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# BMJ Open

## Increased risk of aortic aneurysm and dissection in patients with Sjögren's syndrome: a nationwide population-based cohort study

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| Keywords:                     | Sjögren's syndrome, aortic dissection, aortic aneurysm  |

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Manuscripts

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4 **Increased risk of aortic aneurysm and dissection in patients with Sjögren's**  
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6 **syndrome: a nationwide population-based cohort study**  
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28

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## **Abstract**

### ***Objectives***

Sjögren's syndrome (SS) is a systemic autoimmune disorder. Several molecular pathways and the activation of matrix metalloproteinases associated with the pathogenesis of SS participate in the initiation and progression of aortic aneurysm (AA) and aortic dissection (AD). In this study, we aimed to evaluate whether patients with SS exhibit an increased risk of AA and AD.

### ***Methods***

We conducted a retrospective cohort study using a database extracted from Taiwan's National Health Insurance Research Database (NHIRD). All medical conditions for each case and control were categorized using the International Classification of Diseases, 9<sup>th</sup> Revision (ICD-9). Odds ratios (ORs) and 95% confidence intervals (CIs) for associations between SS and AA/AD were estimated using Cox regression and adjusted for co-morbidities.

### ***Results***

Our analyses included 10,941 SS cases and 43,764 propensity score-matched controls. Compared with the controls, the patients with SS exhibited a significantly increased risk of developing an AA and AD (adjusted OR = 3.642,  $P < 0.001$ ). The subgroup analysis revealed that patients with primary and secondary SS both

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3 exhibited a significantly increased risk of developing AA and AD compared with  
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6 patients without SS (adjusted hazard ratio (HR) = 1.753, P = 0.042; adjusted HR =  
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9 3.693, P < 0.001).  
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### 11 **Conclusion**

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14 Patients with SS exhibit increased risks of developing AA and AD, and  
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17 healthcare professionals should be aware of this risk when treating patients with SS.  
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20 Increased aortic surveillance may be required in patients with SS syndrome.  
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26 **Keywords:** Sjögren's syndrome, aortic dissection, aortic aneurysm  
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### Strengths and limitations of this study

- The strength of our study is its population-based cohort design. We excluded confounding factors, including comorbidities, from our study.
- We intended to control for potential disease-associated confounders to the utmost extent possible, unmeasured or unknown confounders may have existed in our findings.
- This was a retrospective cohort study.
- NHIRD can not provide detailed information regarding the laboratory results or lifestyle factors of the patients.
- Our results are limited to human data. It required both mechanistic and animal studies for further clarification.

## Introduction

Sjögren's syndrome (SS) is a systemic autoimmune disorder commonly presenting with dry eyes and mouth. The prevalence of SS is between 0.1% and 4.8% in various populations when strictly defined according to the American-European Consensus Criteria, and it is one of the most common autoimmune diseases<sup>1</sup>. SS may affect patients at any age, but more cases occur in the fourth decade of life, and there is a female predominance. The female-male ratio is approximately 9:1<sup>2</sup>. Aortic aneurysms (AAs) are often diagnosed inadvertently and are a common cause of sudden death. Enlarged aneurysms can result in rupture. Aortic dissection (AD) is one of the most deadly complications of thoracic aortic disease. The incidence of AD ranges from 6 cases per 100,000 to 9.1 per 100,000 in women and 16.3 per 100,000 in men annually based on studies in England and Sweden<sup>3,4</sup>. Regarding the Asian population, the average annual incidence of AD was 5.6 per 100,000 persons in Taiwan, and the prevalence was 19.9 per 100,000 persons, with a predominance noted among men 50 to 54 years of age (27.3 per 100,000 persons per year)<sup>5</sup>.

Previous studies have demonstrated that AA is more prevalent in patients with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) compared with the general population<sup>6,7</sup>. Compared with age- and sex-matched healthy controls, primary SS (PSS) patients exhibited a 2-fold increased prevalence of hypertension and hypertriglyceridemia. Furthermore, hypertension is underdiagnosed and suboptimally



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3 treated in PSS<sup>8</sup>. SS with positive autoantibodies is associated with a low  
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6 ankle-brachial index, which may indicate an increased risk of early atherosclerosis<sup>9</sup>.  
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9 Nonetheless, previous population-based studies indicated that SS is not associated  
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12 with an increased risk of subsequent acute myocardial infarction (AMI) and ischaemic  
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15 stroke<sup>10 11</sup>.

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18 Several molecular mechanisms, including JNK, NF- $\kappa$ B and TGF- $\beta$  signalling  
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21 pathways, and matrix metalloproteinase (MMP) activation are associated with the  
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24 pathogenesis of SS<sup>12 13</sup>. These molecular mechanisms also actively participate in the  
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27 initiation and progression of AA and AD<sup>14 15</sup>. Taken together, we hypothesized that  
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30 patients with SS may have an increased risk of AA and AD due to SS-related  
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33 cardiovascular risks and shared molecular mechanisms. However, the association  
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36 between SS and AA or AD has not been thoroughly evaluated in large-scale studies.  
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39 Therefore, we aimed to determine whether SS patients exhibit an increased risk of AA  
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41  
42 and AD using a nationwide healthcare insurance claim database.  
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## 46 **Methods**

### 47 ***Data source***

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51 The data described herein were acquired from the Longitudinal Health Insurance  
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54 Database 2005 (LHID 2005), a subgroup database of the Taiwan National Health  
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4 Insurance Research Database (NHIRD) used for the nationwide population-based  
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6 retrospective cohort study. The National Health Insurance programme in Taiwan  
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8 provides health care for 99% of the population (greater than 23 million people) and  
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10 was implemented in 1995. The LHID 2005 provides information on medical service  
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12 utilization using a randomly selected sample of approximately one million people  
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14 receiving benefits, representing approximately 5% of Taiwan's population in 2005.  
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20 The information was obtained from the NHIRD between 2000 and 2010. The  
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22 accuracy of the diagnoses in the NHIRD, particularly the diagnoses of major diseases  
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24 (e.g., acute coronary syndrome and stroke), has been corroborated [16 17](#). The LHID is  
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26 composed of "de-identified" secondary data that are available to the public via open  
27  
28 access for research. ICD-9-CM (International Classification of Diseases, 9th Revision,  
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30 Clinical Modification) diagnostic and procedure codes (up to five each), genders,  
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32 birthdays, patient identification numbers, dates of admission and discharge, and  
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34 outcomes are coded. In addition, information regarding the medical institutions that  
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36 served patients was obtained. Individual information was protected using encoded  
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38 personal identification to prevent ethical violations related to the data. Our study  
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40 conformed to the Declaration of Helsinki and relevant guidelines. This Institutional  
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42 Review Board of the Tri-Service General Hospital, National Defense Medical Center,  
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44 Taipei, Taiwan, permitted this study (TSGH IRB No.2-105-05-082).  
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### *Sampled patients*

This study utilized study and comparison cohorts. Using the LHID 2005, we selected adult patients aged >20 years who were newly diagnosed with SS (ICD-9-CM 710.2) and were followed-up between 2000 and 2010. We excluded patients who were diagnosed with SS, AA and AD (ICD-9-CM 441.0-441.9); Turner syndrome (ICD-9-CM 758.6); aortic coarctation (ICD-9-CM 747.10); bicuspid aortic valve (ICD-9-CM 746.4); Marfan syndrome (ICD-9-CM 759.82); and Ehler-Danlos syndrome (ICD-9-CM 756.83). Patients had a tracking time < 6 months. The date of SS diagnosis was used as the index date. Control candidate sampling comparisons were selected from individuals in the LHID 2005 who lacked a history of SS. The patients and control cohorts were selected by 1:4 matching according to the following baseline variables: age; sex; co-morbidities, including hypertension (ICD-9-CM 401-405), diabetes mellitus (DM) (ICD-9-CM 250), hyperlipidaemia (ICD-9-CM 272.0-272.4), Behcet's disease (ICD-9-CM 136.1), giant cell arteritis (ICD-9-CM 446.5), RA and other inflammatory polyarthropathies (ICD-9-CM 714), relapsing polychondritis (ICD-9-CM 733.99), Takayasu's arteritis (ICD-9-CM 446.7) and chronic obstructive pulmonary disease (COPD) (ICD-9-CM 490-496); and medication history, including  $\beta$ -blocker, calcium channel blocker, angiotensin-converting enzyme

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4 inhibitor, angiotensin receptor blocker, diuretic and steroid history. We also divided  
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6 SS patients into primary SS and secondary SS (SSS) patients and performed a  
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8 subgroup analysis. SS in patients was previously diagnosed as SLE (ICD-9-CM  
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10 710.0), RA (ICD-9-CM 714), systemic sclerosis (ICD-9-CM 701.1), or primary  
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12 biliary cirrhosis (ICD-9-CM 571.6), which was defined as SSS. The index dates for  
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14 control patients were the same as the corresponding dates for patients with AA/AD.  
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16 The study outcome was a diagnosis of AA/AD during the 10-year follow-up period.  
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18 AA/AD was identified using ICD-9 codes. The end point of the follow-up period was  
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20 2010-12-31 or the time at which AA/AD events occurred or the patient died.  
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### 31 ***Statistical analysis***

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34 Categorical variables, which are presented as percentages, were compared using  
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36 the chi-square or Fisher's exact tests. Continuous variables, which are presented as the  
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38 means and standard deviations, were compared using a t-test. The primary goal of the  
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40 study was to determine whether SS patients exhibit an increased risk for developing  
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42 AA/AD. The association between those outcomes (prognoses) and clinical  
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44 characteristics was investigated using Cox regression. The results are presented as  
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46 adjusted hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). The  
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48 threshold for statistical significance was  $P < 0.05$ . All data analyses were conducted  
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4 using SPSS software version 22 (SPSS Inc., Chicago, IL, USA).  
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## 8 9 **Results**

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11 A flow diagram of our patient enrolment scheme is presented in Figure 1. A total  
12 of 10,941 patients diagnosed with SS were identified in the NHIRD, which contains a  
13 total of 986,713 individuals. An additional 43,764 age-, gender-, comorbidity-, and  
14 medication-matched patients were designated controls. As shown in Table 1, no  
15 significant differences in gender, age or co-morbidities, including DM, hypertension,  
16 hyperlipidaemia, Behcet's disease, giant cell arteritis, RA, relapsing polychondritis,  
17 Takayasu's arteritis, COPD, and medications, were noted between the two groups after  
18 matching. Patients with SS exhibited a significantly increased cumulative risk of  
19 developing AA/AD in subsequent years compared with patients without SS (log rank  
20 test < 0.001, Figure 2). Table 2 presents the incidences of AA and AD during the  
21 ten-year follow-up period. At the end of the follow-up period, SS patients exhibited  
22 significantly increased incidences of AA/AAD (0.43% vs. 0.37%,  $P = 0.045$ ) but  
23 lower incidences of DM (7.73% vs. 15.44%,  $P < 0.001$ ) and COPD (5.96% vs. 6.72%,  
24  $P = 0.004$ ). In addition, patients with SS were younger and exhibited an increased CCI  
25 compared with patients without SS. Regarding the use of Cox regression independent  
26 of the effects of gender, age, co-morbidities and medication, patients with SS also  
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4 exhibited a significantly increased risk of developing AA/AD compared with patients  
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6 without SS (adjusted HR = 3.642, 95% CI = 2.527-5.250, P < 0.001, Table 3). The  
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8 subgroup analysis revealed that patients with PSS or SSS both exhibited significantly  
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10 increased risks for developing AA/AD compared with patients without SS (adjusted  
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12 HR = 1.753, 95% CI = 1.108-9.382, P = 0.042; adjusted HR = 3.693, 95% CI =  
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14 2.520-5.411, P < 0.001, Table 4).  
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## 23 Discussion

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26 Our study is a retrospective cohort study that enrolled 10,941 patients with SS  
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28 and 43,764 patients without SS matched by age, sex, year of index date of SS  
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30 diagnosis, co-morbidities and medication from a large-scale nationwide  
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32 population-based database. During follow-up, SS was associated with an increased  
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34 incidence of the development of AA/AD compared with the comparison cohort.  
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40 SS patients exhibit an increased prevalence of developing traditional  
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42 cardiovascular risk factors, such as hypertension and dyslipidaemia, which predispose  
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44 patients to endothelial dysfunction and premature atherosclerosis. However, the  
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46 disease-specific mechanisms associated with premature atherosclerosis in SS are not  
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48 fully understood <sup>18</sup>. In a recent review article, cardiovascular disease was reported to  
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50 be one of the primary causes of mortality in SS patients <sup>19</sup>. Primary SS shares clinical  
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4 and serological features with RA and SLE, and these two diseases are associated with  
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6 acceleration of atherosclerosis <sup>20</sup>. However, the pathophysiology between SS and  
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8 AA/AD remains unclear, although several possible mechanisms have been proposed.  
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11 Previous studies have demonstrated that both SS and AA/AD are induced by chronic  
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13 inflammation. <sup>21-24</sup> Recent studies have provided convincing evidence indicating that  
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15 several signalling pathways are involved in both AA and SS, including the MAPK,  
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17 TGF- $\beta$ , and MMP signalling pathways <sup>12-15</sup>. Activation of the innate immune system  
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19 and the production of interferons (IFNs) could be the first stages of primary SS  
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21 pathogenesis <sup>25</sup>. IFNs and IL-21 could induce B-cell-activating factor (BAFF) and  
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23 further activate B cell activity. In human salivary gland cells, interferon- $\gamma$  modulates  
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25 and increases MMP-2 and MMP-9 expression <sup>26</sup>. The circulating levels of MMP-9  
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27 were increased in patients with definite SS compared with patients with possible SS <sup>27</sup>.  
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29 Furthermore, MMP-2 and MMP-9 also display a critical role in AAA formation <sup>28</sup>.  
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As a downstream effector molecule of CD40, the JNK cascade is activated in salivary infiltrating T cells and mononucleated cells in patients with SS <sup>12 13</sup>. JNK plays a pivotal role in IL-1 $\beta$ -mediated inhibition of lacrimal gland secretion and

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4 subsequent dry eye <sup>30</sup>. JNK is not only involved in T cell infiltration in salivary glands  
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6 but is also associated with subsequent NF-κB activation, MMP activation and reactive  
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8 oxygen species (ROS) production <sup>21 31</sup>. Increased TGF-β signalling was observed in  
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10 salivary glands with increased Smad2 phosphorylation and concomitant increases in  
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12 extracellular matrix deposition. In a mouse study of SS, aberrant TGF-β  
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14 overexpression caused salivary gland hypofunction <sup>32</sup>. In addition, TGFBR1 and  
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16 TGFBR2 mutations result in up-regulation of TGF-β signalling and lead to  
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18 extracellular matrix deposition and matrix degradation, which represent critical steps  
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20 in AA or AD <sup>33</sup>.

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29 Low-dose steroids, such as prednisone, may be used to treat SS-induced joint and  
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31 muscle pain. Prolonged or high-dose corticosteroid treatment likely causes  
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33 disintegration of connective tissue of the media possibly together with primary aortic  
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35 wall involvement and/or vascular damage in patients with autoimmune disorders,  
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37 which can result in aortic aneurysmal enlargement and AD <sup>29 34</sup>. In this study, the  
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39 medical condition of steroids was matched. Therefore, the effect of steroids was  
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41 mitigated. The strength of our study involves its population-based database design. We  
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43 accounted for several aneurysm-related confounding factors. Although we adjusted  
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45 the results extensively using multivariate logistic regression models, there were  
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47 several limitations and unmeasured confounders in our study. The NHIRD registry is  
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4 not able to provide detailed information on laboratory results, family histories and  
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6 health-related lifestyle factors, such as alcohol consumption and tobacco use, which  
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8 can increase the risk of AA/AD and were potential confounding factors in this study.  
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12 In our study, we also considered COPD incidence as a proxy variable for tobacco use  
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14 to eliminate its potential confounding effect <sup>35</sup>. Although our study identified the  
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16 association between SS and AA/AD, the cohort study design did not enable  
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18 determination of the cause-effect relationship. Further prospective follow-up studies,  
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20 mechanistic studies and animal experiments should be performed.  
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## 29 **Conclusion**

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31 Patients with SS exhibit an increased risk for developing AA and AD, and  
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33 healthcare professionals should be aware of this risk when treating patients with SS.  
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36 Increased aortic surveillance may be required in patients with SS.  
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## 43 **Author contributions**

44  
45 Y-DT, J-CW, and S-HT conceived and designed the study.  
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49 W-CC provided the materials for the study. C-HC and S-JC analysed the data. C-JY  
50  
51 and M-TL contributed reagents, materials and analysis tools. Y-DT, J-CW, W-IL and  
52  
53 S-HT wrote the manuscript. All the authors approved the manuscript.  
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**Competing interests**

None declared.

**Data sharing statement**

No additional data sharing available.

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**Legends to tables and figures**

Table 1. Characteristics of the study participants at baseline

Table 2. Incidences of aortic aneurysm and dissection and other characteristics during the ten-year follow-up period

Table 3. Factors associated with aortic aneurysm and dissection according to Cox regression

Table 4. Factors associated with aortic aneurysm and dissection stratified by primary/secondary SS using Cox regression

Figure 1. Patient selection flowchart

Figure 2. Kaplan-Meier curve of the cumulative risk of aortic aneurysm and dissection due to Sjögren's syndrome

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For peer review only

Table 1 Characteristics of the study participants at baseline

| Sjögren's syndrome       | Total<br>N (%)  | With<br>N (%)   | Without<br>N (%) | P-value |
|--------------------------|-----------------|-----------------|------------------|---------|
| Total                    | 54,705          | 10,941 (20.00%) | 43,764(80.00%)   |         |
| Gender                   |                 |                 |                  | 0.999   |
| Male                     | 10,187 (18.63%) | 2,011 (18.44%)  | 8,176 (18.68%)   |         |
| Female                   | 44,485 (81.37%) | 8,897 (81.56%)  | 35,588 (81.32%)  |         |
| Age (years)              | 55.78±17.09     | 55.80±16.65     | 55.77±17.20      | 0.897   |
| DM                       | 3,553 (6.49%)   | 724 (6.62%)     | 2,829 (6.46%)    | 0.558   |
| Hypertension             | 8,091 (14.79%)  | 1,578 (14.42%)  | 6,513 (14.88%)   | 0.228   |
| Hyperlipidaemia          | 1,145 (2.09%)   | 234 (2.14%)     | 911 (2.08%)      | 0.709   |
| Behcet's disease         | 321 (0.59%)     | 62 (0.57%)      | 259 (0.59%)      | 0.834   |
| Giant cell arteritis     | 15 (0.03%)      | 3 (0.03%)       | 12 (0.03%)       | 0.999   |
| Rheumatoid arthritis     | 8,907 (16.28%)  | 1,784 (16.31%)  | 7,123 (16.28)    | 0.942   |
| Relapsing polychondritis | 71 (0.13%)      | 14 (0.13%)      | 57 (0.13%)       | 0.953   |
| Takayasu's arteritis     | 15 (0.03%)      | 3 (0.03%)       | 12 (0.03%)       | 0.999   |
| COPD                     | 2,931 (5.36%)   | 581 (5.3%)      | 2,350 (5.37%)    | 0.831   |
| Steroid                  | 16,799 (30.71%) | 3,345 (30.57%)  | 13,454 (30.74%)  | 0.737   |
| β blocker                | 12,588 (23.01%) | 2,513 (22.97%)  | 10,075 (23.02%)  | 0.919   |
| CCB                      | 11,553 (21.12%) | 2,342 (21.41%)  | 9,211 (21.05%)   | 0.409   |
| ACEI                     | 13,586 (24.84%) | 2,711 (24.78%)  | 10,875 (24.85%)  | 0.878   |
| ARB                      | 12,718 (23.25%) | 2,620 (23.95%)  | 10,098 (23.07%)  | 0.054   |
| Diuretic                 | 12,440 (22.74%) | 2,429 (22.20%)  | 10,011 (22.87%)  | 0.136   |
| Statin                   | 13,922 (25.45%) | 2,811 (25.69%)  | 11,111 (25.39%)  | 0.516   |

P-value (categorical variable: chi-square/Fisher's exact test; continuous variable: t-test)

DM = diabetes mellitus; COPD = chronic obstructive pulmonary disease; CCB = calcium channel blocker; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker

Table 2 Incidences of aortic aneurysm and dissection and other characteristics during the ten-year follow-up period

| Sjögren's syndrome                    | Total<br>N (%)  | With<br>N (%)  | Without<br>N (%) | P-value |
|---------------------------------------|-----------------|----------------|------------------|---------|
| <b>Total</b>                          | 54,705          | 10,941(20.00%) | 43,764(80.00%)   |         |
| <b>Aortic aneurysm and dissection</b> | 207 (0.38%)     | 47(0.43%)      | 160(0.37%)       | 0.045   |
| <b>Gender</b>                         |                 |                |                  | 0.999   |
| Male                                  | 10,187 (18.63%) | 2,011(18.44%)  | 8,176(18.68%)    |         |
| Female                                | 44,485 (81.37%) | 8,897(81.56%)  | 35,588(81.32%)   |         |
| <b>Age (years)</b>                    | 61.36±5.41      | 60.90±4.98     | 61.47±5.51       | <0.001  |
| <b>DM</b>                             | 7,603 (13.90%)  | 846(7.73%)     | 6,757(15.44%)    | <0.001  |
| <b>Hypertension</b>                   | 8,821 (16.12%)  | 1,708(15.61%)  | 7,113(16.25%)    | 0.102   |
| <b>Hyperlipidaemia</b>                | 1,128 (2.06%)   | 240(2.19%)     | 888(2.03%)       | 0.279   |
| <b>Behcet's disease</b>               | 324 (0.59%)     | 63(0.58%)      | 261(0.60%)       | 0.802   |
| <b>Giant cell arteritis</b>           | 16 (0.03%)      | 3(0.03%)       | 13(0.03%)        | 0.901   |
| <b>Rheumatoid arthritis</b>           | 9,033 (16.51%)  | 1,774(16.21%)  | 7,259(16.59%)    | 0.348   |
| <b>Relapsing polychondritis</b>       | 80 (0.15%)      | 19 (0.17%)     | 61 (0.14%)       | 0.401   |
| <b>Takayasu's arteritis</b>           | 15 (0.03%)      | 3 (0.03%)      | 12 (0.03%)       | 0.999   |
| <b>COPD</b>                           | 3,593 (6.57%)   | 652 (5.96%)    | 2,941 (6.72%)    | 0.004   |
| <b>CCI_R</b>                          | 0.78±1.53       | 0.83±1.39      | 0.77±1.56        | <0.001  |
| <b>Steroid</b>                        | 17,112 (31.28%) | 3,511 (32.09%) | 13,601 (31.08%)  | 0.041   |
| <b>β blockers</b>                     | 13,750 (25.13%) | 2,674 (24.44%) | 11,076 (25.31%)  | 0.061   |
| <b>CCB</b>                            | 11,833 (21.63%) | 2,397 (21.91%) | 9,436 (21.56%)   | 0.430   |
| <b>ACEI</b>                           | 13,793 (25.21%) | 2,784 (25.45%) | 11,009 (25.16%)  | 0.532   |
| <b>ARB</b>                            | 12,976 (23.72%) | 2,681 (24.50%) | 10,295 (23.52%)  | 0.031   |
| <b>Diuretic</b>                       | 12,692 (23.20%) | 2,507 (22.91%) | 10,185 (23.27%)  | 0.427   |
| <b>Statin</b>                         | 14,123 (25.82%) | 2,828 (25.85%) | 11,295 (25.81%)  | 0.934   |

P-value (categorical variable: chi-square/Fisher's exact test; continuous variable: t-test)

CCI\_R = Charlson comorbidity index removed DM, COPD; DM = diabetes mellitus; COPD = chronic obstructive pulmonary disease; CCB = calcium channel blocker; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker

Table 3 Factors associated with aortic aneurysm and dissection according to Cox regression

| Variables            | Crude HR | 95% CI      | P      | Adjusted HR | 95% CI      | P      |
|----------------------|----------|-------------|--------|-------------|-------------|--------|
| Sjögren's syndrome   | 3.205    | 2.254-3.565 | <0.001 | 3.642       | 2.527-5.250 | <0.001 |
| Gender (male)        | 2.645    | 1.974-3.597 | <0.001 | 2.035       | 1.534-2.700 | <0.001 |
| Age (years)          | 1.049    | 1.032-1.057 | <0.001 | 1.043       | 1.032-1.055 | <0.001 |
| DM                   | 1.704    | 1.389-1.944 | 0.024  | 1.674       | 1.065-1.976 | 0.037  |
| Hypertension         | 1.165    | 1.022-1.454 | 0.038  | 1.305       | 0.973-1.751 | 0.075  |
| Hyperlipidaemia      | 1.211    | 0.594-2.436 | 0.618  | 1.343       | 0.656-2.751 | 0.420  |
| Rheumatoid arthritis | 1.645    | 0.774-3.496 | 0.196  | 0.801       | 0.362-1.769 | 0.583  |
| COPD                 | 1.838    | 1.256-2.691 | 0.002  | 1.170       | 0.790-1.735 | 0.433  |
| CCI_R                | 1.036    | 0.945-1.087 | 0.074  | 1.016       | 0.968-1.065 | 0.527  |
| Steroid              | 1.497    | 0.598-2.976 | 0.495  | 1.501       | 0.339-3.298 | 0.617  |
| $\beta$ blockers     | 1.468    | 0.453-2.772 | 0.862  | 1.398       | 0.401-2.895 | 0.803  |
| CCB                  | 1.345    | 0.343-2.901 | 0.372  | 1.402       | 0.452-2.806 | 0.280  |
| ACEI                 | 1.298    | 0.426-3.041 | 0.601  | 1.288       | 0.395-2.845 | 0.334  |
| ARB                  | 1.346    | 0.379-1.986 | 0.711  | 1.345       | 0.343-1.886 | 0.682  |
| Diuretic             | 1.198    | 0.598-2.511 | 0.652  | 1.201       | 0.490-2.907 | 0.703  |
| Statin               | 1.364    | 0.667-4.972 | 0.798  | 1.335       | 0.679-4.787 | 0.897  |

HR= hazard ratio; CI = confidence interval; Adjusted HR: adjusted variables listed in the table;

CCI\_R = Charlson comorbidity index removed DM, COPD; DM = diabetes mellitus; COPD = chronic obstructive pulmonary disease; CCB = calcium channel blocker; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker

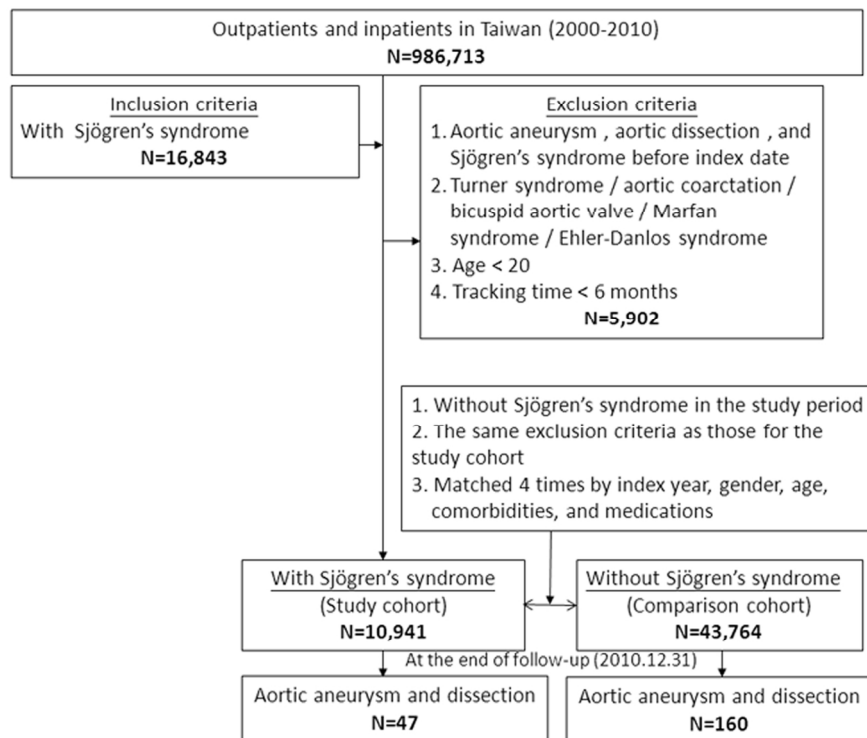
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**Table 4. Factors associated with aortic aneurysm and dissection stratified by primary/secondary Sjögren's syndrome using Cox regression**

|                            | Patients with Sjögren's syndrome |           |  | Patients without Sjögren's syndrome |            |  | Ratio | Adjusted HR* | 95% CI      | P-value |
|----------------------------|----------------------------------|-----------|--|-------------------------------------|------------|--|-------|--------------|-------------|---------|
|                            | Events                           | PY        | Incidence rate<br>(per 10 <sup>5</sup> PY) | Events                              | PY         | Incidence rate<br>(per 10 <sup>5</sup> PY) |       |              |             |         |
| Total                      | 47                               | 55,860.08 | 84.14                                      | 160                                 | 253,779.88 | 63.05                                      | 1.335 | 3.642        | 2.527-5.250 | <0.001  |
| Without RA / SLE / SS /PBC | 30                               | 36,607.55 | 81.95                                      | 158                                 | 248,694.36 | 63.53                                      | 1.290 | 1.753        | 1.108-9.382 | 0.042   |
| With RA / SLE / SS /PBC    | 17                               | 19,252.53 | 88.30                                      | 2                                   | 5,085.52   | 39.33                                      | 2.245 | 3.693        | 2.520-5.411 | <0.001  |

PYs = person-years; Ratio = incidence of patients with AA/AD divided by the incidence of patients without AA/AD; \*Adjusted HR = adjusted hazard ratio: adjusted for age, sex, comorbidities, and medications, as listed in Table 3, using Cox regression; CI = confidence interval; RA = rheumatoid arthritis ; SLE = systemic lupus erythematosus ; SS = systemic sclerosis ; PBC = primary biliary cirrhosis

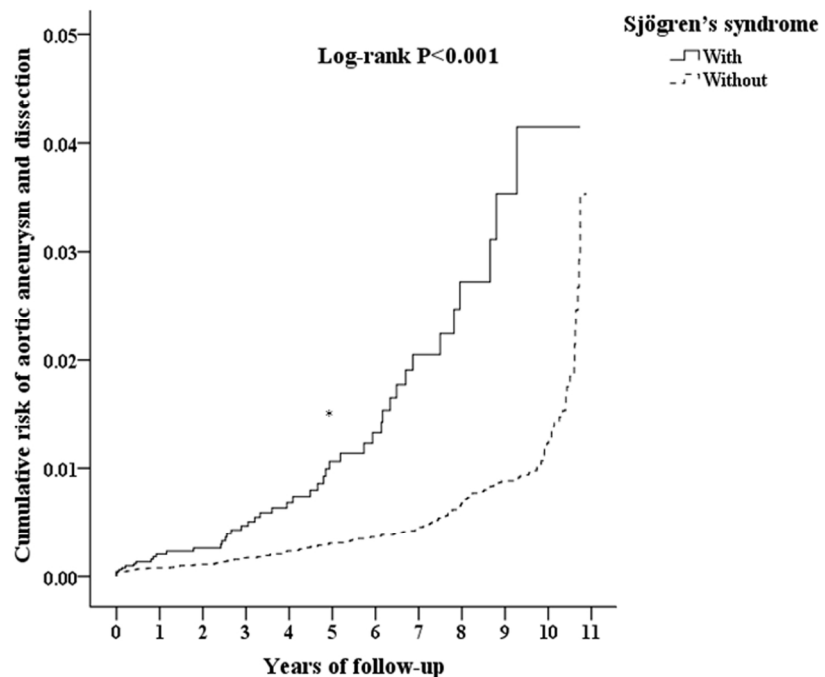
Primary Sjögren's syndrome: Sjögren's syndrome without systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, or primary biliary cirrhosis; Secondary Sjögren's syndrome: Sjögren's syndrome with systemic lupus erythematosus, rheumatoid arthritis , systemic sclerosis, or primary biliary cirrhosis



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| <b>With Sjögren's syndrome (N=10,941)</b>    | 13    | 15    | 21    | 26    | 32    | 35    | 41    | 44     | 46     | 47     | 47     |
| <b>Without Sjögren's syndrome (N=43,764)</b> | 27    | 36    | 49    | 63    | 77    | 81    | 94    | 113    | 130    | 146    | 160    |
| <b>P value</b>                               | 0.897 | 0.513 | 0.275 | 0.102 | 0.036 | 0.015 | 0.001 | <0.001 | <0.001 | <0.001 | <0.001 |

\*P<0.05 is considered statistically significant

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## Risk of aortic aneurysm and dissection in patients with Sjögren's syndrome: a nationwide population-based cohort study in Taiwan

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Manuscripts

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4 **1 Increased risk of aortic aneurysm and dissection in patients with Sjögren's**  
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6 **2 syndrome: a nationwide population-based cohort study in Taiwan**  
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4 **1 ABSTRACT**

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6 **2 Objectives:** Sjögren's syndrome (SS) is a systemic autoimmune disorder. Several  
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molecular pathways and the activation of matrix metalloproteinases associated with  
the pathogenesis of SS participate in the initiation and progression of aortic aneurysm  
(AA) and aortic dissection (AD). In this study, we aimed to evaluate whether patients  
with SS exhibit an increased risk of AA or AD.

**7 Methods:** We conducted a retrospective cohort study using a database extracted from  
8 Taiwan's National Health Insurance Research Database (NHIRD). All medical  
9 conditions for each case and control were categorized using the International  
10 Classification of Diseases, 9<sup>th</sup> Revision (ICD-9). Hazard ratios (HRs) and 95%  
11 confidence intervals (CIs) for associations between SS and AA/AD were estimated  
12 using Cox regression and adjusted for co-morbidities.

**13 Results:** Our analyses included 10,941 SS cases and 43,764 propensity score-matched  
14 controls. Compared with the controls, the patients with SS exhibited a significantly  
15 increased risk of developing an AA or AD (adjusted HR = 3.642, P < 0.001).

16 Subgroup analysis revealed that compared with patients without SS, patients with  
17 primary and secondary SS both exhibited a significantly increased risk of developing  
18 AA or AD (adjusted HR = 1.753, P = 0.042; adjusted HR = 3.693, P < 0.001).

**19 Conclusion:** Patients with SS exhibit increased risks of developing AA or AD, and

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4 1 healthcare professionals should be aware of this risk when treating patients with SS.  
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7 2 Increased aortic surveillance may be required for patients with SS syndrome.  
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12 4 **Keywords:** Sjögren's syndrome, aortic dissection, aortic aneurysm  
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## 1    **STRENGTHS AND LIMITATIONS OF THIS STUDY**

- 2    ●    The strength of our study is its population-based cohort design with a large  
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4    sample size.
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6    ●    The patients and controls were selected by 1:4 matching according to the  
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8    following baseline variables: age; sex; co-morbidities; and medications used.  
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10    This population-based cohort study was adjusted for potential risk factors to  
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12    minimize study bias.
- 13    ●    This was a retrospective cohort study.
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15    ●    NHIRD cannot provide detailed information regarding the laboratory results  
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17    or lifestyle factors of the patients.
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19    ●    Our results are limited to human data. Both mechanistic and animal studies are  
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21    required for further clarification.  
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## 1 INTRODUCTION

2 Sjögren's syndrome (SS) is a systemic autoimmune disorder commonly  
3 presenting with dry eyes and mouth. The prevalence of SS is between 0.1% and 4.8%  
4 in various populations when strictly defined according to the American-European  
5 Consensus Criteria, and it is one of the most common autoimmune diseases.[1] SS  
6 may affect patients at any age, but more cases occur in the fourth decade of life, and  
7 there is a female predominance. The female-male ratio is approximately 9:1.[2] Aortic  
8 aneurysms (AAs) are often diagnosed inadvertently and are a common cause of  
9 sudden death. Enlarged aneurysms can result in rupture. Aortic dissection (AD) is one  
10 of the deadliest complications of thoracic aortic disease. Estimates of the incidence of  
11 AD range from 6 cases per 100,000 to 16.3 per 100,000 in England and Sweden,  
12 respectively.[3,4] Regarding the Asian population, the average annual incidence of  
13 AD is 5.6 per 100,000 persons in Taiwan and the prevalence is 19.9 per 100,000  
14 persons, with a predominance noted among men 50 to 54 years of age (27.3 per  
15 100,000 persons per year).[5]

16 Previous studies have demonstrated that AA is more prevalent in patients with  
17 rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) compared with the  
18 general population.[6,7] Compared with age- and sex-matched healthy controls,  
19 primary SS (PSS) patients exhibited a 2-fold increased prevalence of hypertension



1 and hypertriglyceridemia. Furthermore, hypertension is underdiagnosed and  
2 suboptimally treated in PSS.[8] SS with positive autoantibodies is associated with a  
3 low ankle-brachial index, which may indicate an increased risk of early  
4 atherosclerosis.[9] Nonetheless, previous population-based studies indicated that SS is  
5 not associated with an increased risk of subsequent acute myocardial infarction (AMI)  
6 and ischaemic stroke.[10,11]

7       Several molecular mechanisms, including JNK, NF- $\kappa$ B and TGF- $\beta$  signalling  
8 pathways, and matrix metalloproteinase (MMP) activation are associated with the  
9 pathogenesis of SS.[12,13] These molecular mechanisms also actively participate in  
10 the initiation and progression of AA or AD.[14,15] Based on these findings, we  
11 hypothesized that patients with SS may have an increased risk of AA or AD due to  
12 SS-related cardiovascular risks and shared molecular mechanisms. However, the  
13 association between SS and AA or AD has not been thoroughly evaluated in  
14 large-scale studies. Therefore, we aimed to determine whether SS patients exhibited  
15 an increased risk of AA or AD using a nationwide healthcare insurance claim  
16 database.

## 17 **METHODS**

### 18 **Data source**

1           The data described herein were acquired from the Longitudinal Health Insurance  
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4           Database 2005 (LHID 2005), a subgroup database of the Taiwan National Health  
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6           Insurance Research Database (NHIRD) used for the nationwide population-based  
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8           retrospective cohort study. The National Health Insurance programme in Taiwan  
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10          provides health care for 99% of the population (greater than 23 million people) and  
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12          was implemented in 1995. The LHID 2005 provides information on medical service  
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14          utilization using a randomly selected sample of approximately one million people  
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16          receiving benefits, representing approximately 5% of Taiwan’s population in 2005.  
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18          The information was obtained from the NHIRD between 2000 and 2010. The  
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20          accuracy of the diagnoses in the NHIRD, particularly the diagnoses of major diseases  
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22          (e.g., acute coronary syndrome and stroke), has been corroborated.[16,17] The LHID  
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24          is composed of “de-identified” secondary data that are available to the public via open  
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26          access for research. ICD-9-CM (International Classification of Diseases, 9th Revision,  
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28          Clinical Modification) diagnostic and procedure codes (up to five each), sex,  
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30          birthdays, patient identification numbers, dates of admission and discharge, and  
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32          outcomes are coded. In addition, information regarding the medical institutions that  
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34          served patients was obtained. Individual information was protected using encoded  
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36          personal identification to prevent ethical violations related to the data. Our study  
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38          conformed to the Declaration of Helsinki and relevant guidelines. This Institutional  
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4 1 Review Board of the Tri-Service General Hospital, National Defense Medical Center,  
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7 2 Taipei, Taiwan, permitted this study (TSGH IRB No.2-105-05-082).

### 3 **Patient and public involvement**

4 This is a database study using NHIRD. No patients or public were involved in setting  
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4 This is a database study using NHIRD. No patients or public were involved in setting  
5 out the research question or developing the outcome measures. No patients or public  
6 involved in developing plans for design or implementation of the study. No patients or  
7 public were asked to advise on interpretation or writing up of results. No patients or  
8 public were the burden of the interventions on patients assessed. The results of the  
9 research were not disseminated to those study patients.

### 10 **Sampled patients**

11 We utilized study and comparison cohorts. Using the LHID 2005, we selected  
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11 We utilized study and comparison cohorts. Using the LHID 2005, we selected  
12 adult patients aged > 20 years who were newly diagnosed with SS (recorded from  
13 both the LHID 2005 and the Registry of Catastrophic Illness Patient Database) after  
14 2000 and who were followed-up between 2000 and 2010. We excluded patients who  
15 were diagnosed with SS before 2000 and AA or AD, Turner syndrome, aortic  
16 coarctation, bicuspid aortic valve, Marfan syndrome, or Ehler-Danlos syndrome.  
17 Patients had a tracking time < 6 months. The date of SS diagnosis was used as the  
18 index date. Control candidate sampling comparisons were selected from individuals in  
19 the LHID 2005 who lacked a history of SS. The patient and control cohorts were

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4 1 selected by 1:4 matching according to the following baseline variables: age; sex;  
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6 2 co-morbidities, including hypertension, diabetes mellitus (DM), hyperlipidaemia,  
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9 3 Behcet's disease, giant cell arteritis, RA and other inflammatory polyarthropathies,  
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12 4 relapsing polychondritis, Takayasu's arteritis, and chronic obstructive pulmonary  
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15 5 disease (COPD); and medication history, including  $\beta$ -blockers, calcium channel  
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18 6 blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers,  
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21 7 diuretics, and steroid history. We used COPD as a proxy variable for tobacco use to  
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24 8 eliminate its potential confounding effect as previously described.[18] The SS patient  
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27 9 and control cohorts were matched 1:4 based on their propensity score matching, for  
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30 10 which the matching tolerance was 0.15 with the nearest neighbour method. The  
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33 11 independent variables were demographics, co-morbidities, medications, and SS. The  
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36 12 propensity matching analysis was performed in the logistic regression model. We also  
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39 13 divided SS patients into PSS and secondary SS (SSS) patients and performed a  
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42 14 subgroup analysis. SS previously diagnosed as SLE, RA, systemic sclerosis, or  
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45 15 primary biliary cirrhosis were defined as SSS. We integrated the ICD-9-CM codes of  
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48 16 the above diseases into a table in the supplementary materials (Supplement Table 1).  
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51 17 The index dates for control patients were the same as the corresponding dates for  
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54 18 patients with AA/AD. The study outcome was a diagnosis of AA/AD during the  
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57 19 10-year follow-up period. AA/AD was identified using ICD-9 codes. The end point of

1 the follow-up period was 2010-12-31 or the time at which AA/AD events occurred or  
2 the patient died or was lost to follow-up. We integrated the median follow-up time and  
3 follow-up year with AA/AD events in the supplementary materials (Supplement  
4 Tables 2 and 3).

## 5 **Statistical analysis**

6       Categorical variables, which are presented as percentages, were compared using  
7 the chi-square or Fisher's exact tests. Continuous variables, which are presented as the  
8 means and standard deviations, were compared using a t-test. The primary goal of the  
9 study was to determine whether SS patients exhibit an increased risk for developing  
10 AA/AD. The associations between those outcomes (prognoses) and clinical  
11 characteristics were investigated using Cox regression. The results are presented as  
12 adjusted hazard ratios (HRs) with corresponding 95% confidence intervals (CIs).  
13 Kaplan-Meier curves with the log-rank test were used to compare patients with and  
14 without SS in terms of the cumulative risk of AA or AD. The threshold for statistical  
15 significance was  $P < 0.05$ . All data analyses were conducted using SPSS software  
16 version 22 (SPSS Inc., Chicago, IL, USA).

## 17 **RESULTS**

18       A flow diagram of our patient enrolment scheme is presented in Figure 1. A total  
19 of 10,941 patients diagnosed with SS were identified in the NHIRD, which contains a

1 total of 986,713 individuals. An additional 43,764 age-, sex-, comorbidity-, and  
2 medication-matched patients were designated controls. As shown in Table 1, no  
3 significant differences in sex, age, co-morbidities, including DM, hypertension,  
4 hyperlipidaemia, Behcet's disease, giant cell arteritis, RA, relapsing polychondritis,  
5 Takayasu's arteritis, and COPD, or medications were noted between the two groups  
6 after matching. Patients with SS exhibited a significantly increased cumulative risk of  
7 developing AA/AD in subsequent years compared with patients without SS (log- rank  
8 test < 0.001, Figure 2). Table 2 presents the incidences of AA or AD during the  
9 ten-year follow-up period. At the end of the follow-up period, SS patients exhibited  
10 significantly increased incidences of AA or AD (0.43% vs. 0.37%,  $P = 0.045$ ) but  
11 lower incidences of DM (7.73% vs. 15.44%,  $P < 0.001$ ) and COPD (5.96% vs. 6.72%,  
12  $P = 0.004$ ). In addition, patients with SS were younger and exhibited higher Charlson  
13 comorbidity index (CCI) than patients without SS. The incidence for AA or AD was  
14 higher in males and older patients regardless of whether patients had SS or not  
15 (Supplement Figures 1 and 2). Regarding the use of Cox regression independent of  
16 the effects of sex, age, co-morbidities, and medication, compared with patients  
17 without SS, patients with SS also exhibited a significantly increased risk of  
18 developing AA or AD (adjusted HR = 3.642, 95% CI = 2.527-5.250,  $P < 0.001$ , Table  
19 3). The subgroup analysis revealed that patients with PSS or SSS both exhibited

1 significantly increased risks for developing AA/AD compared with patients without  
 2 SS (adjusted HR = 1.753, 95% CI = 1.108-9.382, P = 0.042; adjusted HR = 3.693,  
 3 95% CI = 2.520-5.411, P < 0.001, Table 4). We also integrated the first event of  
 4 AA/AD coding into the distribution analysis in the supplemental material  
 5 (Supplement Table 4). All patients were coded with AA/AD for the first time in the  
 6 Inpatient and ER sections.

7 Table 1 Characteristics of the study participants at baseline

| Sjögren's syndrome       | Total<br>N (%)  | With<br>N (%)   | Without<br>N (%) | P-value |
|--------------------------|-----------------|-----------------|------------------|---------|
| Total                    | 54,705          | 10,941 (20.00%) | 43,764 (80.00%)  |         |
| Sex                      |                 |                 |                  | 0.999   |
| Male                     | 10,187 (18.63%) | 2,011 (18.44%)  | 8,176 (18.68%)   |         |
| Female                   | 44,485 (81.37%) | 8,897 (81.56%)  | 35,588 (81.32%)  |         |
| Age (years)              | 55.78 ± 17.09   | 55.80 ± 16.65   | 55.77 ± 17.20    | 0.897   |
| DM                       | 3,553 (6.49%)   | 724 (6.62%)     | 2,829 (6.46%)    | 0.558   |
| Hypertension             | 8,091 (14.79%)  | 1,578 (14.42%)  | 6,513 (14.88%)   | 0.228   |
| Hyperlipidaemia          | 1,145 (2.09%)   | 234 (2.14%)     | 911 (2.08%)      | 0.709   |
| Behcet's disease         | 321 (0.59%)     | 62 (0.57%)      | 259 (0.59%)      | 0.834   |
| Giant cell arteritis     | 15 (0.03%)      | 3 (0.03%)       | 12 (0.03%)       | 0.999   |
| Rheumatoid arthritis     | 8,907 (16.28%)  | 1,784 (16.31%)  | 7,123 (16.28%)   | 0.942   |
| Relapsing polychondritis | 71 (0.13%)      | 14 (0.13%)      | 57 (0.13%)       | 0.953   |
| Takayasu's arteritis     | 15 (0.03%)      | 3 (0.03%)       | 12 (0.03%)       | 0.999   |
| COPD                     | 2,931 (5.36%)   | 581 (5.3%)      | 2,350 (5.37%)    | 0.831   |
| Steroid                  | 16,799 (30.71%) | 3,345 (30.57%)  | 13,454 (30.74%)  | 0.737   |
| β blocker                | 12,588 (23.01%) | 2,513 (22.97%)  | 10,075 (23.02%)  | 0.919   |
| CCB                      | 11,553 (21.12%) | 2,342 (21.41%)  | 9,211 (21.05%)   | 0.409   |
| ACEI                     | 13,586 (24.84%) | 2,711 (24.78%)  | 10,875 (24.85%)  | 0.878   |
| ARB                      | 12,718 (23.25%) | 2,620 (23.95%)  | 10,098 (23.07%)  | 0.054   |
| Diuretic                 | 12,440 (22.74%) | 2,429 (22.20%)  | 10,011 (22.87%)  | 0.136   |
| Statin                   | 13,922 (25.45%) | 2,811 (25.69%)  | 11,111 (25.39%)  | 0.516   |

P-value (categorical variable: Chi-square/Fisher's exact test; continuous variable: t-test)

DM = diabetes mellitus; COPD = chronic obstructive pulmonary disease; CCB = calcium channel blocker; ACEI =  
angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker

1 Table 2 Incidences of aortic aneurysm and dissection and other characteristics during  
2 the ten-year follow-up period

| Sjögren's syndrome                        | Total<br>N (%)  | With<br>N (%)   | Without<br>N (%) | P-value |
|---|-----------------|-----------------|------------------|---------|
| <b>Total</b>                              | 54,705          | 10,941 (20.00%) | 43,764 (80.00%)  |         |
| <b>Aortic aneurysm<br/>and dissection</b> | 207 (0.38%)     | 47 (0.43%)      | 160 (0.37%)      | 0.045   |
| <b>Sex</b>                                |                 |                 |                  | 0.999   |
| Male                                      | 10,187 (18.63%) | 2,011 (18.44%)  | 8,176 (18.68%)   |         |
| Female                                    | 44,485 (81.37%) | 8,897 (81.56%)  | 35,588 (81.32%)  |         |
| <b>Age (years)</b>                        | 61.36 ± 5.41    | 60.90 ± 4.98    | 61.47 ± 5.51     | <0.001  |
| <b>DM</b>                                 | 7,603 (13.90%)  | 846 (7.73%)     | 6,757 (15.44%)   | <0.001  |
| <b>Hypertension</b>                       | 8,821 (16.12%)  | 1,708 (15.61%)  | 7,113 (16.25%)   | 0.102   |
| <b>Hyperlipidaemia</b>                    | 1,128 (2.06%)   | 240 (2.19%)     | 888 (2.03%)      | 0.279   |
| <b>Behcet's disease</b>                   | 324 (0.59%)     | 63 (0.58%)      | 261 (0.60%)      | 0.802   |
| <b>Giant cell arteritis</b>               | 16 (0.03%)      | 3 (0.03%)       | 13 (0.03%)       | 0.901   |
| <b>Rheumatoid arthritis</b>               | 9,033 (16.51%)  | 1,774 (16.21%)  | 7,259 (16.59%)   | 0.348   |
| <b>Relapsing<br/>polychondritis</b>       | 80 (0.15%)      | 19 (0.17%)      | 61 (0.14%)       | 0.401   |
| <b>Takayasu's arteritis</b>               | 15 (0.03%)      | 3 (0.03%)       | 12 (0.03%)       | 0.999   |
| <b>COPD</b>                               | 3,593 (6.57%)   | 652 (5.96%)     | 2,941 (6.72%)    | 0.004   |
| <b>CCI_R</b>                              | 0.78 ± 1.53     | 0.83 ± 1.39     | 0.77 ± 1.56      | <0.001  |
| <b>Steroid</b>                            | 17,112 (31.28%) | 3,511 (32.09%)  | 13,601 (31.08%)  | 0.041   |
| <b>β blockers</b>                         | 13,750 (25.13%) | 2,674 (24.44%)  | 11,076 (25.31%)  | 0.061   |
| <b>CCB</b>                                | 11,833 (21.63%) | 2,397 (21.91%)  | 9,436 (21.56%)   | 0.430   |
| <b>ACEI</b>                               | 13,793 (25.21%) | 2,784 (25.45%)  | 11,009 (25.16%)  | 0.532   |
| <b>ARB</b>                                | 12,976 (23.72%) | 2,681 (24.50%)  | 10,295 (23.52%)  | 0.031   |
| <b>Diuretic</b>                           | 12,692 (23.20%) | 2,507 (22.91%)  | 10,185 (23.27%)  | 0.427   |
| <b>Statin</b>                             | 14,123 (25.82%) | 2,828 (25.85%)  | 11,295 (25.81%)  | 0.934   |

P-value (categorical variable: Chi-square/Fisher's exact test; continuous variable: t-test)

CCI\_R = Charlson comorbidity index removed DM, COPD; DM = diabetes mellitus; COPD = chronic obstructive pulmonary disease; CCB = calcium channel blocker; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker



1 Table 3 Factors associated with aortic aneurysm and dissection according to Cox  
 2 regression

| Variables            | Crude HR | 95% CI      | P-value | Adjusted HR | 95% CI      | P-value |
|----------------------|----------|-------------|---------|-------------|-------------|---------|
| Sjögren's syndrome   | 3.205    | 2.254-3.565 | < 0.001 | 3.642       | 2.527-5.250 | < 0.001 |
| Sex (male)           | 2.645    | 1.974-3.597 | < 0.001 | 2.035       | 1.534-2.700 | < 0.001 |
| Age (years)          | 1.049    | 1.032-1.057 | < 0.001 | 1.043       | 1.032-1.055 | < 0.001 |
| DM                   | 1.704    | 1.389-1.944 | 0.024   | 1.674       | 1.065-1.976 | 0.037   |
| Hypertension         | 1.165    | 1.022-1.454 | 0.038   | 1.305       | 0.973-1.751 | 0.075   |
| Hyperlipidaemia      | 1.211    | 0.594-2.436 | 0.618   | 1.343       | 0.656-2.751 | 0.420   |
| Rheumatoid arthritis | 1.645    | 0.774-3.496 | 0.196   | 0.801       | 0.362-1.769 | 0.583   |
| COPD                 | 1.838    | 1.256-2.691 | 0.002   | 1.170       | 0.790-1.735 | 0.433   |
| CCI_R                | 1.036    | 0.945-1.087 | 0.074   | 1.016       | 0.968-1.065 | 0.527   |
| Steroid              | 1.497    | 0.598-2.976 | 0.495   | 1.501       | 0.339-3.298 | 0.617   |
| $\beta$ blockers     | 1.468    | 0.453-2.772 | 0.862   | 1.398       | 0.401-2.895 | 0.803   |
| CCB                  | 1.345    | 0.343-2.901 | 0.372   | 1.402       | 0.452-2.806 | 0.280   |
| ACEI                 | 1.298    | 0.426-3.041 | 0.601   | 1.288       | 0.395-2.845 | 0.334   |
| ARB                  | 1.346    | 0.379-1.986 | 0.711   | 1.345       | 0.343-1.886 | 0.682   |
| Diuretic             | 1.198    | 0.598-2.511 | 0.652   | 1.201       | 0.490-2.907 | 0.703   |
| Statin               | 1.364    | 0.667-4.972 | 0.798   | 1.335       | 0.679-4.787 | 0.897   |

HR= hazard ratio; CI = confidence interval; Adjusted HR: adjusted variables listed in the table;

CCI\_R = Charlson comorbidity index removed DM, COPD; DM = diabetes mellitus; COPD = chronic obstructive pulmonary disease; CCB = calcium channel blocker; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker

Table 4 Factors associated with aortic aneurysm and dissection stratified by primary/secondary Sjögren's syndrome using Cox regression

|                       | Patients with Sjögren's syndrome |           |  | Patients without Sjögren's syndrome |            |  | Ratio | Adjusted HR* | 95% CI      | P-value |
|-----------------------|----------------------------------|-----------|--|-------------------------------------|------------|--|-------|--------------|-------------|---------|
|                       | Events                           | PY        | Incidence rate<br>(per 10 <sup>5</sup> PY) | Events                              | PY         | Incidence rate<br>(per 10 <sup>5</sup> PY) |       |              |             |         |
| Total                 | 47                               | 55,860.08 | 84.14                                      | 160                                 | 253,779.88 | 63.05                                      | 1.335 | 3.642        | 2.527-5.250 | < 0.001 |
| Without RA/SLE/SS/PBC | 30                               | 36,607.55 | 81.95                                      | 158                                 | 248,694.36 | 63.53                                      | 1.290 | 1.753        | 1.108-9.382 | 0.042   |
| With RA/SLE/SS/PBC    | 17                               | 19,252.53 | 88.30                                      | 2                                   | 5,085.52   | 39.33                                      | 2.245 | 3.693        | 2.520-5.411 | < 0.001 |

PYs = person-years; Ratio = incidence of patients with AA/AD divided by the incidence of patients without AA/AD; \*Adjusted HR = adjusted hazard ratio: adjusted for age, sex, co-morbidities, and medications, as listed in Table 3, using Cox regression; CI = confidence interval; RA = rheumatoid arthritis ; SLE = systemic lupus erythematosus ; SS = systemic sclerosis ; PBC = primary biliary cirrhosis

Primary Sjögren's syndrome: Sjögren's syndrome without systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, or primary biliary cirrhosis; Secondary Sjögren's syndrome: Sjögren's syndrome with systemic lupus erythematosus, rheumatoid arthritis , systemic sclerosis, or primary biliary cirrhosis

## 1 DISCUSSION

2 This is a retrospective cohort study including 10,941 patients with SS and  
3 43,764 patients without SS matched by age, sex, year of index date of the SS  
4 diagnosis, co-morbidities, and medication use from a large-scale nationwide  
5 population-based database. During follow-up, SS was associated with an increased  
6 incidence of the development of AA/AD compared with the comparison cohort.

7 Our research findings should remind healthcare providers of new  
8 information that SS patients exhibit an increased risk for AA or AD. Healthcare  
9 professionals should be aware of these life-threatening aortic events and aim to make  
10 early diagnosis of AA or AD. When SS patients present with chest, back, or  
11 abdominal symptoms, the possibility of AA or AD should be considered, with a  
12 specific and rapid examination.

13 SS patients exhibit an increased prevalence of developing traditional  
14 cardiovascular risk factors, such as hypertension and dyslipidaemia, which predispose  
15 patients to endothelial dysfunction and premature atherosclerosis. However, the  
16 disease-specific mechanisms associated with premature atherosclerosis in SS are not  
17 fully understood.[19] In a recent review article, cardiovascular disease was reported to  
18 be one of the primary causes of mortality in SS patients.[20] PSS shares clinical and  
19 serological features with RA and SLE, and these two diseases are associated with

1 acceleration of atherosclerosis.[21] However, the pathophysiology between SS and  
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4 AA or AD remains unclear, although several possible mechanisms have been  
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7 proposed. Previous studies have demonstrated that both SS and AA/AD are induced  
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10 by chronic inflammation.[22-25] Recent studies have provided convincing evidence  
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13 indicating that several signalling pathways are involved in both AA and SS, including  
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16 the MAPK, TGF- $\beta$ , and MMP signalling pathways.[12-15] Activation of the innate  
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19 immune system and the production of interferons (IFNs) could be the first stages of  
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22 PSS pathogenesis.[26] IFNs and IL-21 could induce B-cell-activating factor (BAFF)  
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25 and further activate B cell activity. In human salivary gland cells, interferon- $\gamma$   
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28 modulates and increases MMP-2 and MMP-9 expression.[27] The circulating levels  
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31 of MMP-9 were increased in patients with definite SS compared with patients with  
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34 possible SS.[28] Furthermore, MMP-2 and MMP-9 also display a critical role in AAA  
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37 formation.[29] MMPs play roles in tissue destruction and the weakening of the matrix,  
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40 as noted in liver cirrhosis, fibrotic lung disease, otosclerosis, atherosclerosis, and  
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43 multiple sclerosis.[30] Several molecules that are activated in the salivary glands,  
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46 including JNK, NF- $\kappa$ B, and TGF- $\beta$ , also lead to inflammation and reactive oxygen  
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49 species (ROS) production in the aortic matrix. This process may be a possible  
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52 mechanistic pathway by which SS aggravates AA or AD.[12,13,22,31-34]

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55 Low-dose steroids, such as prednisone, may be used to treat SS-induced  
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1 joint and muscle pain. Prolonged or high-dose corticosteroid treatment likely causes  
2 disintegration of connective tissue of the media possibly together with primary aortic  
3 wall involvement and/or vascular damage in patients with autoimmune disorders,  
4 which can result in aortic aneurysmal enlargement and AD.[30,35] In this study, the  
5 medical condition of steroids was matched. Therefore, the effect of steroids was  
6 mitigated. The strength of our study involves its population-based database design.  
7 We accounted for several aneurysm-related confounding factors. Although we  
8 adjusted the results extensively using Cox regression models, our study had several  
9 limitations and unmeasured confounders. The NHIRD registry is not able to provide  
10 detailed information on laboratory results, family histories and health-related lifestyle  
11 factors, such as alcohol consumption and tobacco use, which can increase the risk of  
12 AA/AD and were potential confounding factors in this study. In our study, we also  
13 considered COPD incidence as a proxy variable for tobacco use to eliminate its  
14 potential confounding effect.[18] The limitation is that not all smokers develop  
15 disease. Although our study identified the association between SS and AA/AD, the  
16 cohort study design did not enable determination of the cause-effect relationship.  
17 Further prospective follow-up studies, mechanistic studies and animal experiments  
18 should be performed.

## 19 **CONCLUSION**

1 Patients with SS exhibit an increased risk for developing AA or AD, and  
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1 Patients with SS exhibit an increased risk for developing AA or AD, and  
2 healthcare professionals should be aware of this risk when treating patients with SS.  
3 Increased aortic surveillance may be required in patients with SS.

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13 Hospital, National Defense Medical Center, Taipei, Taiwan (TSGH-C105-173),  
14 Taoyuan Armed Forces General Hospital, Taoyuan, Taiwan (10514), and the Ministry  
15 of Science and Technology (MOST 106-2314-B-016 -008 -MY3).

#### 16 **COMPETING INTERESTS**

17 None declared.

#### 18 **AUTHOR CONTRIBUTIONS**

19 Y-DT, J-CW, and S-HT conceived and designed the study.

1 W-CC provided the materials for the study. C-HC and S-JC analysed the data.

2 C-JY and M-TL contributed reagents, materials, and analysis tools. Y-DT, J-CW,

3 W-IL, and S-HT wrote the manuscript. All the authors approved the manuscript.

#### 4 **DATA SHARING STATEMENT**

5 No additional data sharing available.

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For peer review only

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4 **1 FIGURE LEGENDS**

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7 2 Figure 1. Patient selection flowchart

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9 3 Figure 2. Kaplan-Meier curve of the cumulative risk of aortic aneurysm or dissection  
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12 4 due to Sjögren's syndrome

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18 **6 TABLE LEGENDS**

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21 7 Table 1. Characteristics of the study participants at baseline

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23 8 Table 2. Incidences of aortic aneurysm and dissection and other characteristics during  
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26 9 the ten-year follow-up period

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29 10 Table 3. Factors associated with aortic aneurysm and dissection according to Cox  
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32 11 regression

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34  
35 12 Table 4. Factors associated with aortic aneurysm or dissection stratified by  
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38 13 primary/secondary SS using Cox regression

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43 **15 SUPPLEMENTARY MATERIAL**

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46 16 Supplement Table 1 ICD-9-CM coding of diseases in the manuscript

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49 17 Supplement Table 2 Years of follow-up

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52 18 Supplement Table 3 Years to AA /AD

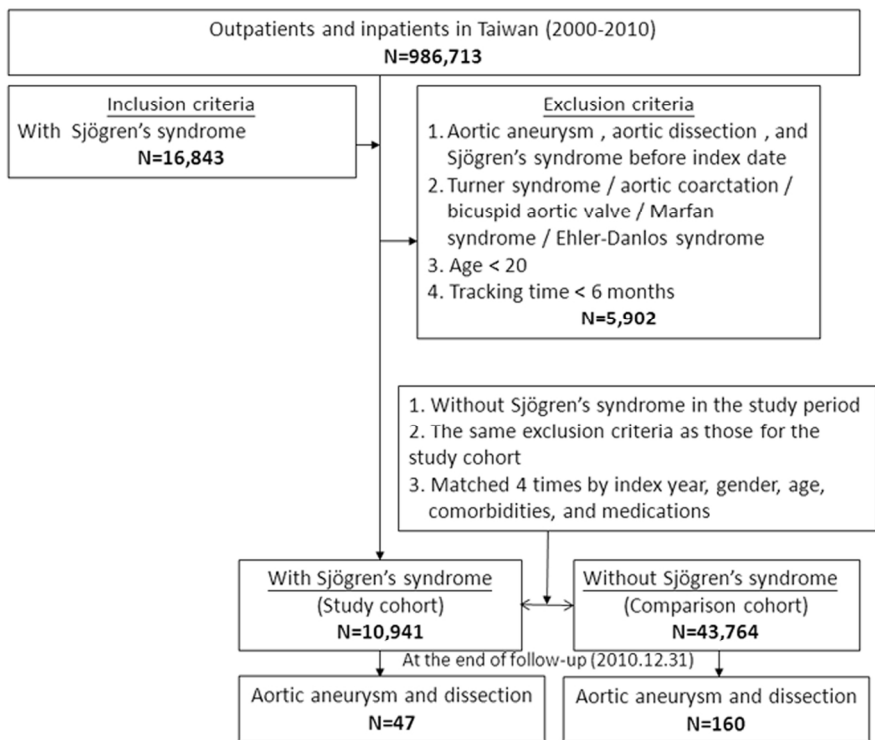
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55 19 Supplement Table 4 First event of the (AA/AD) coding distribution

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- 4 1 Supplement Figure 1. Sex-specific incidence of AA or AD in the study cohort, control
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- 6 2 cohort, and general population.
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- 9 3 Supplement Figure 2. Age-specific incidence of AA or AD in the study cohort, control
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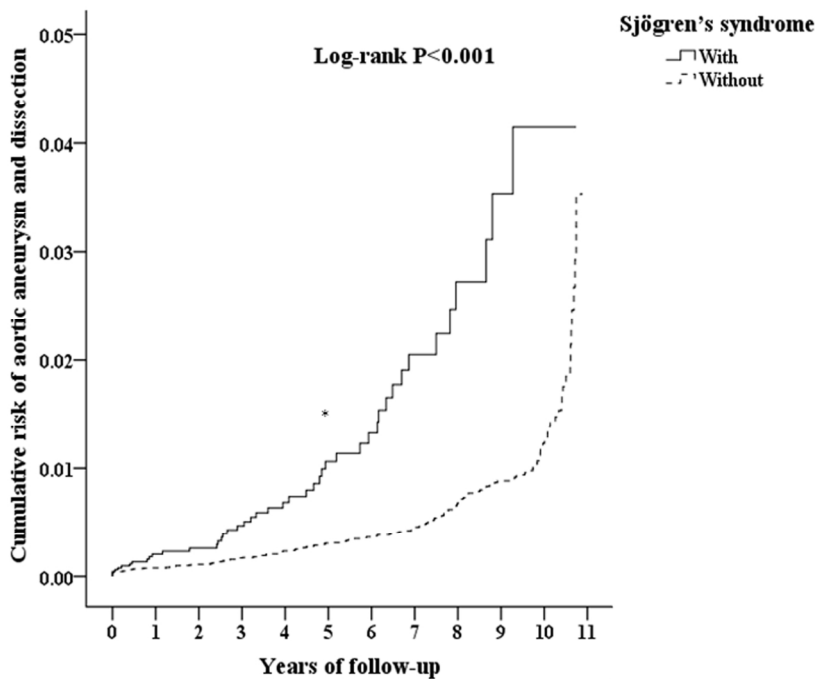


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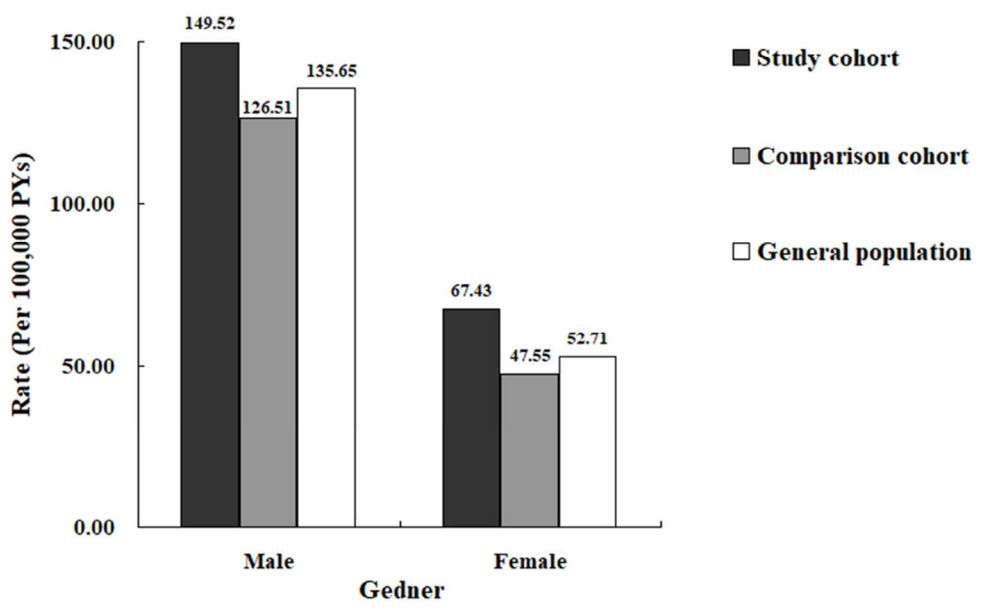
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|---------------------------------------|-------|-------|-------|-------|-------|-------|-------|--------|--------|--------|--------|
| With Sjögren's syndrome (N=10,941)    | 13    | 15    | 21    | 26    | 32    | 35    | 41    | 44     | 46     | 47     | 47     |
| Without Sjögren's syndrome (N=43,764) | 27    | 36    | 49    | 63    | 77    | 81    | 94    | 113    | 130    | 146    | 160    |
| <b>P value</b>                        | 0.897 | 0.513 | 0.275 | 0.102 | 0.036 | 0.015 | 0.001 | <0.001 | <0.001 | <0.001 | <0.001 |

\*:  $P < 0.05$  is considered statistically significant

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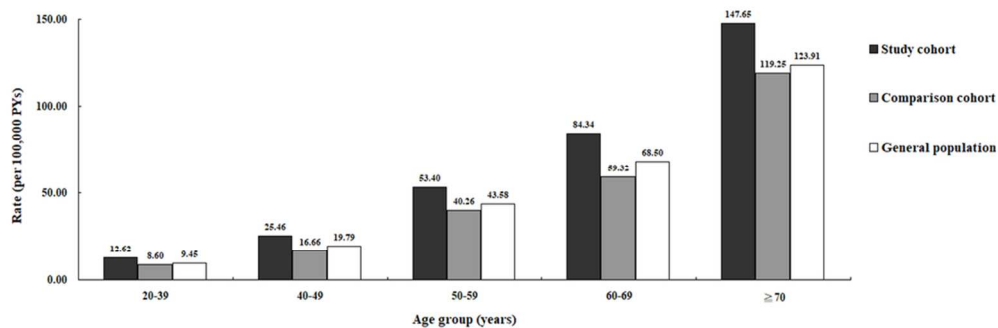
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Supplement Table 1 ICD-9-CM coding of diseases in the manuscript

| Disease                        | ICD-9-CM    | Disease                   | ICD-9-CM |
|--------------------------------|-------------|---------------------------|----------|
| Aortic aneurysm and dissection | 441.0-441.9 | Behcet's disease          | 136.1    |
| Sjögren's syndrome             | 710.2       | Giant cell arteritis      | 446.5    |
| Turner syndrome                | 758.6       | RA                        | 714      |
| Aortic coarctation             | 747.10      | Relapsing polychondritis  | 733.99   |
| Bicuspid aortic valve          | 746.4       | Takayasu's arteritis      | 446.7    |
| Marfan syndrome                | 759.82      | COPD                      | 490-496  |
| Ehler-Danlos syndrome          | 756.83      | SLE                       | 710.0    |
| Diabetes mellitus              | 250         | Systemic sclerosis        | 701.1    |
| Hypertension                   | 401-405     | Primary biliary cirrhosis | 571.6    |
| Hyperlipidaemia                | 272.0-272.4 |                           |          |

RA = rheumatoid arthritis and other inflammatory polyarthropathies; COPD = chronic obstructive pulmonary disease; SLE = systemic lupus erythematosus

Supplement Table 2 Years of follow-up

| <b>Sjögren's syndrome</b> | <b>Min</b> | <b>Middle</b> | <b>Max</b> | <b>Mean ± SD</b> |
|---------------------------|------------|---------------|------------|------------------|
| <b>With</b>               | 0.50       | 3.26          | 10.91      | 5.11 ± 7.52      |
| <b>Without</b>            | 0.50       | 4.57          | 10.98      | 5.80 ± 5.53      |
| <b>Total</b>              | 0.50       | 3.69          | 10.98      | 5.66 ± 5.99      |

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Supplement Table 3 Years to AA/AD

| <b>Sjögren's syndrome</b> | <b>Min</b> | <b>Middle</b> | <b>Max</b> | <b>Mean ± SD</b> |
|---------------------------|------------|---------------|------------|------------------|
| <b>With</b>               | 0.51       | 3.32          | 9.27       | 4.67 ± 3.82      |
| <b>Without</b>            | 0.52       | 5.07          | 10.87      | 5.53 ± 3.65      |
| <b>Total</b>              | 0.51       | 4.93          | 10.87      | 5.12 ± 3.49      |

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Supplement Table 4 First event of the (AA/AD) coding distribution

| Sjögren's syndrome | Inpatient |       | Emergency Room |       |
|--------------------|-----------|-------|----------------|-------|
|                    | N         | %     | N              | %     |
| With               | 40        | 85.11 | 7              | 14.89 |
| Without            | 141       | 88.12 | 19             | 11.88 |
| Total              | 181       | 87.44 | 26             | 12.56 |

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**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies**

| Section/Topic             | Item # | Recommendation   | Reported on page # |
|---------------------------|--------|--|--------------------|
| Title and abstract        | 1      | (a) Indicate the study’s design with a commonly used term in the title or the abstract   | 3                  |
|                           |        | (b) Provide in the abstract an informative and balanced summary of what was done and what was found  | 3-4                |
| <b>Introduction</b>       |        |  |                    |
| Background/rationale      | 2      | Explain the scientific background and rationale for the investigation being reported   | 6                  |
| Objectives                | 3      | State specific objectives, including any prespecified hypotheses   | 7                  |
| <b>Methods</b>            |        |  |                    |
| Study design              | 4      | Present key elements of study design early in the paper  | 11                 |
| Setting                   | 5      | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection  | 10-11              |
| Participants              | 6      | (a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up   | 8                  |
|                           |        | (b) For matched studies, give matching criteria and number of exposed and unexposed  | 10                 |
| Variables                 | 7      | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable   | 9-10               |
| Data sources/ measurement | 8*     | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 10                 |
| Bias                      | 9      | Describe any efforts to address potential sources of bias  | 19                 |
| Study size                | 10     | Explain how the study size was arrived at  | 17                 |
| Quantitative variables    | 11     | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why   | 9-10               |
| Statistical methods       | 12     | (a) Describe all statistical methods, including those used to control for confounding  | 10                 |
|                           |        | (b) Describe any methods used to examine subgroups and interactions  | 11                 |
|                           |        | (c) Explain how missing data were addressed  | 11                 |
|                           |        | (d) If applicable, explain how loss to follow-up was addressed   | 11                 |
|                           |        | (e) Describe any sensitivity analyses  | 11                 |
| <b>Results</b>            |        |  |                    |

|                          |     |  |     |
|--------------------------|-----|--|-----|
| Participants             | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed            | 11  |
|                          |     | (b) Give reasons for non-participation at each stage   | 8-9 |
|                          |     | (c) Consider use of a flow diagram   | 11  |
| Descriptive data         | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders   | 11  |
|                          |     | (b) Indicate number of participants with missing data for each variable of interest  | 11  |
|                          |     | (c) Summarise follow-up time (eg, average and total amount)  | 11  |
| Outcome data             | 15* | Report numbers of outcome events or summary measures over time   | 12  |
| Main results             | 16  | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 12  |
|                          |     | (b) Report category boundaries when continuous variables were categorized  | 11  |
|                          |     | (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period   | 12  |
| Other analyses           | 17  | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses   | 12  |
| <b>Discussion</b>        |     |  |     |
| Key results              | 18  | Summarise key results with reference to study objectives   | 17  |
| <b>Limitations</b>       |     |  |     |
| Interpretation           | 20  | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence                                   | 19  |
| Generalisability         | 21  | Discuss the generalisability (external validity) of the study results  | 19  |
| <b>Other information</b> |     |  |     |
| Funding                  | 22  | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based  | 20  |

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## Risk of aortic aneurysm and dissection in patients with Sjögren's syndrome: a nationwide population-based cohort study in Taiwan

|                                 |   |
|---------------------------------|---|
| Journal:                        | <i>BMJ Open</i>   |
| Manuscript ID                   | bmjopen-2018-022326.R2  |
| Article Type:                   | Research  |
| Date Submitted by the Author:   | 18-Aug-2018   |
| Complete List of Authors:       | <p>Tsai, Yi-Da; Tri-Service General Hospital, National Defense Medical Center, Department of Emergency medicine</p> <p>Chien, Wu-Chien ; Tri-Service General Hospital, National Defense Medical Center, Department of Medical Research; National Defense Medical Center, School of Public Health</p> <p>Tsai, Shih-Hung ; Tri-Service General Hospital, National Defense Medical Center, Department of Emergency Medicine</p> <p>Chung, Chi-Hsiang; Tri-Service General Hospital, National Defense Medical Center, Department of Medical Research; National Defense Medical Center, School of Public Health</p> <p>Chu, Shi-Jye ; Tri-Service General Hospital, National Defense Medical Center, Division of Rheumatology, Immunology and Allergy, Department of Internal Medicine</p> <p>Chen, Sy-Jou ; Tri-Service General Hospital, National Defense Medical Center, Department of Emergency Medicine</p> <p>Liao, Wen-I; Tri-Service General Hospital, National Defense Medical Center, Department of Emergency Medicine</p> <p>Yang, Chih-Jen; Tri-Service General Hospital, National Defense Medical Center, Emergency Medicine</p> <p>Liao, Min-Tser ; Taoyuan Armed Forces General Hospital,, Department of Pediatrics</p> <p>Wang, Jen-Chun; Tri-Service General Hospital, National Defense Medical Center, department of Emergency Medicine, Emergency Department</p> |
| <b>Primary Subject Heading</b>: | Rheumatology  |
| Secondary Subject Heading:      | Cardiovascular medicine   |
| Keywords:                       | Sjögren's syndrome, aortic dissection, aortic aneurysm  |
|                                 |   |

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Manuscripts

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4 **1 Increased risk of aortic aneurysm and dissection in patients with Sjögren's**  
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6 **2 syndrome: a nationwide population-based cohort study in Taiwan**  
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12 4 Yi-Da Tsai MD<sup>1</sup>, Wu-Chien Chien PhD<sup>2,3</sup>, Shih-Hung Tsai MD, PhD<sup>1</sup>, Chi-Hsiang  
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15 5 Chung PhD<sup>2,3,4</sup>, Shi-Jye Chu MD<sup>5</sup>, Sy-Jou Chen MD, MS<sup>1,6</sup>, Wen-I Liao MD<sup>1</sup>,  
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10 Word count:

11 2752

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4 **1 ABSTRACT**

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6 **2 Objectives:** Sjögren's syndrome (SS) is a systemic autoimmune disorder. Several  
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molecular pathways and the activation of matrix metalloproteinases associated with  
the pathogenesis of SS participate in the initiation and progression of aortic aneurysm  
(AA) and aortic dissection (AD). In this study, we aimed to evaluate whether patients  
with SS exhibit an increased risk of AA or AD.

**7 Methods:** We conducted a retrospective cohort study using a database extracted from  
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Taiwan's National Health Insurance Research Database (NHIRD). All medical  
conditions for each case and control were categorised using the International  
Classification of Diseases, 9<sup>th</sup> Revision (ICD-9). Hazard ratios (HRs) and 95%  
confidence intervals (CIs) for associations between SS and AA/AD were estimated  
using Cox regression and adjusted for co-morbidities.

**13 Results:** Our analyses included 10,941 SS cases and 43,764 propensity score-matched  
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controls. Compared with the controls, the patients with SS exhibited a significantly  
increased risk of developing an AA or AD (adjusted HR = 3.642, P < 0.001).

Subgroup analysis revealed that compared with patients without SS, patients with  
primary and secondary SS both exhibited a significantly increased risk of developing  
AA or AD (adjusted HR = 1.753, P = 0.042; adjusted HR = 3.693, P < 0.001).

**19 Conclusion:** Patients with SS exhibit increased risks of developing AA or AD, and

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4 1 healthcare professionals should be aware of this risk when treating patients with SS.  
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7 2 Increased aortic surveillance may be required for patients with SS syndrome.  
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12 4 **Keywords:** Sjögren's syndrome, aortic dissection, aortic aneurysm  
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## 1    **STRENGTHS AND LIMITATIONS OF THIS STUDY**

- 2    ●    The strength of our study is its population-based cohort design with a large  
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4    sample size.
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6    ●    The patients and controls were selected by 1:4 matching according to the  
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8    following baseline variables: age; sex; co-morbidities; and medications used.  
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10    This population-based cohort study was adjusted for potential risk factors to  
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12    minimize study bias.
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14    ●    This was a retrospective cohort study.
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16    ●    NHIRD cannot provide detailed information regarding the laboratory results  
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18    or lifestyle factors of the patients.
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20    ●    Our results are limited to human data. Both mechanistic and animal studies are  
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22    required for further clarification.  
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## 1 INTRODUCTION

2 Sjögren's syndrome (SS) is a systemic autoimmune disorder commonly  
3 presenting with dry eyes and mouth. The prevalence of SS is between 0.1% and 4.8%  
4 in various populations when strictly defined according to the American-European  
5 Consensus Criteria, and it is one of the most common autoimmune diseases.[1] SS  
6 may affect patients at any age, but more cases occur in the fourth decade of life, and  
7 there is a female predominance. The female-male ratio is approximately 9:1.[2] Aortic  
8 aneurysms (AAs) are often diagnosed inadvertently and are a common cause of  
9 sudden death. Enlarged aneurysms can result in rupture. Aortic dissection (AD) is one  
10 of the deadliest complications of thoracic aortic disease. Estimates of the incidence of  
11 AD range from 6 cases per 100,000 to 16.3 per 100,000 in England and Sweden,  
12 respectively.[3,4] Regarding the Asian population, the average annual incidence of  
13 AD is 5.6 per 100,000 persons in Taiwan and the prevalence is 19.9 per 100,000  
14 persons, with a predominance noted among men 50 to 54 years of age (27.3 per  
15 100,000 persons per year).[5]

16 Previous studies have demonstrated that AA is more prevalent in patients with  
17 rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) compared with the  
18 general population.[6,7] Compared with age- and sex-matched healthy controls,  
19 primary SS (PSS) patients exhibited a 2-fold increased prevalence of hypertension

1 and hypertriglyceridemia. Furthermore, hypertension is underdiagnosed and  
2 suboptimally treated in PSS.[8] SS with positive autoantibodies is associated with a  
3 low ankle-brachial index, which may indicate an increased risk of early  
4 atherosclerosis.[9] Nonetheless, previous population-based studies indicated that SS is  
5 not associated with an increased risk of subsequent acute myocardial infarction (AMI)  
6 and ischaemic stroke.[10,11]

7       Several molecular mechanisms, including JNK, NF- $\kappa$ B and TGF- $\beta$  signalling  
8 pathways, and matrix metalloproteinase (MMP) activation are associated with the  
9 pathogenesis of SS.[12,13] These molecular mechanisms also actively participate in  
10 the initiation and progression of AA or AD.[14,15] Based on these findings, we  
11 hypothesized that patients with SS may have an increased risk of AA or AD due to  
12 SS-related cardiovascular risks and shared molecular mechanisms. However, the  
13 association between SS and AA or AD has not been thoroughly evaluated in  
14 large-scale studies. Therefore, we aimed to determine whether SS patients exhibited  
15 an increased risk of AA or AD using a nationwide healthcare insurance claim  
16 database.

## 17 **METHODS**

### 18 **Data source**

1           The data described herein were acquired from the Longitudinal Health Insurance  
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4           Database 2005 (LHID 2005), a subgroup database of the Taiwan National Health  
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6           Insurance Research Database (NHIRD) used for the nationwide population-based  
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8           retrospective cohort study. The National Health Insurance programme in Taiwan  
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10          provides health care for 99% of the population (greater than 23 million people) and  
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12          was implemented in 1995. The LHID 2005 provides information on medical service  
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14          utilization using a randomly selected sample of approximately one million people  
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16          receiving benefits, representing approximately 5% of Taiwan's population in 2005.  
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18          The information was obtained from the NHIRD between 2000 and 2010. The  
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20          accuracy of the diagnoses in the NHIRD, particularly the diagnoses of major diseases  
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22          (e.g., acute coronary syndrome and stroke), has been corroborated.[16,17] The LHID  
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24          is composed of "de-identified" secondary data that are available to the public via open  
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26          access for research. ICD-9-CM (International Classification of Diseases, 9th Revision,  
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28          Clinical Modification) diagnostic and procedure codes (up to five each), sex,  
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30          birthdays, patient identification numbers, dates of admission and discharge, and  
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32          outcomes are coded. In addition, information regarding the medical institutions that  
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34          served patients was obtained. Individual information was protected using encoded  
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36          personal identification to prevent ethical violations related to the data. Our study  
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38          conformed to the Declaration of Helsinki and relevant guidelines. This Institutional  
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4 1 Review Board of the Tri-Service General Hospital, National Defense Medical Center,  
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7 2 Taipei, Taiwan, permitted this study (TSGH IRB No.2-105-05-082).  
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### 9 3 **Patient and public involvement**

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12 4 This is a database study using NHIRD. No patients or public were involved in setting  
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15 5 out the research question or developing the outcome measures. No patients or public  
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18 6 involved in developing plans for design or implementation of the study. No patients or  
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21 7 public were asked to advise on interpretation or writing up of results. No patients or  
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24 8 public were the burden of the interventions on patients assessed. The results of the  
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27 9 research were not disseminated to those study patients.  
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### 29 10 **Sampled patients**

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32 11 We utilized study and comparison cohorts. Using the LHID 2005, we selected  
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35 12 adult patients aged > 20 years who were newly diagnosed with SS (recorded from  
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38 13 both the LHID 2005 and the Registry of Catastrophic Illness Patient Database) after  
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41 14 2000 and who were followed-up between 2000 and 2010. We excluded patients who  
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44 15 were diagnosed with SS before 2000 and had AA or AD, Turner syndrome, aortic  
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47 16 coarctation, bicuspid aortic valve, Marfan syndrome, or Ehler-Danlos syndrome.  
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50 17 Patients who had a tracking time < 6 months were also excluded in order to decrease  
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53 18 the probability of including AA/AD cases that went undiagnosed before SS diagnosis.  
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56 19 The date of SS diagnosis was used as the index date. Control candidate sampling  
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1 comparisons were selected from individuals in the LHID 2005 who lacked a history  
2 of SS. The patient and control cohorts were selected by 1:4 matching according to the  
3 following baseline variables: age; sex; co-morbidities, including hypertension,  
4 diabetes mellitus (DM), hyperlipidaemia, Behcet's disease, giant cell arteritis, RA and  
5 other inflammatory polyarthropathies, relapsing polychondritis, Takayasu's arteritis,  
6 and chronic obstructive pulmonary disease (COPD); and medication history, including  
7  $\beta$ -blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors,  
8 angiotensin receptor blockers, diuretics, and steroid history. We used COPD as a  
9 proxy variable for tobacco use to eliminate its potential confounding effect as  
10 previously described.[18] The SS patient and control cohorts were matched 1:4 based  
11 on their propensity score matching, for which the matching tolerance was 0.15 with  
12 the nearest neighbour method. The independent variables were demographics,  
13 co-morbidities, medications, and SS. The dependent variables were AA and AD. We  
14 also divided SS patients into PSS and secondary SS (SSS) patients and performed a  
15 subgroup analysis. SS previously diagnosed as SLE, RA, systemic sclerosis, or  
16 primary biliary cirrhosis were defined as SSS. We integrated the ICD-9-CM codes of  
17 the above diseases into a table in the supplementary materials (Supplement Table 1).  
18 The index dates for control patients were the same as the corresponding dates for  
19 patients with AA/AD. The study outcome was a diagnosis of AA/AD during the

1 10-year follow-up period. AA/AD was identified using ICD-9 codes. The end point of  
2 the follow-up period was 2010-12-31 or the time at which AA/AD events occurred or  
3 the patient died or was lost to follow-up. We integrated the median follow-up time and  
4 follow-up year with AA/AD events in the supplementary materials (Supplement  
5 Tables 2 and 3).

## 6 **Statistical analysis**

7 Propensity matching analysis was performed in the logistic regression model.  
8 The potential confounders were index year, gender, age, comorbidities, and  
9 medications. The match tolerance was 0.15 with the nearest neighbour method. The  
10 study comparison cohort-matching ratio was 4-fold (study: comparison = 1:4).  
11 Categorical variables, which are presented as percentages, were compared using the  
12 chi-square or Fisher's exact tests. Continuous variables, which are presented as the  
13 means and standard deviations, were compared using a t-test. The primary goal of the  
14 study was to determine whether SS patients exhibit an increased risk for developing  
15 AA/AD. The associations between those outcomes (prognoses) and clinical  
16 characteristics were investigated using Cox regression. As shown in Supplement  
17 Tables 4, all explanatory variables in the fully adjusted model were retained. The  
18 results are presented as adjusted hazard ratios (HRs) with corresponding 95%  
19 confidence intervals (CIs). Kaplan-Meier curves with the log-rank test were used to

1 compare patients with and without SS in terms of the cumulative risk of AA or AD.

2 The threshold for statistical significance was  $P < 0.05$ . All data analyses were

3 conducted using SPSS software version 22 (SPSS Inc., Chicago, IL, USA).

#### 4 **RESULTS**

5 A flow diagram of our patient enrolment scheme is presented in Figure 1. A total  
6 of 10,941 patients diagnosed with SS were identified in the NHIRD, which contains a  
7 total of 986,713 individuals. An additional 43,764 age-, sex-, comorbidity-, and  
8 medication-matched patients were designated controls. As shown in Table 1, no  
9 significant differences in sex, age, co-morbidities, including DM, hypertension,  
10 hyperlipidaemia, Behcet's disease, giant cell arteritis, RA, relapsing polychondritis,  
11 Takayasu's arteritis, and COPD, or medications were noted between the two groups  
12 after matching. Patients with SS exhibited a significantly increased cumulative risk of  
13 developing AA/AD in subsequent years compared with patients without SS (log- rank  
14 test  $< 0.001$ , Figure 2). Table 2 presents the incidences of AA or AD during the  
15 ten-year follow-up period. At the end of the follow-up period, SS patients exhibited  
16 significantly increased incidences of AA or AD (0.43% vs. 0.37%,  $P = 0.045$ ) but  
17 lower incidences of DM (7.73% vs. 15.44%,  $P < 0.001$ ) and COPD (5.96% vs. 6.72%,  
18  $P = 0.004$ ). In addition, patients with SS were younger and exhibited higher Charlson  
19 comorbidity index (CCI) than patients without SS. The incidence for AA or AD was

1 higher in males and older patients regardless of whether patients had SS or not  
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6 (Supplement Figures 1 and 2). Regarding the use of Cox regression independent of  
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9 the effects of sex, age, co-morbidities, and medication, compared with patients  
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12 without SS, patients with SS also exhibited a significantly increased risk of  
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15 developing AA or AD (adjusted HR = 3.642, 95% CI = 2.527-5.250, P < 0.001, Table  
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18 3). The subgroup analysis revealed that patients with PSS or SSS both exhibited  
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21 significantly increased risks for developing AA/AD compared to patients without SS  
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24 (adjusted HR = 1.753, 95% CI = 1.108-9.382, P = 0.042; adjusted HR = 3.693, 95%  
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27 CI = 2.520-5.411, P < 0.001, Table 4). We also have included the first event of  
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30 AA/AD coding into the distribution analysis in the supplemental material  
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32 (Supplement Table 5). All patients were coded with AA/AD for the first time in the  
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35 Inpatient and ER sections.  
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3 Table 1 Characteristics of the study participants at baseline

| Sjögren's syndrome       | Total<br>N (%)  | With<br>N (%)   | Without<br>N (%) | P-value |
|--------------------------|-----------------|-----------------|------------------|---------|
| Total                    | 54,705          | 10,941 (20.00%) | 43,764 (80.00%)  |         |
| Sex                      |                 |                 |                  | 0.999   |
| Male                     | 10,187 (18.63%) | 2,011 (18.44%)  | 8,176 (18.68%)   |         |
| Female                   | 44,485 (81.37%) | 8,897 (81.56%)  | 35,588 (81.32%)  |         |
| Age (years)              | 55.78 ± 17.09   | 55.80 ± 16.65   | 55.77 ± 17.20    | 0.897   |
| DM                       | 3,553 (6.49%)   | 724 (6.62%)     | 2,829 (6.46%)    | 0.558   |
| Hypertension             | 8,091 (14.79%)  | 1,578 (14.42%)  | 6,513 (14.88%)   | 0.228   |
| Hyperlipidaemia          | 1,145 (2.09%)   | 234 (2.14%)     | 911 (2.08%)      | 0.709   |
| Behcet's disease         | 321 (0.59%)     | 62 (0.57%)      | 259 (0.59%)      | 0.834   |
| Giant cell arteritis     | 15 (0.03%)      | 3 (0.03%)       | 12 (0.03%)       | 0.999   |
| Rheumatoid arthritis     | 8,907 (16.28%)  | 1,784 (16.31%)  | 7,123 (16.28%)   | 0.942   |
| Relapsing polychondritis | 71 (0.13%)      | 14 (0.13%)      | 57 (0.13%)       | 0.953   |
| Takayasu's arteritis     | 15 (0.03%)      | 3 (0.03%)       | 12 (0.03%)       | 0.999   |
| COPD                     | 2,931 (5.36%)   | 581 (5.3%)      | 2,350 (5.37%)    | 0.831   |
| Steroid                  | 16,799 (30.71%) | 3,345 (30.57%)  | 13,454 (30.74%)  | 0.737   |
| β blocker                | 12,588 (23.01%) | 2,513 (22.97%)  | 10,075 (23.02%)  | 0.919   |
| CCB                      | 11,553 (21.12%) | 2,342 (21.41%)  | 9,211 (21.05%)   | 0.409   |
| ACEI                     | 13,586 (24.84%) | 2,711 (24.78%)  | 10,875 (24.85%)  | 0.878   |
| ARB                      | 12,718 (23.25%) | 2,620 (23.95%)  | 10,098 (23.07%)  | 0.054   |
| Diuretic                 | 12,440 (22.74%) | 2,429 (22.20%)  | 10,011 (22.87%)  | 0.136   |
| Statin                   | 13,922 (25.45%) | 2,811 (25.69%)  | 11,111 (25.39%)  | 0.516   |

P-value (categorical variable: Chi-square/Fisher's exact test; continuous variable: t-test)

DM = diabetes mellitus; COPD = chronic obstructive pulmonary disease; CCB = calcium channel blocker; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker

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9 3 Table 2 Incidences of aortic aneurysm and dissection and other characteristics during  
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12 4 the ten-year follow-up period  
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| Sjögren's syndrome                        | Total<br>N (%)  | With<br>N (%)   | Without<br>N (%) | P-value |
|---|-----------------|-----------------|------------------|---------|
| <b>Total</b>                              | 54,705          | 10,941 (20.00%) | 43,764 (80.00%)  |         |
| <b>Aortic aneurysm<br/>and dissection</b> | 207 (0.38%)     | 47 (0.43%)      | 160 (0.37%)      | 0.045   |
| <b>Sex</b>                                |                 |                 |                  | 0.999   |
| Male                                      | 10,187 (18.63%) | 2,011 (18.44%)  | 8,176 (18.68%)   |         |
| Female                                    | 44,485 (81.37%) | 8,897 (81.56%)  | 35,588 (81.32%)  |         |
| <b>Age (years)</b>                        | 61.36 ± 5.41    | 60.90 ± 4.98    | 61.47 ± 5.51     | <0.001  |
| <b>DM</b>                                 | 7,603 (13.90%)  | 846 (7.73%)     | 6,757 (15.44%)   | <0.001  |
| <b>Hypertension</b>                       | 8,821 (16.12%)  | 1,708 (15.61%)  | 7,113 (16.25%)   | 0.102   |
| <b>Hyperlipidaemia</b>                    | 1,128 (2.06%)   | 240 (2.19%)     | 888 (2.03%)      | 0.279   |
| <b>Behcet's disease</b>                   | 324 (0.59%)     | 63 (0.58%)      | 261 (0.60%)      | 0.802   |
| <b>Giant cell arteritis</b>               | 16 (0.03%)      | 3 (0.03%)       | 13 (0.03%)       | 0.901   |
| <b>Rheumatoid arthritis</b>               | 9,033 (16.51%)  | 1,774 (16.21%)  | 7,259 (16.59%)   | 0.348   |
| <b>Relapsing<br/>polychondritis</b>       | 80 (0.15%)      | 19 (0.17%)      | 61 (0.14%)       | 0.401   |
| <b>Takayasu's arteritis</b>               | 15 (0.03%)      | 3 (0.03%)       | 12 (0.03%)       | 0.999   |
| <b>COPD</b>                               | 3,593 (6.57%)   | 652 (5.96%)     | 2,941 (6.72%)    | 0.004   |
| <b>CCI_R</b>                              | 0.78 ± 1.53     | 0.83 ± 1.39     | 0.77 ± 1.56      | <0.001  |
| <b>Steroid</b>                            | 17,112 (31.28%) | 3,511 (32.09%)  | 13,601 (31.08%)  | 0.041   |
| <b>β blockers</b>                         | 13,750 (25.13%) | 2,674 (24.44%)  | 11,076 (25.31%)  | 0.061   |
| <b>CCB</b>                                | 11,833 (21.63%) | 2,397 (21.91%)  | 9,436 (21.56%)   | 0.430   |
| <b>ACEI</b>                               | 13,793 (25.21%) | 2,784 (25.45%)  | 11,009 (25.16%)  | 0.532   |
| <b>ARB</b>                                | 12,976 (23.72%) | 2,681 (24.50%)  | 10,295 (23.52%)  | 0.031   |
| <b>Diuretic</b>                           | 12,692 (23.20%) | 2,507 (22.91%)  | 10,185 (23.27%)  | 0.427   |
| <b>Statin</b>                             | 14,123 (25.82%) | 2,828 (25.85%)  | 11,295 (25.81%)  | 0.934   |

P-value (categorical variable: Chi-square/Fisher's exact test; continuous variable: t-test)

CCI\_R = Charlson comorbidity index removed DM, COPD; DM = diabetes mellitus; COPD = chronic obstructive pulmonary disease; CCB = calcium channel blocker; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor

blocker

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3 Table 3 Factors associated with aortic aneurysm and dissection according to Cox

4 regression

| Variables            | Crude HR | 95% CI      | P-value | Adjusted HR | 95% CI      | P-value |
|----------------------|----------|-------------|---------|-------------|-------------|---------|
| Sjögren's syndrome   | 3.205    | 2.254-3.565 | < 0.001 | 3.642       | 2.527-5.250 | < 0.001 |
| Sex (male)           | 2.645    | 1.974-3.597 | < 0.001 | 2.035       | 1.534-2.700 | < 0.001 |
| Age (years)          | 1.049    | 1.032-1.057 | < 0.001 | 1.043       | 1.032-1.055 | < 0.001 |
| DM                   | 1.704    | 1.389-1.944 | 0.024   | 1.674       | 1.065-1.976 | 0.037   |
| Hypertension         | 1.165    | 1.022-1.454 | 0.038   | 1.305       | 0.973-1.751 | 0.075   |
| Hyperlipidaemia      | 1.211    | 0.594-2.436 | 0.618   | 1.343       | 0.656-2.751 | 0.420   |
| Rheumatoid arthritis | 1.645    | 0.774-3.496 | 0.196   | 0.801       | 0.362-1.769 | 0.583   |
| COPD                 | 1.838    | 1.256-2.691 | 0.002   | 1.170       | 0.790-1.735 | 0.433   |
| CCI_R                | 1.036    | 0.945-1.087 | 0.074   | 1.016       | 0.968-1.065 | 0.527   |
| Steroid              | 1.497    | 0.598-2.976 | 0.495   | 1.501       | 0.339-3.298 | 0.617   |
| β blockers           | 1.468    | 0.453-2.772 | 0.862   | 1.398       | 0.401-2.895 | 0.803   |
| CCB                  | 1.345    | 0.343-2.901 | 0.372   | 1.402       | 0.452-2.806 | 0.280   |
| ACEI                 | 1.298    | 0.426-3.041 | 0.601   | 1.288       | 0.395-2.845 | 0.334   |
| ARB                  | 1.346    | 0.379-1.986 | 0.711   | 1.345       | 0.343-1.886 | 0.682   |
| Diuretic             | 1.198    | 0.598-2.511 | 0.652   | 1.201       | 0.490-2.907 | 0.703   |
| Statin               | 1.364    | 0.667-4.972 | 0.798   | 1.335       | 0.679-4.787 | 0.897   |

HR= hazard ratio; CI = confidence interval; Adjusted HR: adjusted variables listed in the table;

CCI\_R = Charlson comorbidity index removed DM, COPD; DM = diabetes mellitus; COPD = chronic obstructive pulmonary disease; CCB = calcium channel blocker; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker

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Table 4 Factors associated with aortic aneurysm and dissection stratified by primary/secondary Sjögren's syndrome using Cox regression

|                       | Patients with Sjögren's syndrome |           |  | Patients without Sjögren's syndrome |            |  | Ratio | Adjusted HR* | 95% CI      | P-value |
|-----------------------|----------------------------------|-----------|--|-------------------------------------|------------|--|-------|--------------|-------------|---------|
|                       | Events                           | PY        | Incidence rate<br>(per 10 <sup>5</sup> PY) | Events                              | PY         | Incidence rate<br>(per 10 <sup>5</sup> PY) |       |              |             |         |
| Total                 | 47                               | 55,860.08 | 84.14                                      | 160                                 | 253,779.88 | 63.05                                      | 1.335 | 3.642        | 2.527-5.250 | < 0.001 |
| Without RA/SLE/SS/PBC | 30                               | 36,607.55 | 81.95                                      | 158                                 | 248,694.36 | 63.53                                      | 1.290 | 1.753        | 1.108-9.382 | 0.042   |
| With RA/SLE/SS/PBC    | 17                               | 19,252.53 | 88.30                                      | 2                                   | 5,085.52   | 39.33                                      | 2.245 | 3.693        | 2.520-5.411 | < 0.001 |

PYs = person-years; Ratio = incidence of patients with AA/AD divided by the incidence of patients without AA/AD; \*Adjusted HR = adjusted hazard ratio: adjusted for age, sex, co-morbidities, and medications, as listed in Table 3, using Cox regression; CI = confidence interval; RA = rheumatoid arthritis ; SLE = systemic lupus erythematosus ; SS = systemic sclerosis ; PBC = primary biliary cirrhosis

Primary Sjögren's syndrome: Sjögren's syndrome without systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, or primary biliary cirrhosis; Secondary Sjögren's syndrome: Sjögren's syndrome with systemic lupus erythematosus, rheumatoid arthritis , systemic sclerosis, or primary biliary cirrhosis

## 1 DISCUSSION

2 This is a retrospective cohort study including 10,941 patients with SS and 43,764  
3 patients without SS matched by age, sex, year of index date of the SS diagnosis,  
4 co-morbidities, and medication use from a large-scale nationwide population-based  
5 database. During follow-up, SS was associated with an increased incidence of the  
6 development of AA/AD compared with the comparison cohort.

7 Our research findings should remind healthcare providers of new information  
8 that SS patients exhibit an increased risk for AA or AD. Healthcare professionals  
9 should be aware of these life-threatening aortic events and aim to make early  
10 diagnosis of AA or AD. When SS patients present with chest, back, or abdominal  
11 symptoms, the possibility of AA or AD should be considered, with a specific and  
12 rapid examination.

13 SS patients exhibit an increased prevalence of developing traditional  
14 cardiovascular risk factors, such as hypertension and dyslipidaemia, which predispose  
15 patients to endothelial dysfunction and premature atherosclerosis. However, the  
16 disease-specific mechanisms associated with premature atherosclerosis in SS are not  
17 fully understood.[19] In a recent review article, cardiovascular disease was reported to  
18 be one of the primary causes of mortality in SS patients.[20] PSS shares clinical and  
19 serological features with RA and SLE, and these two diseases are associated with

1 acceleration of atherosclerosis.[21] However, the pathophysiology between SS and  
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1 acceleration of atherosclerosis.[21] However, the pathophysiology between SS and  
2 AA or AD remains unclear, although several possible mechanisms have been  
3 proposed. Previous studies have demonstrated that both SS and AA/AD are induced  
4 by chronic inflammation.[22-25] Recent studies have provided convincing evidence  
5 indicating that several signalling pathways are involved in both AA and SS, including  
6 the MAPK, TGF- $\beta$ , and MMP signalling pathways.[12-15] Activation of the innate  
7 immune system and the production of interferons (IFNs) could be the first stages of  
8 PSS pathogenesis.[26] IFNs and IL-21 could induce B-cell-activating factor (BAFF)  
9 and further activate B cell activity. In human salivary gland cells, interferon- $\gamma$   
10 modulates and increases MMP-2 and MMP-9 expression.[27] The circulating levels  
11 of MMP-9 were increased in patients with definite SS compared with patients with  
12 possible SS.[28] Furthermore, MMP-2 and MMP-9 also display a critical role in AAA  
13 formation.[29] MMPs play roles in tissue destruction and the weakening of the matrix,  
14 as noted in liver cirrhosis, fibrotic lung disease, otosclerosis, atherosclerosis, and  
15 multiple sclerosis.[30] Several molecules that are activated in the salivary glands,  
16 including JNK, NF- $\kappa$ B, and TGF- $\beta$ , also lead to inflammation and reactive oxygen  
17 species (ROS) production in the aortic matrix. This process may be a possible  
18 mechanistic pathway by which SS aggravates AA or AD.[12,13,22,31-34]

19 Low-dose steroids, such as prednisone, may be used to treat SS-induced joint and

1 muscle pain. Prolonged or high-dose corticosteroid treatment likely causes  
2 disintegration of connective tissue of the media possibly together with primary aortic  
3 wall involvement and/or vascular damage in patients with autoimmune disorders,  
4 which can result in aortic aneurysmal enlargement and AD.[30,35] In this study, the  
5 medical condition of steroids was matched. Therefore, the effect of steroids was  
6 mitigated. The strength of our study involves its population-based database design.  
7 We accounted for several aneurysm-related confounding factors. Although we  
8 adjusted the results extensively using Cox regression models, our study had several  
9 limitations and unmeasured confounders. The NHIRD registry is not able to provide  
10 detailed information on laboratory results, family histories and health-related lifestyle  
11 factors, such as alcohol consumption and tobacco use, which can increase the risk of  
12 AA/AD and were potential confounding factors in this study. This is a database study  
13 using NHIRD. All medical conditions for each case and the controls were categorized  
14 using the ICD-9-CM, in which diagnostic codes (up to five each) are coded. There  
15 may be a small number of coding errors or missing information when using this kind  
16 of administrative data, and limitations are bound to exist in any statistical method,  
17 even the propensity score matching. In our study, we also considered COPD incidence  
18 as a proxy variable for tobacco use to eliminate its potential confounding effect.[18]  
19 The limitation is that not all smokers develop disease. Although our study identified

1 the association between SS and AA/AD, the cohort study design did not enable  
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1 the association between SS and AA/AD, the cohort study design did not enable  
2 determination of the cause-effect relationship. Further prospective follow-up studies,  
3 mechanistic studies and animal experiments should be performed.

#### 4 **CONCLUSION**

5 Patients with SS exhibit an increased risk for developing AA or AD, and  
6 healthcare professionals should be aware of this risk when treating patients with SS.  
7 Increased aortic surveillance may be required in patients with SS.

#### 8 **ACKNOWLEDGEMENTS**

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10 Defense Medical Center, Taipei, Taiwan (TSGH-C105-058), Tri-Service General  
11 Hospital, National Defense Medical, Taipei, Taiwan (TSGH-C105-173), Taoyuan  
12 Armed Forces General Hospital, Taoyuan, Taiwan (10514), and the Ministry of  
13 Science and Technology (MOST 106-2314-B-016 -008 -MY3).

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16 Defense Medical Center, Taipei, Taiwan (TSGH-C105-058), Tri-Service General  
17 Hospital, National Defense Medical Center, Taipei, Taiwan (TSGH-C105-173),  
18 Taoyuan Armed Forces General Hospital, Taoyuan, Taiwan (10514), and the Ministry  
19 of Science and Technology (MOST 106-2314-B-016 -008 -MY3).



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4 **1 COMPETING INTERESTS**  
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6  
7 2 None declared.  
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9  
10 **3 AUTHOR CONTRIBUTIONS**  
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12 4 Y-DT, J-CW, and S-HT conceived and designed the study.  
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14  
15 5 W-CC provided the materials for the study. C-HC and S-JC analysed the data.  
16

17  
18 6 C-JY and M-TL contributed reagents, materials, and analysis tools. Y-DT, J-CW,  
19

20  
21 7 W-IL, and S-HT wrote the manuscript. All the authors approved the manuscript.  
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24 **8 DATA SHARING STATEMENT**  
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27 9 No additional data sharing available.  
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4 **1 FIGURE LEGENDS**

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6  
7 2 Figure 1. Patient selection flowchart

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9 3 Figure 2. Kaplan-Meier curve of the cumulative risk of aortic aneurysm or dissection  
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12 4 due to Sjögren's syndrome

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18 **6 TABLE LEGENDS**

19  
20  
21 7 Table 1. Characteristics of the study participants at baseline

22  
23 8 Table 2. Incidences of aortic aneurysm and dissection and other characteristics during  
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26 9 the ten-year follow-up period

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29 10 Table 3. Factors associated with aortic aneurysm and dissection according to Cox  
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31  
32 11 regression

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34  
35 12 Table 4. Factors associated with aortic aneurysm or dissection stratified by  
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38 13 primary/secondary SS using Cox regression

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43 **15 SUPPLEMENTARY MATERIAL**

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46 16 Supplement Table 1 ICD-9-CM coding of diseases in the manuscript

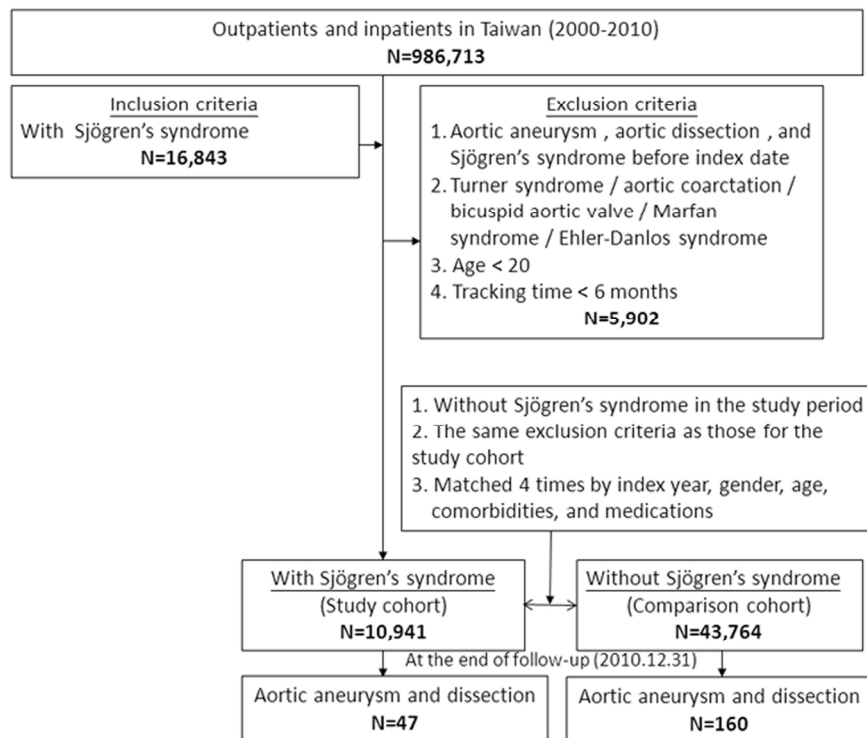
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49 17 Supplement Table 2 Years of follow-up

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52 18 Supplement Table 3 Years to AA /AD

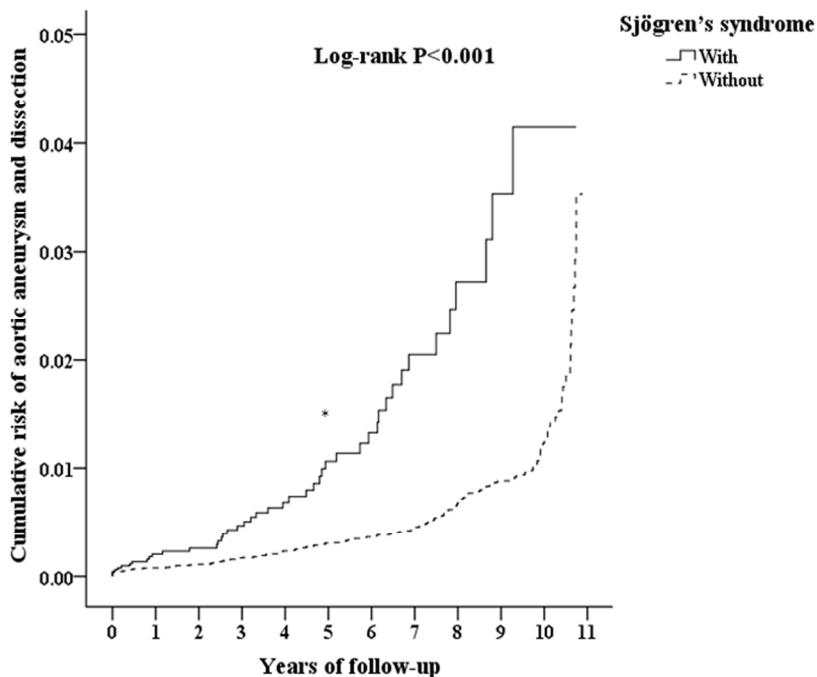
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55 19 Supplement Table 4 Variables including in the Cox regression



- 1 Supplement Table 5 First event of the (AA/AD) coding distribution
- 2 Supplement Figure 1. Sex-specific incidence of AA or AD in the study cohort, control
- 3 cohort, and general population.
- 4 Supplement Figure 2. Age-specific incidence of AA or AD in the study cohort, control
- 5 cohort, and general population.
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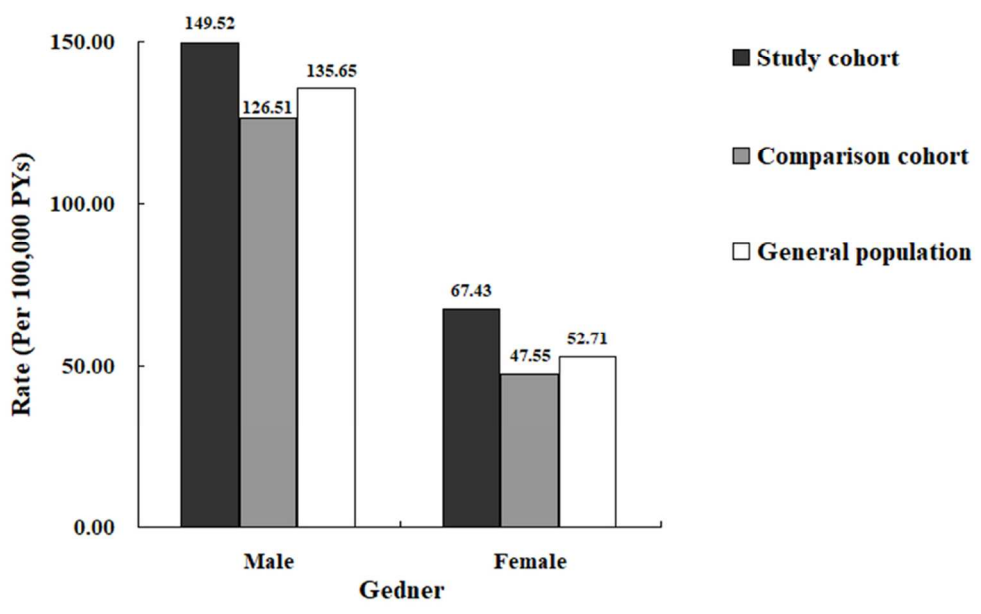
|                                       |       |       |       |       |       |       |       |        |        |        |        |
|---------------------------------------|-------|-------|-------|-------|-------|-------|-------|--------|--------|--------|--------|
| With Sjögren's syndrome (N=10,941)    | 13    | 15    | 21    | 26    | 32    | 35    | 41    | 44     | 46     | 47     | 47     |
| Without Sjögren's syndrome (N=43,764) | 27    | 36    | 49    | 63    | 77    | 81    | 94    | 113    | 130    | 146    | 160    |
| <b>P value</b>                        | 0.897 | 0.513 | 0.275 | 0.102 | 0.036 | 0.015 | 0.001 | <0.001 | <0.001 | <0.001 | <0.001 |

\*:P<0.05 is considered statistically significant

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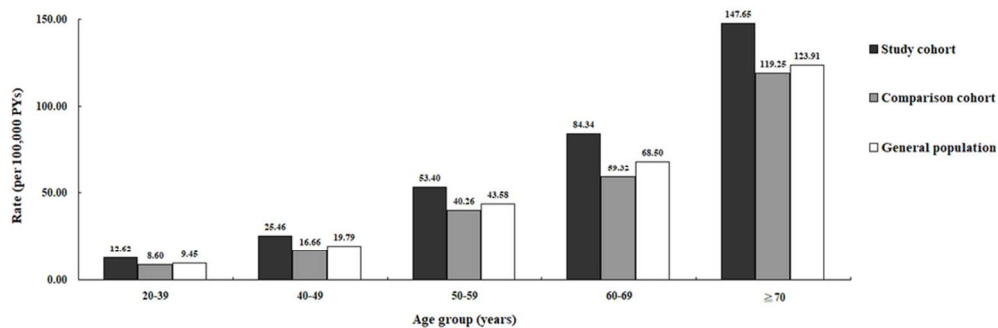
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Supplement Table 1 ICD-9-CM coding of diseases in manuscript

| Disease                           | ICD-9-CM    | Disease                   | ICD-9-CM |
|-----------------------------------|-------------|---------------------------|----------|
| Aortic aneurysm<br>and dissection | 441.0-441.9 | Behcet's disease          | 136.1    |
| Sjögren's syndrome                | 710.2       | Giant cell arteritis      | 446.5    |
| Turner syndrome                   | 758.6       | RA                        | 714      |
| Aortic coarctation                | 747.10      | Relapsing polychondritis  | 733.99   |
| Bicuspid aortic valve             | 746.4       | Takayasu's arteritis      | 446.7    |
| Marfan syndrome                   | 759.82      | COPD                      | 490-496  |
| Ehler-Danlos syndrome             | 756.83      | SLE                       | 710.0    |
| Diabetes mellitus                 | 250         | Systemic sclerosis        | 701.1    |
| Hypertension                      | 401-405     | Primary biliary cirrhosis | 571.6    |
| Hyperlipidaemia                   | 272.0-272.4 |                           |          |

RA = Rheumatoid arthritis and other inflammatory polyarthropathies; COPD = chronic obstructive pulmonary disease; SLE = systemic lupus erythematosus

Supplement Table 2 Years of follow-up

| <b>Sjögren's syndrome</b> | <b>Min</b> | <b>Middle</b> | <b>Max</b> | <b>Mean±SD</b> |
|---------------------------|------------|---------------|------------|----------------|
| <b>With</b>               | 0.50       | 3.26          | 10.91      | 5.11±7.52      |
| <b>Without</b>            | 0.50       | 4.57          | 10.98      | 5.80±5.53      |
| <b>Total</b>              | 0.50       | 3.69          | 10.98      | 5.66±5.99      |

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Supplement Table 3 Years to AA /AD

| <b>Sjögren's syndrome</b> | <b>Min</b> | <b>Middle</b> | <b>Max</b> | <b>Mean±SD</b> |
|---------------------------|------------|---------------|------------|----------------|
| <b>With</b>               | 0.51       | 3.32          | 9.27       | 4.67±3.82      |
| <b>Without</b>            | 0.52       | 5.07          | 10.87      | 5.53±3.65      |
| <b>Total</b>              | 0.51       | 4.93          | 10.87      | 5.12±3.49      |

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Supplement Table 4 Variables including in the Cox regression

| Variables            | Variables        |
|----------------------|------------------|
| Sjögren's syndrome   | CCI_R            |
| Sex (male)           | Steroid          |
| Age (years)          | $\beta$ blockers |
| DM                   | CCB              |
| Hypertension         | ACEI             |
| Hyperlipidaemia      | ARB              |
| Rheumatoid arthritis | Diuretic         |
| COPD                 | Statin           |

DM = diabetes mellitus; COPD = chronic obstructive pulmonary disease; CCB = calcium channel blocker; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker

Supplement Table 5 First event of (AA / AD) coding distribution

| Sjögren's syndrome | Inpatient |       | ER |       |
|--------------------|-----------|-------|----|-------|
|                    | N         | %     | N  | %     |
| With               | 40        | 85.11 | 7  | 14.89 |
| Without            | 141       | 88.12 | 19 | 11.88 |
| Total              | 181       | 87.44 | 26 | 12.56 |

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**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies***

| Section/Topic                | Item # | Recommendation   | Reported on page # |
|------------------------------|--------|--|--------------------|
| Title and abstract           | 1      | (a) Indicate the study's design with a commonly used term in the title or the abstract   | 3                  |
|                              |        | (b) Provide in the abstract an informative and balanced summary of what was done and what was found  | 3-4                |
| <b>Introduction</b>          |        |  |                    |
| Background/rationale         | 2      | Explain the scientific background and rationale for the investigation being reported   | 6                  |
| Objectives                   | 3      | State specific objectives, including any prespecified hypotheses   | 7                  |
| <b>Methods</b>               |        |  |                    |
| Study design                 | 4      | Present key elements of study design early in the paper  | 11                 |
| Setting                      | 5      | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection  | 10-11              |
| Participants                 | 6      | (a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up   | 9                  |
|                              |        | (b) For matched studies, give matching criteria and number of exposed and unexposed  | 11                 |
| Variables                    | 7      | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable   | 9-10               |
| Data sources/<br>measurement | 8*     | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 10                 |
| Bias                         | 9      | Describe any efforts to address potential sources of bias  | 19                 |
| Study size                   | 10     | Explain how the study size was arrived at  | 17                 |
| Quantitative variables       | 11     | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why   | 9-10               |
| Statistical methods          | 12     | (a) Describe all statistical methods, including those used to control for confounding  | 11                 |
|                              |        | (b) Describe any methods used to examine subgroups and interactions  | 11                 |
|                              |        | (c) Explain how missing data were addressed  | 11                 |
|                              |        | (d) If applicable, explain how loss to follow-up was addressed   | 11                 |
|                              |        | (e) Describe any sensitivity analyses  | 11                 |
| <b>Results</b>               |        |  |                    |

|                          |     |  |       |
|--------------------------|-----|--|-------|
| Participants             | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed            | 12-13 |
|                          |     | (b) Give reasons for non-participation at each stage   | 7-8   |
|                          |     | (c) Consider use of a flow diagram   | 12    |
| Descriptive data         | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders   | 12    |
|                          |     | (b) Indicate number of participants with missing data for each variable of interest  | 11    |
|                          |     | (c) Summarise follow-up time (eg, average and total amount)  | 11    |
| Outcome data             | 15* | Report numbers of outcome events or summary measures over time   | 12-13 |
| Main results             | 16  | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 12    |
|                          |     | (b) Report category boundaries when continuous variables were categorized  | 11    |
|                          |     | (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period   | 12    |
| Other analyses           | 17  | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses   | 12    |
| <b>Discussion</b>        |     |  |       |
| Key results              | 18  | Summarise key results with reference to study objectives   | 18    |
| <b>Limitations</b>       |     |  |       |
| Interpretation           | 20  | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence                                   | 20    |
| Generalisability         | 21  | Discuss the generalisability (external validity) of the study results  | 20    |
| <b>Other information</b> |     |  |       |
| Funding                  | 22  | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based  | 21    |

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).