary disease (COPD), peripheral artery occlusive disease (PAOD), chronic renal disease, stroke, cirrhosis and alcohol-related illness, we randomly selected the individuals without a history of GD or cholecystectomy as the control cohort. The main possible aetiologies of AD/AN might include genetic disorders, syphilis, arteritis and trauma, but these aforementioned causes were

relatively uncommon. In contrast, atherosclerosis is a common degenerative pathology and has been shown closely related to AD/AN with a causal or epiphenomenal relationship.<sup>29</sup> Therefore, hypertension, diabetes, hyperlipidaemia, CHD, heart failure, COPD, PAOD, chronic renal disease and stroke were selected as the explanatory variables. Since it remained debated for alcohol to be a risk factor of AN, we still listed cirrhosis and alcohol-related illness as the explanatory variables.<sup>30</sup> The index date for control patients was randomly appointed a month and day with the same index year of the matched GD cases. The patients with a history of AD or AN (ICD-9-CM 441) or those without complete information on age or sex were excluded from the study. We only considered the major diagnosis (first three diagnoses) with AD/AN (ICD-9-CM 441) for hospitalisation as the main outcome. We followed each individual from the enrolment to the event of AD or AN, deceased or retraction from the NHI programme due to emigration, or up to 31 December 2011. We included the cause-specific and non-cause-specific deaths for analysis, but we censor the deaths when the causes of deaths were not identifiable. A history of hypertension, diabetes mellitus, hyperlipidaemia, CHD, heart failure, COPD, PAOD, chronic renal disease, stroke, cirrhosis, and alcohol-related illness after the baseline and before the endpoints were included as a time-dependent covariate for comorbidities.

### Statistical analysis

The categorical distribution of age, sex and comorbidities were analysed by the  $\chi^2$  test; nevertheless, the continuous variables of mean ages (SDs) and mean follow-up period (SDs) were analysed by the Student's t test. The Kaplan-Meier method was used to compare the survival and cumulative incidence of AD/AN between the non-GD, GD with cholecystectomy and GD without cholecystectomy cohorts; nevertheless, we used the log-rank test to examine the differences between the cohorts. We estimated the incidence density rates of AD/AN (expressed as dividing the event number of AD/AN by the number of person-years for each variable) by stratification of age, sex and presence or absence of a comorbidity. The proportional hazard model assumption was also examined by using a test of scaled Schoenfeld residuals. In the model evaluating the risk of AD/AN throughout the follow-up period, it revealed a significant relationship between Schoenfeld residuals for gallstones and follow-up time, suggesting the proportionality assumption was violated ( $p$  value  $< 0.001$ ). In the subsequent analyses, we stratified the follow-up duration to deal with the violation of proportional hazard assumption. The risk of AD/AN (expressed as aHRs and 95% CIs) was analysed by univariable and multivariable Cox proportional hazard regression models. The multivariable Cox proportional hazard regression model included age, sex and comorbidities of hypertension, diabetes mellitus, hyperlipidaemia, CHD, heart failure, COPD, PAOD, chronic renal disease, stroke, cirrhosis and alcohol-related illness. The

comorbidities after the baseline and before the endpoints were included as a time-dependent covariate in the Cox model. Death could be a competing risk for the outcome in this study. Therefore, we conducted the competing risk analysis for AD/AN with death as a competing risk. However, the original National Health Research Institute (NHRI) database did not include mortality information. We used the discontinuity of NHI as a proxy of death for the mortality calculation. We calculated the correlation matrix of regression coefficients, and we find lower correlations among the regression coefficients for all covariates. The highest correlation in our data was 0.003 between the regression coefficients of cirrhosis and alcohol-related illness. We performed all statistical analyses with SAS V.9.4, and statistical significance was defined based on a two-tailed  $p < 0.05$ .

### Patient and public involvement

Patients and members of the public were not involved with the experimental design or carrying out the study.

## RESULTS

Table 1 presents the baseline characteristics of the GD and the non-GD cohort. With comparable matching for age, sex and each comorbidity, the study consisted of 343 300 individuals in each cohort, respectively. The mean age was  $60.3 \pm 16.8$  year for the GD cohorts and  $60.6 \pm 16.8$  years for the non-GD cohort, respectively. With comparable gender distribution between women (50.7%) and men (49.3%), about 44.6% of the patients with GD were older than 65 years. The most common comorbidities in the GD cohort included hypertension (31.6%), followed by diabetes (20.5%), CHD (12.7%) and stroke (11.3) in the order of the frequency. Among the 343 300 patients with GD, cholecystectomy was performed in 191 111 patients and no history of cholecystectomy was observed in the other 152 189 patients. The rate of ageing population (aged  $\geq 65$  years) was relatively greater in the non-cholecystectomy cohort, but women was more prevalent in the cholecystectomy cohort.

**Table 1** Distribution of age, gender and comorbidity between gallstones and comparison cohort

	Gallstones						Comparison		
	Total N=343 300		Without cholecystectomy N=152 189		With cholecystectomy N=191 111		N=343 300		Standardised mean difference*
	n	%	n	%	n	%	n	%	
<b>Sex</b>									
Female	173 053	50.4	69 832	45.9	103 221	54.0	173 917	50.7	0.01
Male	170 247	49.6	82 357	54.1	87 890	46.0	169 383	49.3	0.01
<b>Age, years</b>									
20–49	98 965	28.8	29 891	19.6	69 074	36.1	97 431	28.4	0.01
50–64	94 046	27.4	36 453	24.0	57 593	30.1	92 874	27.1	0.01
$\geq 65$	150 289	43.8	85 845	56.4	64 444	33.7	152 995	44.6	0.02
Mean (SD)	60.3	(16.8)	65.3	(16.2)	56.4	(16.1)	60.6	(16.8)	0.01
<b>Comorbidity</b>									
Hypertension	108 515	31.6	58 839	38.7	49 676	26.0	110 392	32.2	0.01
Diabetes mellitus	70 485	20.5	39 825	26.2	30 660	16.0	68 753	20.0	0.01
Hyperlipidaemia	24 960	7.27	14 264	9.37	10 696	5.60	23 883	6.96	0.01
CHD	43 582	12.7	26 812	17.6	16 770	8.78	39 850	11.6	0.03
Heart failure	17 675	5.15	12 608	8.28	5 067	2.65	14 503	4.22	0.04
COPD	24 405	7.11	17 065	11.2	7 340	3.84	20 860	6.08	0.04
PAOD	3 057	0.89	2 155	1.42	902	0.47	2 604	0.76	0.02
Chronic renal disease	9 034	2.63	6 329	4.16	2 705	1.42	7 193	2.10	0.04
Stroke	38 717	11.3	25 998	17.1	12 719	6.66	35 564	10.4	0.01
Cirrhosis	32 508	9.47	22 530	14.8	9 978	5.22	30 048	8.75	0.03
Alcohol-related illness	10 186	2.97	7 538	4.95	2 648	1.39	9 380	2.73	0.01

\*A standardised mean difference of  $\leq 0.10$  indicates a negligible difference between the total stroke versus comparison cohorts. CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; PAOD, peripheral artery occlusive disease.

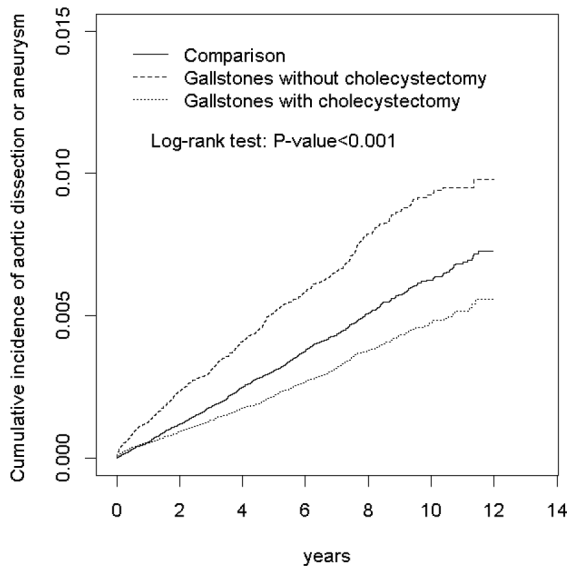
**Table 2** Incidence and HR of aortic dissection or aneurysm for associated-risk factors

	Event no.	Person-years	Rate	Crude HR (95% CI)	Adjusted HR (95% CI)*
<b>Gallstones</b>					
No	1172	1 878 072	6.24	1.00	1.00
Yes	1147	1 724 678	6.65	1.07 (1.05 to 1.08)***	1.12 (1.10 to 1.14)***
Without cholecystectomy	652	656 350	9.93	1.59 (1.56 to 1.62)***	1.37 (1.34 to 1.39)***
With cholecystectomy	495	1 068 328	4.63	0.74 (0.73 to 0.76)***	0.90 (0.88 to 0.92)***
<b>Age, years</b>					
20–49	104	1 165 442	0.89	1.00	1.00
50–64	373	1 054 393	3.54	3.96 (3.79 to 4.14)***	3.75 (3.59 to 3.92)***
65+	1842	1 382 916	13.3	14.9 (14.3 to 15.5)***	12.6 (12.1 to 13.1)***
<b>Sex</b>					
Women	778	1 872 705	4.15	1.00	1.00
Men	1541	1 730 045	8.91	2.14 (2.11 to 2.18)***	2.05 (2.02 to 2.09)***
<b>Comorbidity during study period</b>					
<b>Hypertension</b>					
No	1663	2 951 552	5.63	1.00	1.00
Yes	656	651 199	10.1	1.79 (1.75 to 1.82)***	1.23 (1.21 to 1.26)***
<b>Diabetes mellitus</b>					
No	2070	3 220 244	6.43	1.00	1.00
Yes	249	382 507	6.51	1.01 (0.99 to 1.04)	0.67 (0.65 to 1.00)
<b>Hyperlipidaemia</b>					
No	2174	3 412 974	6.37	1.00	1.00
Yes	145	189 777	7.64	1.20 (1.16 to 1.24)***	0.94 (0.90 to 1.01)
<b>CHD</b>					
No	1885	3 295 400	5.73	1.00	1.00
Yes	434	310 210	14.0	2.44 (2.39 to 2.50)***	1.40 (1.37 to 1.43)***
<b>Heart failure</b>					
No	1997	3 396 461	5.88	1.00	1.00
Yes	322	206 290	15.6	2.65 (2.60 to 2.72)***	1.30 (1.27 to 1.33)***
<b>COPD</b>					
No	2025	3 404 114	5.95	1.00	1.00
Yes	294	198 636	14.8	2.49 (2.42 to 2.55)***	1.07 (1.04 to 1.10)***
<b>PAOD</b>					
No	2192	3 555 084	6.17	1.00	1.00
Yes	127	47 666	26.6	4.32 (4.16 to 4.49)***	2.33 (2.24 to 2.42)***
<b>Chronic renal disease</b>					
No	2220	3 513 607	6.32	1.00	1.00
Yes	99	89 144	11.1	1.76 (1.68 to 1.83)***	0.89 (0.85 to 1.01)
<b>Stroke</b>					
No	1998	3 299 207	6.03	1.00	1.00
Yes	331	303 544	10.9	1.81 (1.77 to 1.85)***	0.96 (0.93 to 1.02)
<b>Cirrhosis</b>					
No	2123	3 297 549	6.44	1.00	1.00
Yes	196	305 201	6.42	1.00 (0.97 to 1.03)	0.88 (0.85 to 1.00)
<b>Alcohol-related illness</b>					
No	2309	3 563 621	6.48	1.00	1.00
Yes	10	39 130	2.56	0.39 (0.46 to 1.00)	0.58 (0.51 to 1.00)

\*\*\*p&lt;0.001

\*Model was adjusted for age, sex and comorbidities of hypertension, diabetes mellitus, hyperlipidaemia, CHD, heart failure, COPD, PAOD, chronic renal disease, stroke, cirrhosis and alcohol-related illness.

CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; ; PAOD, peripheral artery occlusive disease; Rate, per 10 000 person-years;.



**Figure 1** Cumulative incidence of aortic dissection or aneurysm compared among gallstones patients with cholecystectomy or without cholecystectomy, and non-gallstones subjects.

**Table 2** presents the incidence and HR of AD/AN for associated-risk factors. GD (aHR=1.12, 95% CI=1.10 to 1.14,  $p<0.001$ ), aged 50–64 years (aHR=3.75, 95% CI=3.59 to 3.92,  $p<0.001$ ) or  $\geq 65$  years (aHR=12.6, 95% CI=12.1 to 10.0,  $p<0.001$ ), men (aHR=2.05, 95% CI=2.02 to 2.09,  $p<0.001$ ), hypertension (aHR=1.23, 95% CI=1.21 to 1.26,  $p<0.001$ ), CHD (aHR=1.40, 95% CI=1.37 to 1.43,  $p<0.001$ ), heart failure (aHR=1.30, 95% CI=1.27 to 1.33,  $p<0.001$ ), COPD (aHR=1.07, 95% CI=1.04 to 1.10,  $p<0.001$ ) and PAOD (aHR=2.33, 95% CI=2.24 to 2.42,  $p<0.001$ ) were associated with AD/AN in multivariable Cox proportional hazard regression mode. However, it was noted that cholecystectomy (aHR=0.90, 95% CI=0.88 to 0.92,  $p<0.001$ ) were inversely associated with AD/AN in our study.

**Figure 1** shows the cumulative incidence of AD/AN was greatest for the GD cohort without cholecystectomy, followed by the non-GD cohort and then the GD cohort with cholecystectomy (log-rank test  $p<0.001$ ).

With non-GD group as the reference, **table 3** presents the incidence and HR of AD/AN compared between patients with and without gallstones based on the stratification of age, gender and comorbidity. The risk of AD/AN for the GD cohort was greater than that for the non-GD cohort in each stratification of age (except for aged 50–64 group), sex, the absence of a comorbidity and follow-up period. Furthermore, the risk of AD/AN for the GD cohort without cholecystectomy was persistently greater than that for the non-GD cohort in each stratification (except for the presence of a comorbidity). However, compared with the non-GD cohort, the risk of AD/AN was lower for the GD cohort with cholecystectomy in those aged 50–64 years (aHR=0.85, 95% CI=0.81 to 0.88,  $p<0.001$ ), and aged  $\geq 65$  years (aHR=0.92, 95% CI=0.89 to 0.95,  $p<0.001$ ), women (aHR=0.86, 95% CI=0.83 to

0.89,  $p<0.001$ ), those without comorbidity (aHR=0.90, 95% CI=0.88 to 0.93,  $p<0.001$ ) or with comorbidity (aHR=0.80, 95% CI=0.77 to 0.83,  $p<0.001$ ), and those with follow-up period greater than 1 year.

**Table 4** presents the incidence and HR of AD/AN for the GD cohort with cholecystectomy was lower than that for the GD cohort without cholecystectomy in each stratification of age, gender, the presence or absence of a comorbidity and those follow-up period  $<1$  year, follow-up period 1–3 years and follow-up period  $>3$  years. We conducted the competing risk analysis for AD/AN with death as a competing risk (**table 5**). The results were 1.00 (95% CI=0.92 to 1.08) in considering death as a competing risk.

## DISCUSSION

Many epidemiological studies have supported the close association between GD and CVD, but the definition of CVD was limited to stroke and ischaemic heart disease in most of the literature.<sup>13–15</sup> Although the pathophysiological mechanisms are quite similar for the development of CVD and AD/AN, to our knowledge our study is the first epidemiological study to assess the association between GD and the development of AD/AN.<sup>21–23</sup> Along with our former studies regarding the association of GD with stroke, erectile dysfunction and migraine, this study may portend that GD is a predictor or an independent risk factor of systemic atherosclerosis.<sup>31–35</sup> However, it requires more studies using other databases to confirm the association of GSD with atherosclerosis since our studies were conducted based on the same database (NHIRD).

In reviewing the literature (online supplemental table 1), there have been several epidemiological studies examining the effect of cholecystectomy on vascular diseases.<sup>31–33 36–38</sup> All our former studies from the same database supported the ameliorating effect of cholecystectomy on atherosclerotic diseases, including acute myocardial infarction (AMI), stroke, organic erectile erection, migraines.<sup>31–33 36</sup> However, we noted that the risks of atherosclerosis between non-GD group and GD group with cholecystectomy were quite heterogeneous in our studies, including being comparable for erection dysfunction, being greater for AMI in GD with cholecystectomy, and being lower for AD/AN in GD with cholecystectomy. One study from Mexico showed the deteriorating effect of cholecystectomy on the development of CVD, but the comparison group was general population without GD, rather than the GD subjects without cholecystectomy.<sup>37</sup> Therefore, it deserves more studies from other database to clarify the effect of cholecystectomy on the prevention of atherosclerotic diseases and if the ameliorating effect can be supported in the laboratory studies.

We have tried several sensitivity analyses to validate our findings: (1) **figure 1** shows the cumulative incidence of AD/AN for the GD cohort without cholecystectomy was greater than that for the non-GD cohort even though the duration of follow-up was shorter in the GD cohort

**Table 3** Incidence and HR of aortic dissection or aneurysm compared between patients with and without gallstones based on the stratification of age, gender and comorbidity

	Gallstones											
	Comparison N=343300			Total N=343300			Without cholecystectomy N=152189			With cholecystectomy N=191111		
	Event no.	Rate	HR† (95% CI)	Event no.	Rate	HR† (95% CI)	Event no.	Rate	HR† (95% CI)	Event no.	Rate	HR† (95% CI)
Age, years												
20–49	45	0.76	59	1.02	1.06 (1.02 to 1.09)**	24	1.46	1.18 (1.13 to 1.24)***	35	0.85	0.99 (0.95 to 1.03)	
50–64	186	3.42	187	3.66	1.00 (0.96 to 1.03)	89	4.97	1.25 (1.20 to 1.30)***	98	2.96	0.85 (0.81 to 0.88)***	
65+	941	12.6	901	14.1	1.15 (1.12 to 1.18)***	539	17.2	1.40 (1.36 to 1.44)***	362	11.1	0.92 (0.89 to 0.95)***	
Gender												
Women	406	4.20	372	4.11	1.07 (1.05 to 1.10)***	224	7.17	1.28 (1.25 to 1.32)***	148	2.49	0.86 (0.83 to 0.89)***	
Men	766	8.40	775	9.47	1.51 (1.12 to 1.18)***	428	12.5	1.31 (1.27 to 1.35)***	347	7.31	1.00 (0.97 to 1.03)	
Comorbidity during study period‡												
None	463	3.50	309	3.56	1.26 (1.23 to 1.29)***	186	7.23	1.68 (1.64 to 1.73)***	123	2.02	0.90 (0.88 to 0.93)***	
With any one	709	12.8	838	9.77	0.89 (0.87 to 1.00)	466	11.7	0.98 (0.95 to 1.01)	372	8.11	0.80 (0.77 to 0.83)***	
Follow-up period												
<1	186	5.53	280	8.66	1.78 (1.75 to 1.82)***	177	13.0	2.07 (2.02 to 2.11)***	103	5.52	1.44 (1.40 to 1.48)***	
1–3	360	6.23	320	6.06	1.03 (1.01 to 1.05)**	194	9.33	1.23 (1.20 to 1.25)***	126	3.93	0.83 (0.81 to 0.85)***	
>3	626	6.49	547	6.26	0.99 (0.97 to 1.01)	281	9.01	1.13 (1.10 to 1.16)***	266	4.74	0.88 (0.86 to 0.91)***	

\*\*\*p<0.01, \*\*p<0.001.

†With non-GD group as the reference, model was adjusted for age, sex and comorbidities of hypertension, diabetes mellitus, hyperlipidaemia, CHD, heart failure, COPD, PAOD, chronic renal disease, stroke, cirrhosis and alcohol-related illness.

‡Patients with any comorbidity of hypertension, diabetes mellitus, hyperlipidaemia, CHD, heart failure, COPD, PAOD, chronic renal disease, stroke, cirrhosis and alcohol-related illness were defined as the comorbidity group.

CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; GD, gallstone disease; PAOD, peripheral artery occlusive disease; Rate, per 10 000 person-years.

**Table 4** Incidence and HR of aortic dissection or aneurysm compared between gallstones patients with and without cholecystectomy based on the stratification of age, gender and comorbidity

	Gallstones without cholecystectomy N=152 189	Gallstones with cholecystectomy N=191 111
	HR† (95% CI)	HR† (95% CI)
<b>Age, years</b>		
20–49	1.00	0.87 (0.82 to 0.91)***
50–64	1.00	0.67 (0.64 to 0.70)***
65+	1.00	0.66 (0.64 to 0.69)***
<b>Gender</b>		
Women	1.00	0.67 (0.65 to 0.70)***
Men	1.00	0.77 (0.75 to 0.80)***
<b>Comorbidity</b>		
None	1.00	0.59 (0.57 to 0.61)***
With any one	1.00	0.83 (0.80 to 0.86)***
<b>Follow-up period</b>		
<1	1.00	0.69 (0.67 to 0.71)***
1–3	1.00	0.68 (0.66 to 0.70)***
>3	1.00	0.79 (0.77 to 0.82)***

\*\*\*p<0.001.

†Model was adjusted for age, sex and comorbidities of hypertension, diabetes mellitus, hyperlipidaemia, CHD, heart failure, COPD, PAOD, chronic renal disease, stroke, cirrhosis and alcohol-related illness.

.CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; PAOD, peripheral artery occlusive disease; Rate, per 10000 person-years.

without cholecystectomy; (2) [table 3](#) show the risk of AD/AN for the GD cohort without cholecystectomy was persistently greater than that for the non-GD cohort in each stratification of age group, sex, the absence of a comorbidity and the follow-up period; (3) [figure 1](#) shows that the risk of AD/AN for the GD cohort with cholecystectomy was lower than that for the non-GD cohort

**Table 5** Subhazard ratios of aortic dissection or aneurysm and 95% CIs compared between patients without gallstones and gallstones patients with or without cholecystectomy

Variables	cSHR (95% CI)	aSHR (95% CI)†
<b>Gallstones</b>		
No	1 (Reference)	1 (Reference)
Yes	1.00 (0.93 to 1.09)	1.00 (0.92 to 1.08)
Without cholecystectomy	1.36 (1.23 to 1.49)***	1.07 (0.97 to 1.18)
With cholecystectomy	0.75 (0.67 to 0.83)***	0.91 (0.82 to 1.01)

\*\*\*p<0.001.

†Model was adjusted for age, sex and comorbidities of hypertension, diabetes mellitus, hyperlipidaemia, CHD, heart failure, COPD, PAOD, chronic renal disease, stroke, cirrhosis and alcohol-related illness.

aSHR, adjusted subhazard ratio; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; cSHR, crude subhazard ratio; PAOD, peripheral artery occlusive disease.

even though the duration of follow-up was longer in the GD cohort without cholecystectomy; and (4) [table 3](#) has shown that the risk of AD/AN for the GD cohort with cholecystectomy was lower than that for the non-GD cohort without cholecystectomy in each stratification of age greater than 50 years, women, the presence or absence of a comorbidity, and greater than 1 year of follow-up period.

It remains uncertain about the pathophysiological mechanisms for the association of AD/AN with GD and cholecystectomy. However, the following possible explanations have been suggested for the association of AD/AN with GD. First, GD and AD/AN share many common risk factors, such as ageing, sex, hypertension, diabetes and hyperlipidaemia.<sup>15</sup> Second, increased cholesterol accumulation is common for GD with increased cholesterol secretion of bile and for AD/AN with atherosclerosis.<sup>13–15</sup>

Moreover, common genetic linkage for abnormal biosynthesis, metabolism and transport can be observed in GD and atherosclerosis.<sup>19</sup> Third, increased systemic oxidative stress or inflammation can be observed in patients with GD. Moreover, the inflammatory process can enhance atherosclerosis or atherothrombosis.<sup>17</sup> Fourth, dysbiosis in the bowels and biliary tract promotes the development of GD by impairing the enterohepatic circulation of the bile.<sup>18 39 40</sup>

The following mechanisms may explain the protective effect of cholecystectomy against the development of AD/AN. First, increased oxidative stress and free radical reactions have been observed in patients with GD or cholecystitis, and these could be decreased after cholecystectomy.<sup>41</sup> Second, dysbiosis can enhance gallstone formation due to imbalanced bile acid and cholesterol secretion in the bile.<sup>42</sup> However, another study showed that changes in intestinal microbiota composition and diversity was seen after cholecystectomy, not in asymptomatic gallstones.<sup>43</sup> Third, gallstones could be complicated with several bacterial microorganisms and often the indication for cholecystectomy is cholecystitis.<sup>44</sup> Moreover, several of these bacteria have been associated with the development of AD or AN.<sup>45</sup> Bacterial biofilm even has been supposed to be related to the formation of gallstones without symptoms and atherosclerosis.<sup>46</sup> The bacteriology was not available in our database, but cholecystectomy might eliminate the source of bacterial colonisation.

The study has several merits. First, the findings of this study with a 12-year-long follow-up provides the generalisability in Taiwan because the NHI programme is a mandatory and single-payer healthcare system with a coverage of almost every resident in Taiwan (99.6%). Second, the misclassification of asymptomatic gallstones into general population can be mitigated by comparing the risk of AD/AN between the gallstones patients with cholecystectomy and without cholecystectomy, rather than between cholecystectomy and general population. Third, this study also compares the survival and cumulative incidence of AD/AN by Kaplan-Meier method to avoid the detection bias due to temporal effect.

The study has several limitations. First, this study is subject to the limited information on dietary habits and life styles even though we have replaced the diagnosis of smoking with COPD for smoking and alcohol drinking with alcohol-related illness, respectively. Second, we cannot individually validate the accuracy of each medical chart. The study is based on an NHI database, and a risk of selection bias (misclassification) or missing data could not be excluded. However, the Ministry of Health and Welfare in Taiwan has inspected the insurance claims for medical reimbursement, and it has been demonstrated a substantial concordance between the claims data in NHIRD and the patient self-reports.<sup>47 48</sup> Third, the data from 2000 to 2010 seem quite dated. However, this large case-control cohort with 343 300 population and 12-year-long follow-up has empowered the statistical significance and the accuracy of this database has been well recognised.<sup>47 48</sup> Fourth, the original NHRI database could not provide the mortality information. Although death would be the major reason for discontinuing the NHI, the possible reasons for the discontinuity of NHI included death, withdrawal of insurance, immigration, etc. Therefore, the competing risk of death was overestimated and the protective effect of cholecystectomy on the development of AD/AN would be underestimated in our study. Fifth, this observatory study cannot ascertain mechanism for the association of GD with AD/AN and the protective mechanism of cholecystectomy against the development of AD/AN. Furthermore, we acknowledge that we could not exclude the possibility of lifestyle modification, such as dietary habits, exercise or weight reduction, with a resultant of decreased AD/AN risk for the patients after cholecystectomy.

In conclusion, our findings demonstrate that the GD cohort was associated with a greater risk of AD/AN than the non-GD cohort. Nevertheless, the risk of AD/AN in the patients with GD would decrease after cholecystectomy. It needs more studies to ascertain the protective effect of cholecystectomy against the development of AD/AN in patients with GD.

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