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Original Article

The effect of rheumatoid arthritis on the risk of cerebrovascular disease and coronary artery disease in young adults

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Abstract

Background: Only a few studies have investigated the affect of rheumatoid arthritis (RA) on the risk of cerebrovascular disease (CVD)/coronary artery disease (CAD) in young adults. This study, therefore, examined the association between RA and the risk of CVD/CAD in young adults and the interaction effects between cardiovascular risk factors and RA on the risk of CVD/CAD.
Methods: Data regarding 52,840 subjects (10,568 patients with RA and 42,272 age-, sex-, urbanization-, and income-matched non-RA controls) were collected from the National Health Insurance Research Database (NHIRD) in 2006. All subjects were followed until a CVD or CAD diagnosis, or death, or December 31, 2011. The hazard ratios (HRs) of CVD/CAD were estimated using Cox proportional hazard models. The interaction effects between cardiovascular risk factors and RA on the risk of CVD/CAD were assessed using additive and multiplicative models.
Results: RA increased the risk of CVD/CAD in young adults, especially those at risk of ischemic stroke (adjusted HR, 3.48; 95% confidence interval (CI), 2.16–5.61). Even without comorbidity at baseline, patients with RA still had a 2.35-fold greater risk of CVD/CAD relative to those without RA. RA and hypertension interacted positively on the risk of CVD/CAD. The highest CVD/CAD risk was found in patients with RA and hypertension (HR, 9.08; 95% CI, 7.22–11.41) relative to subjects without RA and hypertension.
Conclusion: RA is an independent risk factor for CVD/CAD in young adults. The government should develop policies for preventing early onset hypertension to reduce the incidence of CVD/CAD among young patients with RA.

Keywords: Cerebrovascular disorders; Coronary artery disease; Hypertension; Rheumatoid arthritis

1. Introduction

Rheumatoid arthritis (RA) is the most common inflammatory joint disease with a prevalence between 0.5% and 1.0% in industrialized countries.[1] Systemic release of pro-inflammatory cytokines (i.e., IL-1, IL-6, and TNF-α) from RA synovial tissue may promote the inflammatory process underlying atherogenesis. These cytokines either directly affect plaque progression or indirectly promote insulin resistance, dyslipidemia, prothrombotic and antifibrinolytic effects, endothelial activation and dysfunction that lead to atherosclerosis.[2,3] The cumulative evidence shows that systemic inflammation plays a key role in accelerating the development of cerebrovascular disease (CVD) and coronary artery disease (CAD) in patients with RA.[4–12] Moreover, CVD and CAD are

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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the main causes of death in patients with RA, accounting for nearly 40% of their mortality.[13] Several traditional risk factors for cardiovascular disease, such as obesity, dyslipidemia, diabetes mellitus, hypertension, age, sex, and smoking, are associated with CVD/CAD, and some of these risk factors are common to patients with RA.[14−17] However, the interaction effects between RA and traditional cardiovascular disease risk factors on the risk of CVD/CAD have remained unclear. Therefore, this study explored whether RA was associated with the risk of CVD/CAD in young adults. We also investigated the interaction effects between traditional cardiovascular risk factors and RA on the risk of CVD/CAD. We analyzed data from the National Health Insurance (NHI) program, which covers more than 99% of the population in Taiwan and is one of the largest and most complete population-based datasets in the world.[18]

2. Methods

2.1. Data sources

We used the data contained in the National Health Insurance Research Database (NHIRD), managed by the NHI program, for this nationwide cohort study. The NHIRD contains data on patient demographics, disease diagnoses, and prescription records (including types of medication, time of prescription, duration of drug supply, and dosage). In this database, diseases are classified according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, and all types of drug use are determined from dispensed prescriptions and are defined according to the Anatomical Therapeutic Chemical (ATC) Classification. Data regarding censoring due to death were obtained from the National Death Registry of Taiwan.

2.2. Study population

A total of 52,840 subjects aged less than 45 years (10,568 patients with RA and 42,272 age-, sex-, urbanization-, and income-matched non-RA controls) were enrolled from the NHIRD in 2006. Patients with RA having more than two consecutive ICD-9-CM code 714.0 diagnoses and concurrent prescriptions of RA-related medications in 2006 were recruited as our RA cohort.[19,20] RA-related medications included disease-modifying antirheumatic drugs (DMARDs), nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and biologics. The date of the first diagnosis of RA served as the index date for patients with RA. The index date for non-RA controls was the first day of 2006. We excluded 207 patients with RA and 150,957 non-RA subjects with CVD and CAD histories prior to the respective index dates. Each RA case was frequency matched for four controls by age, sex, urbanization, and monthly income to increase the statistical power and to control for potential confounding factors. We therefore randomly selected 42,272 non-RA controls from 10,036,255 non-RA subjects in 2006 (Fig. 1). This study was approved by the Taipei Medical University Joint Institutional Review Board (Approval No. 201411004).

2.3. Outcome assessment

The study endpoint was the new onset of CVD and CAD, including coronary heart disease, atrial fibrillation, and heart failure, during the six-year follow-up period. We defined patients with coronary heart disease (ICD-9-CM codes 410-414), atrial fibrillation (ICD-9-CM code 427.31), or heart failure (ICD-9-CM code 428) only when the disease was listed as a discharge diagnosis or was confirmed more than twice in the outpatient department. Patients with at least two outpatient visits or one hospital admission for CVD (ICD-9-CM codes 430-437, excluding 432) and who received concomitant imaging of the brain using computed tomography or magnetic resonance imaging were defined as CVD patients. Additionally, CVD patients were divided into the categories of ischemic stroke (ICD-9-CM codes 433-434, 436) and hemorrhagic stroke (ICD-9-CM codes 430-431). All subjects were followed from the index date until the occurrence of CVD/CAD, death, or December 31, 2011.

2.4. Demographic variables and comorbidities

Demographic variables in this study included age, sex, urbanization, and monthly income. In accordance with standards published by the National Health Research Institutes, 359 communities in Taiwan were stratified into seven urbanization levels. Level 1 indicated “most urbanized” and level 7 indicated “least urbanized”.[21] Urbanization levels 1 and 2 were combined and described as urban (high level of urbanization), levels 3 and 4 were combined and described as suburban (medium level of urbanization), and the remaining three levels (5, 6, and 7) were combined and described as rural (low level of urbanization).[22] The insurance premiums were calculated on the basis of the beneficiary's total income; monthly income was estimated for each person. Monthly income was divided into three levels: ≤NT$15,840, NT$15,841−25,000, and ≥NT$25,001.[23] Baseline comorbidities for each patient were hypertension (ICD-9-CM codes 401-405), diabetes mellitus (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM codes 272.0-272.4), chronic kidney disease (CKD) (ICD-9-CM codes 250.4, 274.1, 283.11, 403.1, 404.2, 404.3, 404.1, 442.1, 447.3, 580−583, 585, 587, 792.5, 642.1, and 646.2), cancer (ICD-9-CM codes 140-208), alcoholism (ICD-9-CM codes 303.0 and 303.9), peripheral vascular disease (PVD) (ICD-9-CM codes 440.20-440.24, 440.9, 443.81, 443.9, and 444.22), chronic obstructive pulmonary disease (COPD) (ICD-9-CM codes 403, 416, 491−493, 495−496, 508, 515, 516, and 518), mild liver diseases (ICD-9-CM codes 571.2, 571.3, 571.5, and 573.8), and obesity (ICD-9-CM code 278.0). All comorbidities were required to have been diagnosed at least twice. Medication use included antiplatelets, anticoagulants, DMARDs, NSAIDs, glucocorticoids, and biologics.

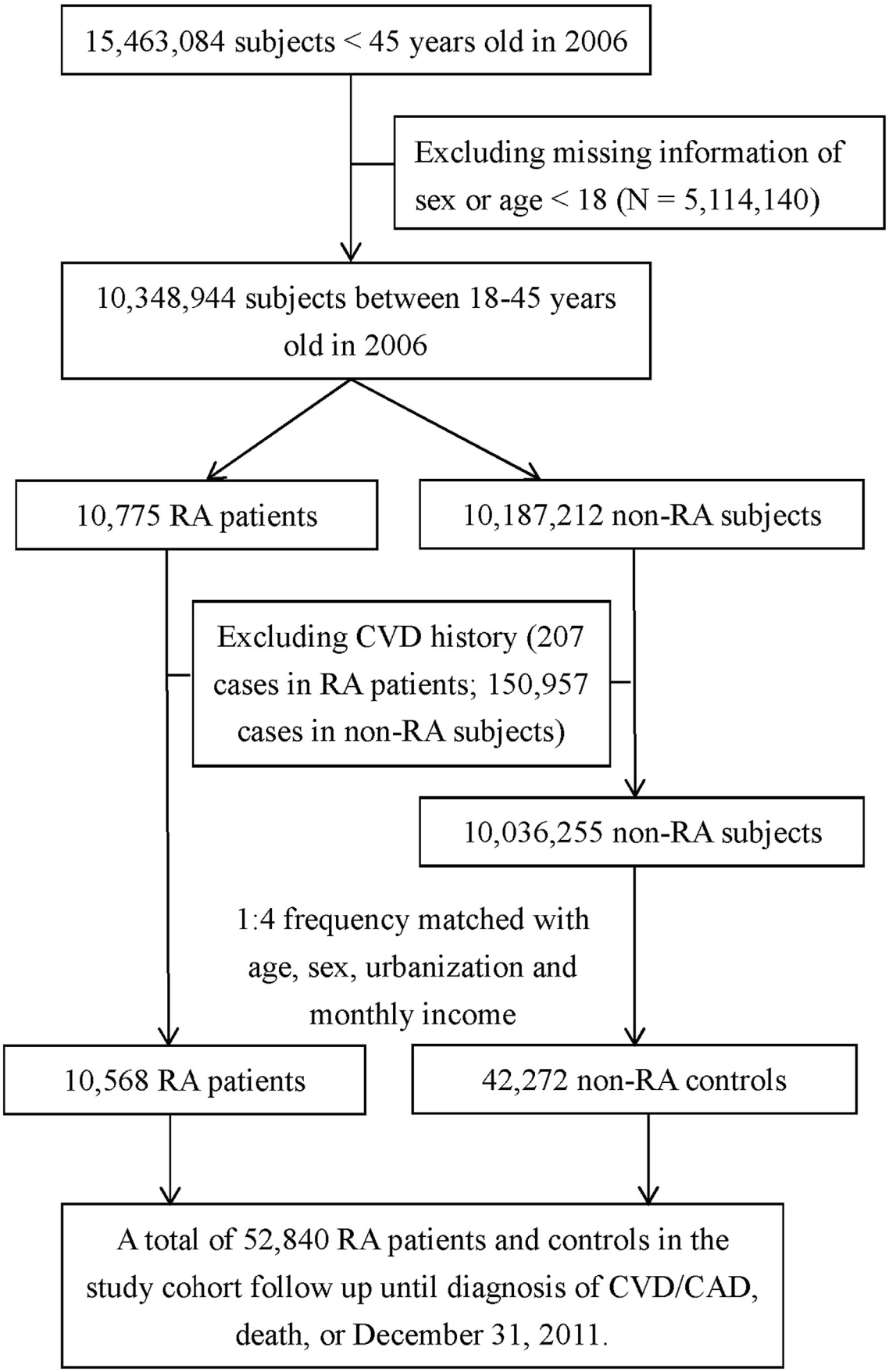

Fig. 1. Flowchart of study sample selection from the NHIRD. CAD = coronary artery disease; CVD = cerebrovascular disease; NHIRD = National Health Insurance Research Database; RA = rheumatoid arthritis.

2.5. Statistical analysis

We compared demographic characteristics and comorbidities using Pearson's chi-squared test. The incidence rate was calculated using the number of CVD/CAD cases during the follow-up period divided by the total person-years. We evaluated the effect of RA on the risk of CVD/CAD using Cox proportional hazard models after adjusting for potential confounding factors, such as age, sex, hypertension, diabetes mellitus, hyperlipidemia, CKD, cancer, PVD, mild liver disease, COPD, anticoagulants, antiplatelets, DMARDs, NSAIDs, glucocorticoids, and biologics. Both additive and multiplicative interactions were used to assess the interaction effects between traditional cardiovascular risk factors and RA on the risk of CVD/CAD. Additive interactions were confirmed using relative excess risk from interaction (RERI), proportion of disease attributable to interaction (AP), and synergy index (S). RERI identifies the excessive risk from interaction relative to the risk without exposure. AP indicates the attributable proportion of disease that is due to interaction among persons with both exposures. The S index is interpreted as the excess risk from both exposures when there is a biological interaction, relative to the risk from both exposures without interaction.[24] RERI = 0, AP = 0, or S = 1 indicates no interaction or exactly additivity; RERI >0, AP >0, or S > 1 indicates a positive interaction or more than additivity; RERI <0, AP <0, or S < 1 indicates negative interaction or less than additivity.[25] Multiplicative interactions were identified using interaction terms and added to the Cox proportional hazard models. A *p*-value of <0.05 was considered statistically significant. All analyses were performed using the SAS statistical package (SAS System for Windows, Version 9.3, SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Clinical characteristics of the study population

Table 1 presents the baseline characteristics and comorbidities of the RA cohort and non-RA cohort. Data of 10,568 patients with and 42,272 age-, sex-, urbanization-, and income-matched controls were included in the study. Most patients were female (75.05%) and aged between 35 and 44 years (62.7%). The patients with RA tended to have more hypertension, diabetes mellitus, hyperlipidemia, CKD, cancer, PVD, mild liver disease, COPD, and obesity than the non-RA controls. The patients with RA also received more anticoagulants and antiplatelets than the non-RA controls. The mean follow-up periods were 5.52 years (standard deviation (SD) ±0.85 years) and 5.94 years (SD ± 0.46 years) for the patients with RA and non-RA controls, respectively.

Table 1
Baseline variables for patients with RA and non-RA controls.

	Non-RA $N = 42,272$		RA $N = 10,568$		*p*
	n	%	n	%	
Age					
18−24	3712	8.78	928	8.78	1.000
25−34	12,056	28.52	3,014	28.52	
35−44	26,504	62.70	6,626	62.70	
Sex (male)	10,968	25.95	2,742	25.95	1.000
Urbanization					
high	25,900	61.27	6,475	61.27	1.000
median	13,956	33.01	3,489	33.01	
low	2416	5.72	604	5.72	
Monthly income					
≤ NT$15,840	13,928	32.95	3,482	32.95	1.000
NT$15,841−25,000	16,120	38.13	4,030	38.13	
≥NT$25,001	12,224	28.92	3,056	28.92	
Hypertension	988	2.34	627	5.93	<0.0001
Diabetes mellitus	481	1.14	294	2.78	<0.0001
Hyperlipidemia	763	1.80	493	4.67	<0.0001
CKD	149	0.35	228	2.16	<0.0001
Cancer	323	0.76	150	1.42	<0.0001
Alcoholism	31	0.07	8	0.08	0.9362
PVD	35	0.08	39	0.37	<0.0001
Mild liver disease	91	0.22	53	0.50	<0.0001
COPD	780	1.85	546	5.17	<0.0001
Obesity	94	0.22	43	0.41	<0.0001
Anticoagulants	173	0.41	133	1.26	<0.0001
Antiplatelets	1,864	4.41	1,103	10.44	<0.0001
Duration, mean ± SD	5.94	±0.46	5.52	±0.85	<0.0001

CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; DMARDs = disease-modifying antirheumatic drugs; NSAIDs = nonsteroidal anti-inflammatory drugs; PVD = peripheral vascular disease; RA = rheumatoid arthritis.

3.2. Association between RA and CVD/CAD

As shown in Table 2, a significantly higher incidence of CVD/CAD was seen in the patients with RA than that in the non-RA controls. In the RA cohort, 456 CVD/CAD events occurred during the follow-up period for an incidence rate of 78.21 events per 10,000 person-years. In the non-RA controls, 722 CVD/CAD events occurred during the follow-up period for an incidence rate of 28.78 events per 10,000 person-years. The crude HR for any CVD/CAD events in the patients with RA was 2.73 (95% CI, 2.43−3.07). After adjusting for age, sex, hypertension, diabetes mellitus, hyperlipidemia, CKD, cancer, PVD, mild liver disease, COPD, obesity, anticoagulants, antiplatelets, DMARDs, NSAIDs, glucocorticoids, and biologics, the HR remained a 2.61-fold increased risk of CVD/CAD (95% CI, 2.24−3.03) for patients with RA compared with non-RA controls. The multivariable-adjusted HR showed a significant association between RA and the CVD and CAD categories of ischemic stroke (HR, 3.48; 95% CI, 2.16−5.61), coronary heart disease (HR, 2.77; 95% CI, 2.32−3.32), atrial fibrillation (HR, 2.90; 95% CI, 1.17−7.20), and heart failure (HR, 2.88; 95% CI, 2.01−4.14). The results of the subgroup analyses, which excluded important cardiovascular risk factors, also documented the independent association between RA and CVD/CAD (Table 3). The risk of CVD/CAD remained high in patients with RA and without any baseline comorbidities (HR, 2.35; 95% CI, 1.88−2.93).

Table 2
Incidence, crude and adjusted HRs, and 95% CIs for CVD/CAD risks in patients with RA and non-RA controls during the follow-up period.

	non-RA				RA				Univariate		Multivariate[b]	
	N	Events	Person-years	Rate[a]	*N*	Events	Person-years	Rate[a]	HR	(95% CI)	HR	(95% CI)
All patients	42,272				10,568							
Any CVD/CAD events		722	250,895.06	28.78		456	58,307.81	78.21	2.73	(2.43−3.07)***	2.61	(2.24−3.03)***
CVD												
Ischemic stroke		68	252,359.28	2.69		46	59,471.51	7.73	2.80	(1.92−4.09)***	3.48	(2.16−5.61)***
Hemorrhagic stroke		61	252,444.87	2.42		18	59,595.48	3.02	1.23	(0.73−2.09)	1.35	(0.67−2.71)
CAD												
Coronary heart disease		459	251,464.83	18.25		315	58,676.51	53.68	2.93	(2.54−3.38)***	2.77	(2.32−3.32)***
Atrial fibrillation		17	252,537.22	0.67		14	59,602.92	2.35	3.40	(1.67−6.90)***	2.90	(1.17−7.20)*
Heart failure		117	252,346.19	4.64		96	59,387.85	16.16	3.54	(2.70−4.64)***	2.88	(2.01−4.14)**

CAD = coronary artery disease; CVD = cerebrovascular disease; DMARDs = disease-modifying antirheumatic drugs; NSAIDs = nonsteroidal anti-inflammatory drugs; RA = rheumatoid arthritis.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.
[a] Rate per 10,000 person-years.
[b] Adjustment for age, sex, hypertension, diabetes mellitus, hyperlipidemia, chronic kidney disease, cancer, peripheral vascular disease, mild liver disease, chronic obstructive pulmonary disease, obesity, anticoagulants, antiplatelets, DMARDs, NSAIDs, glucocorticoids, and biologics.

Table 3
Subgroup analysis for risks of CVD/CAD in patients with RA compared with those without RA.

	No hypertension at baseline[a]		No diabetes mellitus at baseline[b]		No hyperlipidemia at baseline[c]		No hypertension, diabetes mellitus and hyperlipidemia at baseline[d]		No co-morbidity[f] at baseline[e]	
	No RA	RA	No RA	RA	No RA	RA	No RA	RA	No RA	RA
No CVD/CAD	40,677	9,612	41,109	9,863	40,846	9,690	39,961	9,172	37,386	7,792
CVD/CAD	607	329	682	411	663	385	565	273	477	185
Crude HR	1.00	2.43	1.00	2.65	1.00	2.58	1.00	2.24	1.00	1.98
(95% CI)		(2.13−2.78)***		(2.34−2.99)***		(2.28−2.93)***		(1.94−2.59)***		(1.67−2.35)***
Adjusted HR	1.00	2.49	1.00	2.55	1.00	2.49	1.00	2.43	1.00	2.35
(95% CI)		(2.09−2.96)***		(2.18−2.99)***		(2.12−2.94)***		(2.01−2.94)***		(1.88−2.93)***

CAD = coronary artery disease; CVD = cerebrovascular disease; DMARDs = disease-modifying antirheumatic drugs; NSAIDs = nonsteroidal anti-inflammatory drugs.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.
[a] Adjustment for age, sex, diabetes mellitus, hyperlipidemia, chronic kidney disease, cancer, peripheral vascular disease, mild liver disease, chronic obstructive pulmonary disease, obesity, anticoagulants, antiplatelets, DMARDs, NSAIDs, glucocorticoids, and biologics.
[b] Adjustment for age, sex, hypertension, hyperlipidemia, chronic kidney disease, cancer, peripheral vascular disease, mild liver disease, chronic obstructive pulmonary disease, obesity, anticoagulants, antiplatelets, DMARDs, NSAIDs, glucocorticoids, and biologics.
[c] Adjustment for age, sex, hypertension, diabetes mellitus, chronic kidney disease, cancer, peripheral vascular disease, mild liver disease, chronic obstructive pulmonary disease, obesity, anticoagulants, antiplatelets, DMARDs, NSAIDs, glucocorticoids, and biologics.
[d] Adjustment for age, sex, chronic kidney disease, cancer, peripheral vascular disease, mild liver disease, chronic obstructive pulmonary disease, obesity, anticoagulants, antiplatelets, DMARDs, NSAIDs, glucocorticoids, and biologics.
[e] Adjustment for age, sex, anticoagulants, antiplatelets, DMARDs, NSAIDs, glucocorticoids, and biologics.
[f] No co-morbidity means without hypertension, diabetes mellitus, hyperlipidemia, chronic kidney disease, cancer, peripheral vascular disease, mild liver disease, chronic obstructive pulmonary disease, and obesity.

3.3. Interaction between RA and traditional cardiovascular risk factors on the risk of CVD/CAD

Fig. 2 shows the multivariable-adjusted HRs of CVD/CAD stratified by selected baseline cardiovascular risk factors. Patients with RA exhibited a significantly increased risk of CVD/CAD compared with non-RA controls in all subgroups. We did not observe any multiplicative interaction between RA and the selected baseline cardiovascular risk factors. Results of additive interaction between RA and baseline cardiovascular risk factors are displayed in Table 4. We observed a significant additive interaction between RA and hypertension. We estimated the risk of CVD/CAD for each combination of RA and hypertension, using non-RA subjects without hypertension as the reference group. The HRs of CVD/CAD in patients with hypertension alone and patients with RA alone were 3.80 (95% CI, 3.04−4.75) and 2.69 (95% CI, 2.27−3.17), respectively. Furthermore, the HR increased to 9.08 in the patients with both RA and hypertension, which was higher than the risk of CVD/CAD in association with either hypertension or RA alone. RA and hypertension acted synergistically (RERI = 3.59, S = 1.80) to heighten the risk of CVD/CAD

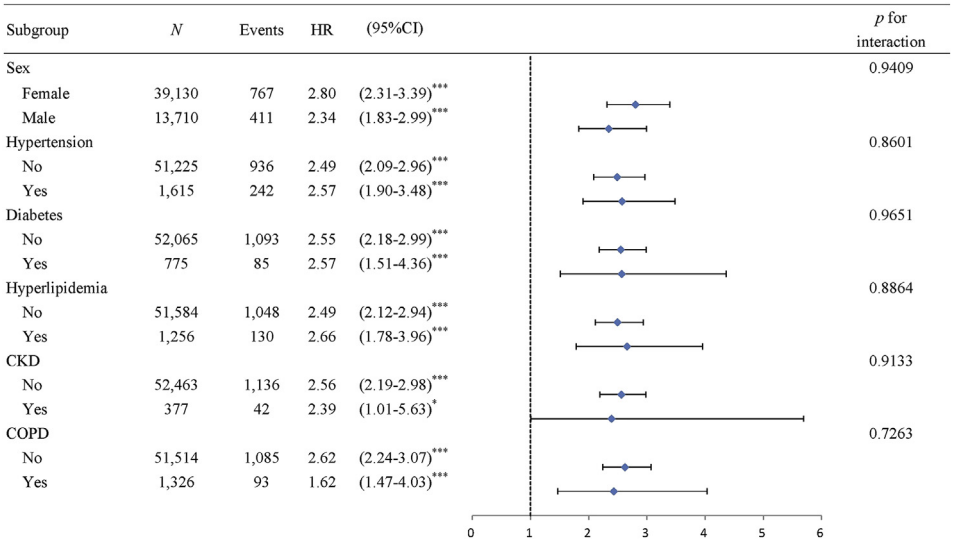

Fig. 2. Stratified analysis using selected cardiovascular risk factors to determine risk of cerebrovascular disease and coronary artery disease. CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; DMARDs = disease-modifying antirheumatic drugs; NSAIDs = nonsteroidal anti-inflammatory drugs. Adjustment for age, sex, diabetes mellitus, hyperlipidemia, chronic kidney disease, cancer, peripheral vascular disease, mild liver disease, chronic obstructive pulmonary disease, obesity, anticoagulants, antiplatelets, DMARDs, NSAIDs, glucocorticoids, biologics, as appropriate. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Table 4
Additive interaction effects between RA and cardiovascular risk factors on the risk of CVD/CAD.

	RA								Additive interaction					
	No				Yes									
	N	Events	HR	(95% CI)	*N*	Events	HR	(95% CI)	RERI	(95% CI)	AP	(95% CI)	S	(95% CI)
Sex[a]									0.43	(−0.24−1.10)	0.12	(−0.05−0.29)	1.20	(0.91−1.59)
Female	31,304	471	1.00		7,826	296	2.70	(2.26−3.22)***						
Male	10,968	251	1.44	(1.23−1.68)***	2,742	160	3.57	(2.93−4.34)***						
Hypertension[b]									3.59	(1.71−5.47)***	0.40	(0.26−0.53)***	1.80	(1.39−2.34)***
No	41,284	607	1.00		9,941	329	2.69	(2.27−3.17)***						
Yes	988	115	3.80	(3.04−4.75)***	627	127	9.08	(7.22−11.41)***						
Diabetes[c]									0.37	(−0.77−1.50)	0.11	(−0.20−0.41)	1.18	(0.72−1.94)
No	41,791	682	1.00		10,274	411	2.63	(2.25−3.07)***						
Yes	481	40	1.39	(0.97−1.97)	294	45	3.38	(2.41−4.73)***						
Hyperlipidemia[d]									0.85	(−0.20−1.90)	0.22	(−0.00−0.44)	1.41	(0.96−2.09)
No	41,509	663	1.00		10,075	385	2.60	(2.22−3.05)***						
Yes	763	59	1.46	(1.09−1.97)*	493	71	3.91	(2.95−5.19)***						
CKD[e]									0.75	(−0.84−2.35)	0.20	(−0.16−0.57)	1.39	(0.73−2.65)
No	42,123	707	1.00		10,340	429	2.61	(2.25−3.04)***						
Yes	149	15	1.70	(0.84−3.45)	228	27	4.28	(1.87−9.82)***						
COPD[f]									0.94	(−0.50−2.38)	0.20	(−0.06−0.46)	1.35	(0.88−2.07)
No	41,492	683	1.00		10,022	402	2.65	(2.27−3.09)***						
Yes	780	39	2.07	(1.49−2.88)***	546	54	4.66	(3.46−6.27)***						

CAD = coronary artery disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CVD = cerebrovascular disease; DMARDs = disease-modifying antirheumatic drugs; NSAIDs = nonsteroidal anti-inflammatory drugs.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

[a] Adjustment for age, hypertension, diabetes mellitus, hyperlipidemia, chronic kidney disease, cancer, peripheral vascular disease, mild liver disease, chronic obstructive pulmonary disease, obesity, anticoagulants, antiplatelets, DMARDs, NSAIDs, glucocorticoids, and biologics.

[b] Adjustment for age, sex, diabetes mellitus, hyperlipidemia, chronic kidney disease, cancer, peripheral vascular disease, mild liver disease, chronic obstructive pulmonary disease, obesity, anticoagulants, antiplatelets, DMARDs, NSAIDs, glucocorticoids, and biologics.

[c] Adjustment for age, sex, hypertension, hyperlipidemia, chronic kidney disease, cancer, peripheral vascular disease, mild liver disease, chronic obstructive pulmonary disease, obesity, anticoagulants, antiplatelets, DMARDs, NSAIDs, glucocorticoids, and biologics.

[d] Adjustment for age, sex, hypertension, diabetes mellitus, chronic kidney disease, cancer, peripheral vascular disease, mild liver disease, chronic obstructive pulmonary disease, obesity, anticoagulants, antiplatelets, DMARDs, NSAIDs, glucocorticoids, and biologics.

[e] Adjustment for age, sex, hypertension, diabetes mellitus, hyperlipidemia, cancer, peripheral vascular disease, mild liver disease, chronic obstructive pulmonary disease, obesity, anticoagulants, antiplatelets, DMARDs, NSAIDs, glucocorticoids, and biologics.

[f] Adjustment for age, sex, hypertension, diabetes mellitus, hyperlipidemia, chronic kidney disease, cancer, peripheral vascular disease, mild liver disease, obesity, anticoagulants, antiplatelets, DMARDs, NSAIDs, glucocorticoids, and biologics.

compared with controls. Among patients with RA and hypertension, 40% (AP = 0.40; 95% CI, 0.26−0.53) of the CVD/CAD risk was attributable to the action of both exposures.

4. Discussion

In this study we found that RA significantly elevated the risk of CVD/CAD in the young population, especially the risk of ischemic stroke, relative to non-RA controls. Even in the absence of cardiovascular risk factors, RA still increased the risk of CVD/CAD among young adult patients with RA relative to controls. We found a significant additive interaction effect on the risk of CVD/CAD between RA and hypertension, suggesting that the presence of both risk factors increased the CVD/CAD risk more than simple summation of the risks attributable to RA and hypertension in isolation. On the basis of this finding, we recommend preventing hypertension to reduce the CVD/CAD risk among young patients with RA. This finding implies that the prevention of hypertension in reducing CVD/CAD risk is a good option among young people with RA. Especially nowadays, the prevalence of hypertension among young population is increasing in the world.[26]

Numerous studies have provided evidence that patients with RA have an increased risk of CVD/CAD in both middle-aged and elderly populations.[5,6,8−12] However, scant research and analysis of the data on young adults had been conducted prior to this study. Solomon et al. reported that the crude RR for the eventual development of cardiovascular events in young patients with RA (aged <50 years) versus controls was 4.3 (95% CI, 3.0−6.2) in a cohort study.[5] Another meta-analysis showed that the RR of cardiovascular events was 2.59 (95%CI, 1.77−3.79) in young patients with RA (aged <50 years) compared with controls.[27] Our results were consistent with these earlier findings. We found that RA was independently associated with a 2.61-fold increased risk of CVD/CAD in young adults relative to controls. The increased CVD/CAD risk for patients with RA that we observed in this study was lower than the risk reported from a previous cohort study, but was similar to the results of the meta-analysis. The difference in the results may be explained in part to adjusting for different confounders, selecting different inclusion or exclusion criteria, setting a different follow-up time, or enrolling different ethnicities. Previous studies demonstrated that atherosclerosis and arterial stiffness cause CVD/CAD, including stroke, coronary heart disease, atrial fibrillation, and heart failure.[28−33] RA induces chronic inflammation and immune dysregulation, and these conditions damage arterial walls through persistent endothelial dysfunction.[34] Patients with RA also experience significantly increased arterial stiffness relative to other populations.[35] Bartoloni Bocci et al. reported that accelerated development of atherosclerosis was found in young patients with RA compared with non-RA controls.[36] Moreover, Vaudo et al. demonstrated that young to middle-aged patients with RA without cardiovascular risk factors exhibit altered endothelial reactivity, which indicates a relatively high susceptibility to the development of atherosclerotic disease.[37] This may imply that RA itself results in CVD and CAD through systemic inflammation. Our research supports the premise of the study conducted by Vaudo et al., and finds that patients with RA who have no comorbidity at baseline still have a 2.35-fold elevated risk of CVD/CAD.

Although previous studies had indicated that RA increases the risk of CVD/CAD in young population, the extent of the interaction between traditional cardiovascular risk factors and RA affecting CVD and CAD had remained unknown.[5,6,27] We investigated this, and a noteworthy finding of our study is that RA and hypertension synergistically affect the development of CVD and CAD. Young patients with RA and hypertension have seriously high risk of CVD/CAD, which is, which may be explained by the following: possibly because inflammation and medications in the RA population exacerbate hypertension.[38] Thus, young patients with RA and hypertension are susceptible to CVD and CAD progression. Further research is needed to clarify the mechanism of interaction effect between RA and hypertension on the risk of CVD/CAD.

This study had several advantages. First, because of the NHIRD we were able to obtain the data of all patients with RA in Taiwan during the study period. Thus, we had a notable capability to detect the increased risk of CVD/CAD from RA because of the large sample size. Second, all available prescription information during the study period was obtained from a historical database, thereby eliminating the possibility of recall bias. Third, since almost the entire population of Taiwan has health insurance coverage, loss of follow-up was minimized.

The results of this study should be carefully interpreted and the following limitations taken into account. First, the study lacked data on biochemistry, smoking, and body mass index (BMI), all of which may be confounding factors. However, we substituted COPD for smoking as a variable in our analyses. COPD is primarily caused by smoking, and the presence of COPD may independently increase the risk of cardiovascular disease.[39] We also substituted obesity (ICD-9-CM code 278.0) for BMI in our analyses. The second limitation involves the complete dependency of the diagnosis of CVD, CAD, RA, and any other comorbid conditions on ICD-9-CM codes. It is possible that diseases were misclassified, but this potential problem is minimized because the NHI Administration of Taiwan randomly reviews medical charts and interviews patients to verify the accuracy of the diagnosis. False diagnostic reports would face severe penalties from the Bureau of the NHI.[40] Third, all study subjects are Han Chinese; therefore, the generalizability of the findings to other ethnicities is limited. Last, because our study was only based on the NHIRD our data could not provide evidence for the mechanism between RA and the risk of CAD/CVD. Further experimental studies are required to evaluate the complex mechanisms between RA and CAD/CVD.

In conclusion, we found RA to be independently associated with CVD/CAD in young adults, particularly ischemic stroke. Furthermore, we found a significant synergistic effect between RA and hypertension on the risk of CVD/CAD in the young population. According to our results, treatment of young RA

patients should focus on preventing the development of hypertension to reduce the risk of CVD/CAD.

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