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Association of Family History With Incidence and Outcomes of Aortic Dissection

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ABSTRACT

BACKGROUND Aortic dissection (AD) is a life-threatening emergency. However, the heritability and association of family history with late outcomes are unclear.

OBJECTIVES The purpose of this study was to evaluate the effect of family history of AD on the incidence and prognosis of AD and estimate the heritability and environmental contribution in AD in Taiwan.

METHODS Both cross-sectional and cohort studies were conducted using Taiwan National Health Insurance database. A registry parent-offspring relationship algorithm was used to reconstruct the genealogy of this population for heritability estimation. The cross-sectional study included 23,868 patients with a diagnosis of AD in 2015. The prevalence and adjusted relative risks (RRs) were evaluated, and the liability threshold model was used to examine the effects of heritability and environmental factors. Furthermore, a 1:10 propensity score–matched cohort comprising AD patients with or without a family history of AD was included to compare late outcomes in the cohort study.

RESULTS A family history of AD in first-degree relatives was associated with an RR of 6.82 (95% confidence interval [CI]: 5.12 to 9.07). The heritability of AD was estimated to be 57.0% for genetic factors, and 3.1% and 40.0% for shared and nonshared environmental factors, respectively. After excluding individuals with Marfan syndrome or bicuspid aortic valve, a family history of AD was associated with an RR of 6.56 (95% CI: 4.92 to 8.77) for AD. Furthermore, patients with AD and a family history of AD had a higher risk of later aortic surgery than those with AD without a family history (subdistribution hazard ratio: 1.40; 95% CI: 1.12 to 1.76).

CONCLUSIONS A family history of AD was a strong risk factor for AD. Furthermore, patients with AD with a family history of AD had a higher risk of later aortic surgery than those with no family history of AD.

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ABBREVIATIONS AND ACRONYMS

AD = aortic dissection

CI = confidence interval

ICD-9-CM = International Classification of Diseases-9th Revision-Clinical Modification

MACCE = major adverse cardiac and cerebral events

NHI = National Health Insurance

NHIRD = National Health Insurance Research Database

RR = relative risk

Aortic dissection (AD) is a life-threatening disease, with a sudden death rate of up to 50% in patients with the acute type of AD (type A) (1). A recent analysis from the International Registry of Acute Aortic Dissection, which included 4,428 patients between 1995 and 2013, reported that the mortality rate was still as high as 22% for patients with acute type A AD and 14% for patients with acute type B AD despite recent advances in diagnostic strategies, medical therapy, and surgical treatment (2). Epidemiology studies from Western countries have reported that AD is an uncommon disease with an incidence of 3.0 to 16 per 100,000 patient-years (3–5). In addition, a previous population-based study from Taiwan reported an average annual incidence of AD of 5.6 per 100,000 persons, and that the incidence increased over time (6). AD is usually asymptomatic until it occurs, and therefore identifying risk factors followed by close surveillance and aggressive control of the risk factors or even preventive ascending aortic replacement in high-risk patients may decrease the frequency of dissection and death.

Several genetic disorders including Marfan syndrome, Ehlers-Danlos syndrome, Turner's Loeys-Dietz's syndrome, and bicuspid aortic valve have been shown to be risk factors for aortic aneurysm and AD (1). Other associated disorders include arterial hypertension, smoking, and vascular inflammation (3). Recently, Ma et al. (7) reported that a positive family history of AD was associated with a higher risk of dissection in family members, with an annual probability of AD per first-degree relative 2.77 times higher in patients with a positive rather than negative family history (7). Accordingly, we hypothesized that there may also be an association between a family history and the prognosis of AD.

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Because no previous study has thoroughly investigated this issue, we conducted this nationwide family study with 2 study designs on nearly the whole population of Taiwan by using genealogy and linked health information. This study had 3 main aims: the first was to evaluate the extent of family aggregation of AD and estimate the relative risk (RR) of AD in individuals with affected first-degree relatives either with or without diagnosed genetic disorders related to aortic disease using a cross-sectional study design with nearly the whole population of Taiwan in 2015; the second was to assess the relative contributions of genetic and environmental factors of AD using a liability threshold model in the cross-sectional population study; and the third was to conduct a longitudinal study to compare the late outcomes between patients with AD and a family history of AD and those without a family history of AD using a cohort of patients who received a diagnosis of AD in Taiwan from 2000 to 2015.

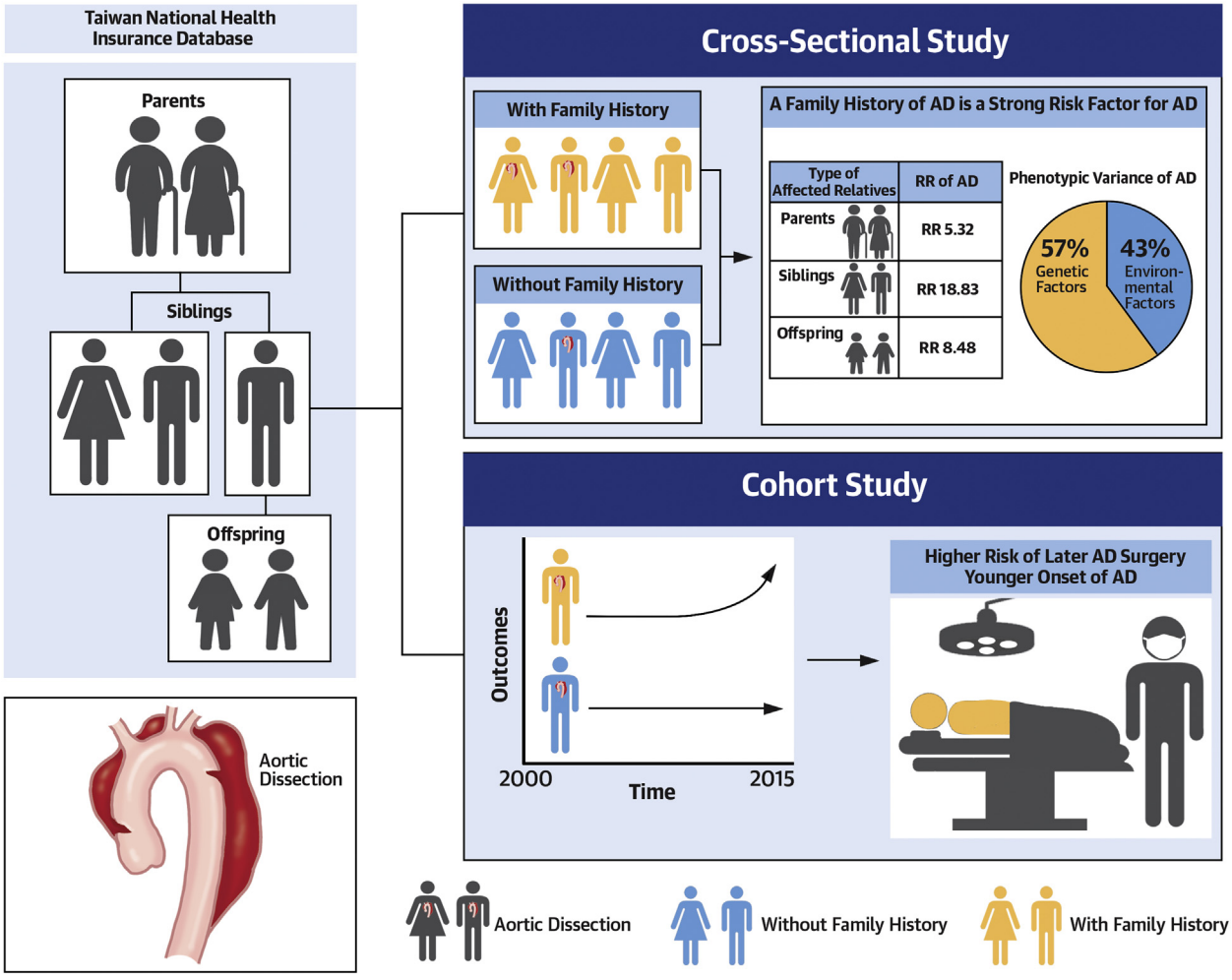
METHODS

DATA SOURCE. This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (approval number 201801531B0) and also by the data holder, the National Health Insurance (NHI) Administration. We identified all people who were actively registered under the NHI program between 2000 and 2015 from the Applied Health Research Data Integration Service provided by the NHI Administration. The NHI program is a government-run universal single-payer health insurance program launched in 1995 and covers over 99% of the population in Taiwan (>24 million residents in 2015). The National Health Insurance Research Database (NHIRD) contains data on all registered beneficiaries, including all outpatient, inpatient, and pharmacy dispensing claims from medical providers contracted with the NHI Administration. All personal registration information in the NHIRD is encrypted and deidentified prior to release to researchers but remains linkable.

STUDY DESIGN, POPULATION, AND IDENTIFICATION OF FAMILY ASCERTAINMENT. This study was conducted in 2 parts: study 1 had a cross-sectional study design; and study 2 had a matched cohort study design (**Central Illustration**). A claims-based registry parent-offspring relationship algorithm was used to reconstruct the genealogy of the study populations for heritability estimation in both study designs. The methods used have been described previously (8,9). Among 38,245,965 beneficiary records included in the registry, 9,296,840 were registered by individuals with no relationships with other people over a span of 20 years (from 1996 to 2015). The remaining beneficiaries were clustered into 4,580,177 families, with a mean family size of 4.74 persons.

In the cross-sectional study (study 1), we identified 23,868 patients with a diagnosis of AD among all beneficiaries under the NHI program in 2015. Furthermore, we identified these patients' family history using the aforementioned rule and compared the prevalence and adjusted RRs of AD and other syndromic diseases associated with aortic disease in individuals with affected first-degree relatives. In addition, we used the standard ACE (additive genetic [A], common environmental factors shared by family

CENTRAL ILLUSTRATION **Summary of Study Design and Results**



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Both cross-sectional and cohort studies were conducted using Taiwan National Health Insurance database. A registry parent-offspring relationship algorithm was used to reconstruct the genealogy of this population. We found that a family history of aortic dissection (AD) was a strong risk of factor of AD, and that genetic relatedness was associated with the magnitude of the risk of AD. We estimated that the heritability of AD was 57.0% for genetic factors and 43.0% for environmental factors. Finally, a family history in the patients with AD was associated with a higher risk of aortic surgery and a younger age at onset of AD. RR = relative risk.

members [C], and nonshared environmental factors [E]) liability threshold model to examine the effects of heritability and/or environmental factors (8-10).

The purpose of study 2 was to compare the late outcomes of patients with AD and a family history of AD with the late outcomes of those without a family history of AD. For this purpose, we recruited a propensity score-matched cohort of AD patients with and without a family history of AD in 2000 at a 1:10 ratio and followed them up to 2015 (Supplemental Figure 1). The variables included in the propensity score matching were age at diagnosis of AD, sex, comorbidities, and medications (Supplemental Table 1). Because of the limited number of AD cases, some cases could not be matched with 10 control subjects. Propensity score matching (PSM) by using greedy nearest neighbor matching (random order) without replacement with a caliper of 0.2 times the SD of the logit of propensity score was used. Finally, 93 cases and 894 matched control subjects were included in the analysis.

TABLE 1 Baseline Characteristics of Individuals With Affected First-Degree Relatives With Aortic Dissection and the General Population

	Women			Men		
	≥1 Affected Relative (n = 10,406)	General Population (n = 11,767,944)	p Value	≥1 Affected Relative (n = 12,792)	General Population (n = 1,661,608)	p Value
Age, yrs	38.79 ± 17.39	40.60 ± 21.34	<0.0001	40.19 ± 15.86	39.20 ± 21.18	<0.0001
Aortic dissection	22 (0.21)	4,041 (0.03)	<0.0001	52 (0.41)	9,630 (0.08)	<0.0001
Place of residence			<0.0001			<0.0001
Urban	7,032 (67.58)	7,301,101 (62.04)		8,168 (63.85)	6,944,321 (59.55)	
Suburban	2,901 (27.88)	3,587,053,(30.48)		3,988 (31.18)	3,791,340 (32.51)	
Rural	454 (4.36)	846,178 (7.19)		620 (4.85)	891,301 (7.64)	
Unknown	19 (0.18)	33,612 (0.29)		16 (0.13)	34,646 (0.30)	
Income levels			<0.0001			<0.0001
Quintile 1	1,786 (17.16)	1,969,690 (16.74)		2,308 (18.04)	2,112,906 (18.12)	
Quintile 2	1,534 (14.74)	1,531,526 (13.01)		1,474 (11.52)	1,295,712 (11.11)	
Quintile 3	2,838 (27.27)	3,848,653 (32.70)		3,218 (25.16)	3,403,899 (29.19)	
Quintile 4	2,149 (20.65)	2,139,830 (18.18)		2,413 (18.86)	2,040,414 (17.50)	
Quintile 5	2,095 (20.13)	2,273,877 (19.32)		3,371 (26.35)	2,804,667 (24.05)	
Unknown	4 (0.04)	4,368 (0.04)		8 (0.06)	4,010 (0.03)	
Occupation			<0.0001			<0.0001
Dependents of the insured individuals	2,591 (24.90)	4,467,816 (37.97)		2,386 (18.65)	3,802,438 (32.61)	
Civil servants, teachers, military personnel, and veterans	561 (5.39)	474,223 (4.03)		852 (6.66)	664,990 (5.70)	
Nonmanual workers and professionals	4,307 (41.39)	3,250,141 (27.62)		5,484 (42.87)	3,634,308 (31.16)	
Manual workers	1,876 (18.03)	2,602,874 (22.12)		2,491 (19.47)	2,289,097 (19.63)	
Other	1,071 (10.29)	972,890 (8.27)		1,579 (12.34)	1,270,775 (10.90)	

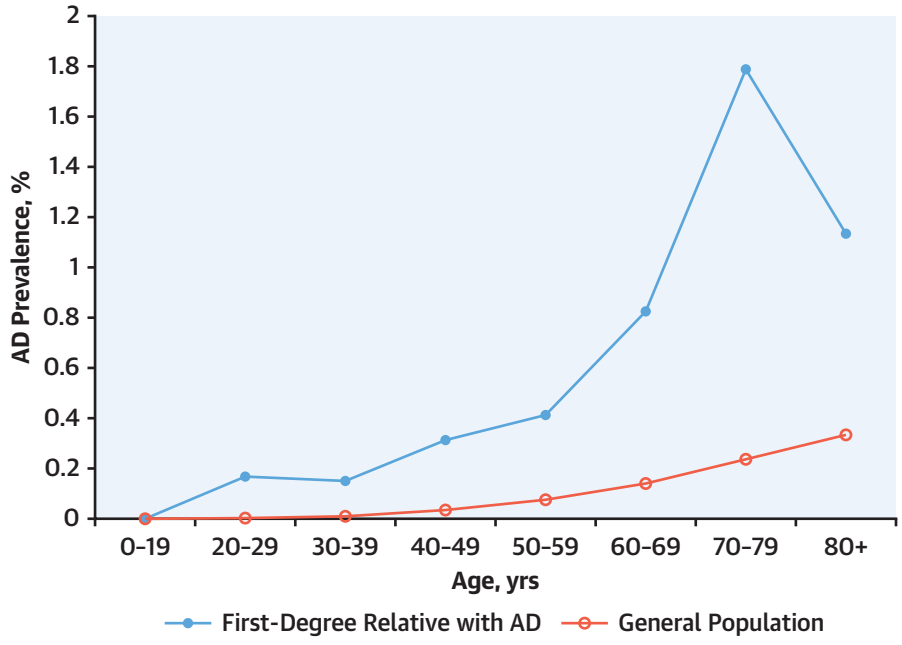
Values are mean ± SD or n (%).

ASCERTAINMENT OF AD. International Classification of Diseases-9th Revision-Clinical Modification (ICD-9-CM) codes were used to identify the patients diagnosed with AD (441.0x). This type of case definition has been applied in previous studies based on administration databases (6,11,12). As AD is a life-threatening acute disease that requires prompt management, most of the patients diagnosed with AD were transferred to a medical center with cardiovascular surgeons. Theoretically, the accuracy of ICD-9-CM coding for AD is higher than for other diseases. Furthermore, the NHI program has strict regulations regarding reimbursements, which include a comprehensive review of all medical records including imaging studies, especially for high-cost diseases such as AD. Reimbursements are only given for cases with an accurate diagnosis as supported by such evidence.

To verify the accuracy of the definition of the included AD population (ICD-9 CM diagnostic code: 441.0) and ensure the internal validity of this study, we performed an internal validation study. This was conducted using a chart review of consecutive patients who were diagnosed with AD at Linkou Chang Gung Memorial Hospital from 2011 to 2013. The data in the NHIRD are anonymized and were therefore linked to our data by sex, birth date, and admission and discharge dates. A total of 306 patients in the NHIRD and our validation cohort were linked. The positive predictive value was 97.06% (297 of 306) (data not shown).

DEFINITION OF OUTCOMES. For the secondary aim of this study, there were 4 outcomes: all-cause mortality, major adverse cardiac and cerebral events (MACCE), later aortic surgery, and readmission due to any cause. Cases of all-cause mortality were identified from the Taiwan Death Registry, which can be linked to NHI data using encrypted civil identification numbers. MACCE included acute myocardial infarction, heart failure, stroke, and cardiovascular death. AMI, heart failure, and stroke were defined as a principal diagnosis of admission. Cardiovascular death was defined according to the criteria of the Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials by the U.S. Food and Drug Administration. Aortic surgery was identified according to NHI reimbursement codes from the inpatient claims data. All-cause readmissions were also identified in the inpatient claims data. Each patient was followed from the discharge date of the index AD admission to the date of an event, death, or December 31, 2015, whichever occurred first. In addition, the ICD-9 diagnostic codes

FIGURE 1 Age-Specific Prevalence of Aortic Dissection in Individuals With a First-Degree Relative With Aortic Dissection and in the General Population in Taiwan in 2015



The age-specific prevalence of aortic dissection was higher in the individuals with an affected relative with aortic dissection than it was in the general population. The difference in the prevalence of aortic dissection between the 2 groups increased with increasing age. AD = aortic dissection.

for detecting comorbidities and outcomes are provided in Supplemental Table 2.

STATISTICAL ANALYSIS. In the cross-sectional study, the prevalence of AD was calculated for the general population with affected first-degree relatives. We calculated the adjusted RRs of AD by sex and relationship (parent, offspring, sibling, twin, and spouse) of the affected relative. In addition, we calculated the adjusted RRs of other diseases (Marfan, Bicuspid, Turner, and Ehlers-Danlos syndromes; inflammatory diseases; type 1 and 2 diabetes mellitus; and hypertension) in first-degree relatives of the patients with AD. Moreover, we applied the liability threshold model to examine the influences of heritability and/or environmental factors.

In the cohort study, the risk of time to an event outcome was compared between the patients with AD with and without a family history of AD using both Cox proportional hazard regression and a Fine and Gray model, which considered all-cause mortality as a competing risk. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina). A 2-sided p value <0.05 was considered statistically significant, and no adjustments for multiple testing (multiplicity) were made in this study.

RESULTS

AD PREVALENCE IN INDIVIDUALS WITH AFFECTED FIRST-DEGREE FAMILY MEMBERS AND IN THE GENERAL POPULATION. The incidence rate of AD significantly increased from 5.2 to 8.5 events per 100,000 person-years from 2001 to 2015 (p trend <0.001) (Supplemental Table 3). Individuals with an affected relative had a higher prevalence of AD than the general population in both women and men (0.21% vs. 0.03% in women; 0.41% vs. 0.08% in men) (**Table 1**). As shown in **Figure 1** and Supplemental Table 4, the age-specific prevalence of AD was higher in the individuals with an affected relative with AD than in the general population. The difference in the prevalence of AD between the 2 groups increased with increasing age (Supplemental Table 4).

THE RR FOR AD IN INDIVIDUALS WITH AFFECTED RELATIVES. **Table 2** lists the prevalence of AD in individuals with affected first-degree relatives. The RRs (95% confidence intervals [CIs]) for AD were associated with the degree of genetic distance between family relatives. The results showed that first-degree relatives (on average 50% genetic similarity) were associated with an adjusted RR of 6.82 (95% CI: 5.12 to 9.07).

TABLE 2 Relative Risks of Aortic Dissection in First-Degree Relatives

Type of Affected Relative	Sex of Affected Relative	Sex of Individual	n	Prevalence (%)	RR (95% CI)*
Any	Male	Male	27	0.28	4.90 (3.02–7.95)†
		Female	19	0.24	9.53 (6.12–14.84)†
		All	46	0.26	6.32 (4.51–8.85)†
	Female	Male	N/A	N/A	8.02 (5.44–11.84)†
		Female	N/A	N/A	5.07 (1.18–21.78)†
		All	28	0.49	7.68 (5.26–11.22)†
	All	Male	52	0.41	6.08 (4.45–8.30)†
		Female	22	0.21	8.55 (5.57–13.13)†
		All	74	0.32	6.82 (5.12–9.07)†
Parent	Male	Male	13	0.15	3.57 (1.99–6.39)†
		Female	0	0	–
		All	13	0.09	3.25 (1.81–5.81)†
	Female	Male	N/A	N/A	8.17 (5.45–12.27)†
		Female	N/A	N/A	4.98 (1.25–19.84)†
		All	25	0.47	7.95 (5.40–11.70)†
	All	Male	N/A	N/A	5.60 (4.01–7.82)†
		Female	N/A	N/A	2.27 (0.57–8.99)
		All	38	0.19	5.32 (3.85–7.36)†
Offspring	Male	Male	6	1.20	4.14 (1.87–9.17)†
		Female	19	2.07	13.38 (8.59–20.82)†
		All	25	1.76	9.01 (6.12–13.27)†
	Female	Male	<5	N/A	4.17 (0.61–28.36)
		Female	<5	N/A	5.62 (0.79–39.92)
		All	<5	N/A	4.89 (1.26–19.03)†
	All	Male	7	1.18	4.13 (1.98–8.64)†
		Female	20	1.92	12.53 (8.14–19.29)†
		All	27	1.65	8.48 (5.85–12.29)†
Sibling	Male	Male	10	1.85	23.35 (10.08–54.06)†
		Female	0	0	–
		All	10	0.98	19.47 (8.43–44.99)†
	Female	Male	<5	N/A	16.73 (2.52–110.95)†
		Female	0	0	–
		All	<5	N/A	13.97 (2.08–94.08)†
	All	Male	11	1.73	22.77 (10.50–49.37)†
		Female	0	0	–
		All	11	0.90	18.83 (8.64–41.07)†
Twin	Male	Male	0	0	–
		Female	0	0	–
		All	0	0	–
	Female	Male	0	0	–
		Female	0	0	–
		All	0	0	–
	All	Male	0	0	–
		Female	0	0	–
		All	0	0	–
Spouse	All	All	10	0.16	1.23 (0.59–2.55)

*Adjusted for age, sex, place of residence, quintiles of income level, occupation and family size. †p <0.05.
CI = confidence interval; RR = relative risk.

After splitting relatives into specific types, the adjusted RRs were significant for parents (RR: 5.32; 95% CI: 3.85 to 7.36), offspring (RR: 8.48; 95% CI: 5.85 to 12.29), and siblings (RR: 18.83; 95% CI: 8.64 to 41.07). There were no AD events in individuals with an affected twin. In contrast, familial aggregation of AD was not seen in individuals with affected spouses without genetic similarities (RR: 1.23; 95% CI: 0.59 to 2.55).

THE RR FOR OTHER DISEASES ASSOCIATED WITH AD IN INDIVIDUALS WITH AFFECTED RELATIVES. Table 3 lists the RRs of other diseases in first-degree relatives of individuals with AD compared to the general population. The results showed that first-degree relatives were associated with an adjusted RR of 31.92 (95% CI: 26.19 to 38.90) for Marfan disease 5.88 (95% CI: 3.62 to 9.53) for bicuspid aortic valve, and 1.19 (95% CI: 1.14 to 1.24) for hypertension. There were no increased risks of Turner or Ehlers-Danlos syndrome and inflammatory diseases in the individuals with affected relatives.

NONSYNDROMIC FAMILIAL AD (SENSITIVITY ANALYSIS). Table 4 lists the results of sensitivity analysis. After excluding individuals with Marfan syndrome, bicuspid aortic valve, and Marfan syndrome or bicuspid aortic valve, a family history of AD was associated with RRs of 5.29 (95% CI: 3.82 to 7.31), 6.32 (95% CI: 4.71 to 8.47), and 6.56 (4.92 to 8.77) for AD, respectively. The results remained the same in subgroups of parents, offspring, and siblings.

FAMILIAL RESEMBLANCE AND HERITABILITY OF AD. Using a liability threshold mode, we estimated that the accountability for the phenotypic variance of AD was 57.0% for genetic factors (heritability), 3.1% for shared environmental factors, and 40.0% for nonshared environmental factors. Given the parameters previously estimated, the probability that a patient had sporadic AD was 84.0%.

AGE AT A DIAGNOSIS OF AD IN PATIENTS WITH A FAMILY HISTORY OF AD. Figure 2 demonstrates the distribution of the age at a diagnosis of AD in those with and without a family history of AD. The age of AD in the patients with a family history was younger than in those without a family history (51.52 years vs. 59.72 years).

LATE OUTCOMES IN THE PATIENTS WITH AD WITH A FAMILY HISTORY OF AD. A total of 93 and 12,633 patients with a new diagnosis of AD with and without a first-degree relative affected by AD between 2000 and 2015, respectively, were identified. Among these patients, the proportion of positive recording of first-degree relatives with dissection showed a borderline increase across the study period. By contrast, the prevalence of known risk factors was significantly decreased across the study period (Supplemental Table 5).

TABLE 3 Relative Risks of Other Diseases in First-Degree Relatives of Patients With Aortic Dissection

Other Diseases	Sex	With an Affected First-Degree Relative		General Population		RR (95% CI)*
		n	Prevalence (%)	n	Prevalence (%)	
Marfan	Male	80	0.63	2,773	0.02	28.12 (22.09–35.80)†
	Female	71	0.68	1,980	0.02	37.76 (29.08–49.04)†
	All	151	0.65	4,753	0.02	31.92 (26.19–38.90)†
Bicuspid	Male	11	0.09	2,069	0.02	5.76 (3.20–10.36)†
	Female	7	0.07	1,482	0.01	5.95 (2.84–12.46)†
	All	18	0.08	3,551	0.02	5.88 (3.62–9.53)†
Turner	Male	0	0	325	0	–
	Female	<5	N/A	1,982	0.02	2.06 (0.78–5.48)
	All	<5	N/A	2,307	0.01	1.80 (0.68–4.78)
E-D syndrome	Male	0	0	172	0	–
	Female	0	0	130	0	–
	All	0	0	302	0	–
Inflammatory diseases (Takayasu, giant cell arteritis, Behçet, AS)	Male	88	0.69	55,626	0.48	1.19 (0.96–1.48)
	Female	29	0.28	30,379	0.26	1.03 (0.72–1.48)
	All	117	0.50	86,005	0.37	1.14 (0.94–1.38)
DM	Male	1,516	11.85	1,588,880	13.62	0.97 (0.93–1.01)
	Female	1,124	10.80	1,692,506	14.38	0.98 (0.93–1.03)
	All	2,640	11.38	3,281,386	14.01	0.98 (0.95–1.02)
T1D	Male	7	0.05	5,201	0.04	1.16 (0.55–2.43)
	Female	9	0.09	6,122	0.05	1.45 (0.75–2.78)
	All	16	0.07	11,323	0.05	1.31 (0.80–2.14)
T2D	Male	1,516	11.85	1,588,251	13.62	0.97 (0.93–1.01)
	Female	1,123	10.79	1,691,814	14.38	0.98 (0.93–1.03)
	All	2,639	11.38	3,280,065	14.00	0.98 (0.95–1.02)
Hypertension	Male	956	7.47	971,467	8.33	1.18 (1.12–1.25)†
	Female	629	6.04	898,365	7.63	1.14 (1.07–1.22)†
	All	1,585	6.73	1,869,832	7.98	1.19 (1.14–1.24)†

*Adjusted for age, sex, place of residence, quintiles of income level, occupation and family size. †$p < 0.05$.
AS = ankylosing spondylitis; DM = diabetes mellitus; E-D = Ehlers-Danlos; T1D = type 1 diabetes; T2D = type 2 diabetes; other abbreviations as in Table 2.

TABLE 4 Sensitivity Analysis of the Relative Risks of Aortic Dissection in First-Degree Relatives

Definition of Individual	Type of Affected Relative	Sex of Affected Relative	Sex of Individual	n	Prevalence (%)	RR (95% CI)*
Without Marfan	Any	All	All	56	0.24	5.29 (3.82–7.31)†
	Parent	All	All	32	0.16	4.66 (3.27–6.64)†
	Offspring	All	All	22	1.35	6.92 (4.59–10.44)†
	Sibling	All	All	<5	N/A	7.03 (2.11–23.35)†
Without bicuspid	Any	All	All	68	0.29	6.32 (4.71–8.47)†
	Parent	All	All	35	0.17	4.96 (3.54–6.96)†
	Offspring	All	All	24	1.47	7.56 (5.10–11.22)†
	Sibling	All	All	11	0.90	19.00 (8.71–41.46)†
Without Marfan or bicuspid	Any	All	All	71	0.31	6.56 (4.92–8.77)†
	Parent	All	All	37	0.18	5.22 (3.76–7.24)†
	Offspring	All	All	25	1.53	7.85 (5.34–11.55)†
	Sibling	All	All	11	0.90	18.91 (8.67–41.25)†
Without any syndromal aortic disease	Any	All	All	53	0.23	5.05 (3.63–7.02)†
	Parent	All	All	30	0.15	4.41 (3.06–6.37)†
	Offspring	All	All	21	1.28	6.64 (4.36–10.12)†
	Sibling	All	All	<5	N/A	7.09 (2.13–23.57)†

*Adjusted for age, sex, place of residence, quintiles of income level, occupation and family size. †$p < 0.05$. Abbreviations as in Table 2.

TABLE 5 Late Outcomes of the Aortic Dissection Patients With and Without First-Degree Relatives With Aortic Dissection in the Propensity Score–Matched Cohort (for Study 2: the Cohort Study)

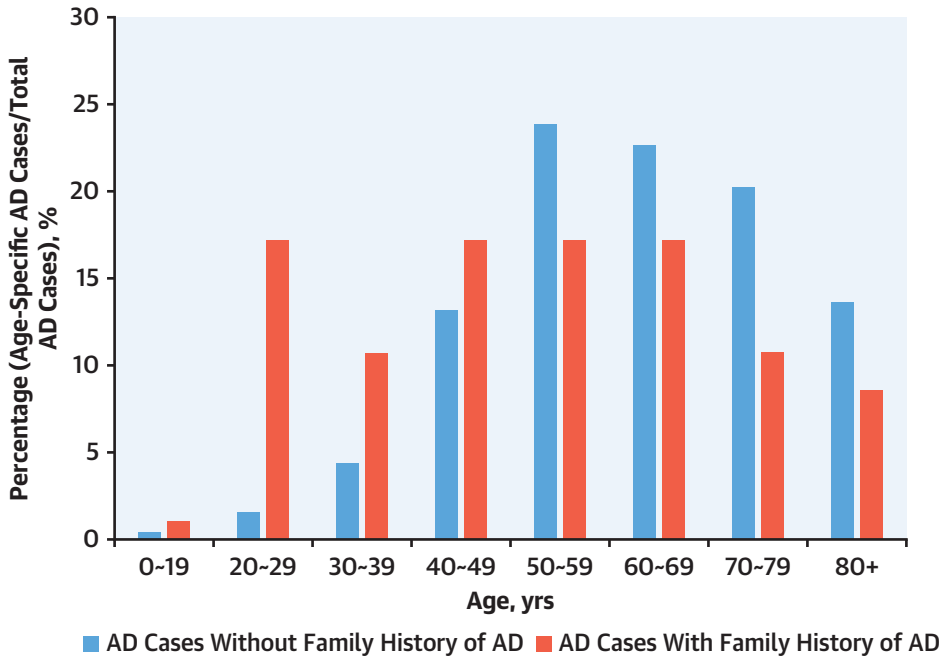
	First-Degree Relatives With Aortic Dissection (n = 93)	First-Degree Relatives Without Aortic Dissection (n = 894)				
	No. of Events (%)	No. of Events (%)	HR	(95% CI)	SHR	(95% CI)
All-cause mortality	34 (36.56)	317 (35.46)	0.98	(0.70–1.37)	–	–
MACCE	11 (11.83)	140 (15.66)	0.71	(0.39–1.28)	0.72	(0.40–1.32)
Later aortic surgery	55 (59.14)	395 (44.18)	1.39	(1.10–1.74)	1.40	(1.12–1.76)
Readmission due to any cause	59 (63.44)	542 (60.63)	0.89	(0.70–1.12)	0.96	(0.77–1.21)

CI = confidence interval; HR = hazard ratio; MACCE = major adverse cardiac and cerebral events; SHR = subdistribution hazard ratio.

After matching, 894 matched control subjects were included in the analysis. No substantial difference in baseline characteristics was noted between the 2 groups (Supplemental Table 1). Among the 987 matched patients, 143 (14.5%) died during the index AD admission. No significant difference in in-hospital mortality rate was observed between patients with and without first-degree relatives with dissection (12.9% vs. 14.7%; data not shown). The mean follow-up times were 3.00 and 3.71 years in the AD patients with or without a family history, respectively. In terms of surgical details, patients with a family history of AD may have significantly higher risks of receiving aortic root replacement in type A aortic dissection (Supplemental Table 6).

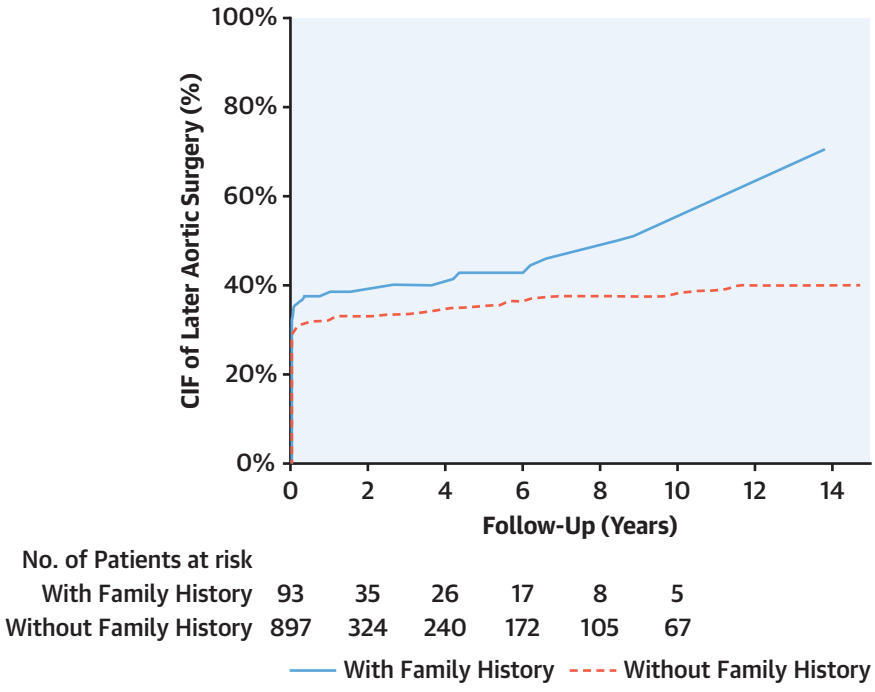
The hazard ratio of all-cause mortality in the patients who had a first-degree relative with AD was 0.98 (95% CI: 0.70 to 1.37). The subdistribution hazard ratios for the patients with a family history were 0.72 (95% CI: 0.40 to 1.32) for MACCE, 1.40 (95% CI: 1.12 to 1.76) for later aortic surgery, and 0.96 (95% CI: 0.77 to 1.21) for readmission due to any cause (**Figure 3, Table 5**).

FIGURE 2 Distribution of Age at Diagnosis of Aortic Dissection in Those With and Without a Family History of Aortic Dissection



The age at diagnosis of aortic dissection in the patients with a family history was less than it was in those without a family history (51.52 years vs. 59.72 years). AD = aortic dissection.

FIGURE 3 Cumulative Incidence Rate of Later Aortic Surgery in Aortic Dissection Patients With and Without First-Degree Relatives With Aortic Dissection in the Propensity Score–Matched Cohort (for Study 2: the Cohort Study)



Patients with a family history of aortic dissection have significantly higher risks of receiving later aortic surgery. CIF = cumulative incidence function.

DISCUSSION

AD is an acute and life-threatening disease associated with a high mortality rate. However, most patients with AD are asymptomatic before onset, and therefore, identifying the risk factors for AD followed by close surveillance and aggressive control of the risk factors or even aggressive treatment in high-risk populations may decrease the risk of AD. To the best of our knowledge, this is the first population-based family study to report that a family history of AD is a strong risk factor for this disease, regardless of the coexistence of genetic disorders associated with aortic disease. In addition, we demonstrated a 6-fold higher risk in the individuals who had first-degree relatives with AD compared with the general population and that genetic relatedness was associated with the magnitude of the risk of AD. Furthermore, we estimated the disease heritability of AD to be 57% and that nonshared environmental factors also contributed to 40% of the cases of AD. Finally, a family history in the patients with AD was associated with a higher risk of aortic surgery and a younger age at onset of AD. The findings of this study may be valuable when counseling families with affected members, and may be applicable for clinical screening including image studies and genetic tests in a subject with an affected family member with AD. This may allow for more aggressive treatment such as preventive aortic replacement to avoid the adverse outcomes of AD.

The risk factors for AD can basically be classified into 2 categories (13): 1) increased aortic wall stress in which the most common condition is hypertension; and 2) genetic risks associated with medial degeneration including Marfan syndrome, congenital bicuspid aortic valve, Loeys-Dietz syndrome, Ehlers-Danlos syndrome, and Turner syndrome (3,13), with the associated genes including *FBN1*, *EFEMP2*, *TGFBR1*, *TGFBR2*, *TGFB3*, *ACTA2*, *COL3A1*, and *SMAD3* (14-18). However, the altered genes can lead to aortic disease without syndromic features, termed nonsyndromic familial thoracic aortic aneurysm or dissections. Our results also demonstrated that family history was a strong predictor of AD after excluding all known associated syndromes related to aortic

disease. There are many previous studies regarding the management of syndromic aortic diseases such as Marfan syndrome to prevent AD (19,20). However, the absence of syndromic features can cause clinicians to overlook the potential risk of aortic emergency in individuals with a family history of AD with genetic alterations associated with aortic disease. Moreover, few previous studies have addressed screening, prevention, and management in these patients. Therefore, further genetic studies and specific management protocols for individuals with a family history of AD are warranted.

Previous familial studies of patients referred for repair of thoracic aortic dissection without a known genetic syndrome have indicated that nearly 20% of these patients have a first-degree relative with dissection, suggesting familial clustering without specific identifiable genetic defect syndromes (21,22). Albornoz et al. (23) reported that thoracic aneurysm and dissection are common familial diseases with a younger age at onset. In addition, a recent study by Ma et al. (7) demonstrated that a positive family history of AD dramatically increased the risk of dissection in family members, with an annual probability of AD per first-degree relative of 2.77 times higher in patients with a positive family history compared with those with a negative family history (7). However, their study was limited by the small sample size and single-center cohort study. In addition, one-third of the patients with a positive family history were syndromic patients, and their results may not represent the risk in nonsyndromic patients. In this study, we demonstrated a 6-fold increased risk of AD in the first-degree relatives of the AD patients after taking associated syndromes related to AD into consideration. To the best of our knowledge, this is the first study to show that a family history of AD is associated with adverse outcomes with a higher risk of later aortic surgery.

There are several strengths to this study. First, we used systematic methods to ascertain first-degree relatives and identify kinship, which allowed for precise estimations of the prevalence and RRs of AD with minimal selection bias. Second, consistent case definitions for individuals at risk and their relatives and complete identification of AD in a large population of Taiwanese patients ensured the absence of information bias. Finally, the nature of prospectively recorded data in the NHIRD for the construction of family relationships and ascertainment of socioeconomic information minimized the errors associated with self-reporting and recall bias.

With regard to the clinical perspectives of this study, given the high mortality rate associated with AD and that it can remain asymptomatic until it occurs, early consultations for aortic disease or genetic disorders, aggressive management of hypertension and smoking cessation, and routine screening with computed tomography scans for individuals with a family history of AD are recommended (24). Moreover, screening should be conducted from a young age because the onset of AD occurs in affected family members at a younger age than in patients with no family history based on our results. Prophylactic resection of ascending aortic aneurysms with a lower trigger of the aortic size in patients with a positive family history may be reasonable for this life-threatening disease (25). Furthermore, extensive surgical treatment during the first onset in AD patients with a family history may be needed due to the higher risk of later aortic surgery in this population. To further apply our findings to clinical perspectives, studies comparing the effect of different treatment strategies including medications and interventions for patients with a family history of AD are warranted.

STUDY LIMITATIONS. First, the diagnoses of AD and other covariates were based on ICD-9-CM codes, and misclassification of the diagnosis and coding errors could have occurred. However, we performed internal validation to verify the accuracy of the diagnosis of AD. In addition, the accuracy of the diagnosis codes of other major cardiovascular diseases has been validated in previous studies, and the NHIRD appears to be a valid resource for population research in cardiovascular diseases (26). Second, the NHIRD does not include data regarding anatomic imaging such as CT scans. CT of the aorta is the gold standard to diagnose AD, and it provides detailed data for the classification of all aortic diseases and extension of dissected segments of the aorta. This lack of imaging data, which would have indicated the severity or subtype of AD, could have had an effect on the outcomes. Notably, we could not identify the type of dissection in patients who did not undergo surgery using the Taiwan NHIRD. However, the NHI program has strict regulations regarding examinations and treatment reimbursements through comprehensive reviews of all medical records including imaging studies and laboratory data, and reimbursements are only granted to patients who are indicated for specific examinations or treatments due to an accurate diagnosis. Thus, this may have limited the potential bias of unavailable data. Last, this was a population-based study conducted in Asia, and the incidence and characteristics of AD may differ between different populations. Therefore, our results may not be directly generalizable to other patient populations and environments. Despite these limitations, we

believe that our results provide a valuable contribution to the knowledge gap in family studies on AD.

CONCLUSIONS

This large Taiwanese population-based family study demonstrated family aggregation in AD. A family history was a strong risk factor for AD with or without syndromes related to aortic disease, and both genetic and environmental factors contributed to the overall risk of AD. Furthermore, a family history of AD in the patients with AD was associated with a higher risk of later aortic surgery. We recommend routine imaging and genetic screening of individuals with a family history of AD. Close surveillance and aggressive control of risk factors or even preventive aortic replacement in high-risk populations may decrease the frequency of dissection and possibly reduce mortality through an earlier preclinical diagnosis in affected families.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: A family history of AD is a powerful risk factor for AD in patients with or without syndromic aortic disease. Both genetic and environmental factors contribute to overall risk.

TRANSLATIONAL OUTLOOK: Future research should focus on defining the optimum screening and imaging surveillance strategies and the aortic diameter at which prophylactic surgical intervention is advantageous for patients with a family history of AD.

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KEY WORDS aortic dissection, family aggregation, family history, long-term prognosis

APPENDIX For supplemental tables and a figure, please see the online version of this paper.