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Temporal trends of aortic stenosis and comorbid chronic kidney disease in the province of Quebec, Canada

Nada Khelifi ,[1,2] Claudia Blais ,[3,4] Sonia Jean ,[2,3] Denis Hamel,[3] Marie-Annick Clavel,[5] Philippe Pibarot ,[5] Fabrice Mac-Way [1,2]

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[1]Division of Nephrology, Endocrinology and Nephrology Axis, CHU de Quebec Research Center, Quebec, Quebec, Canada
[2]Faculty and Department of Medicine, Université Laval, Quebec, Quebec, Canada
[3]Institut National de Santé Publique du Québec, Quebec, Quebec, Canada
[4]Faculty of Pharmacy, Université Laval, Quebec, Quebec, Canada
[5]Medicine, Institut Universitaire de Cardiologie et de Pneumologie de Quebec, Quebec, Quebec, Canada

Correspondence to
Dr Fabrice Mac-Way; fabrice.mac-way.med@ssss.gouv.qc.ca

ABSTRACT

Objective To investigate temporal trends of chronic kidney disease (CKD) among patients with incident aortic stenosis (AS) and to compare these trends with that of a matched control population.

Methods Using the Quebec Integrated Chronic Disease Surveillance System, we performed a population-based nested case-control study including 108 780 patients newly hospitalised with AS and 543 900 age-matched, sex-matched and fiscal year-matched patients without AS from 2000 to 2016 in Quebec (Canada). Three subgroups were considered. Dialysis subgroup had at least two outpatient billing codes of dialysis. The predialysis subgroup had at least one hospital or two billing diagnostic codes of CKD. The remaining individuals were included in the non-CKD subgroup. We estimated overall and sex-specific standardised annual proportions of CKD subgroups through direct standardisation using the 2016–2017 age structure of the incident AS cohort. The trends overtime were estimated through fitting robust Poisson regression models. Age-specific distribution of AS and control population were assessed for each subgroup.

Results From 2000 to 2016, age-standardised proportions of patients with AS with dialysis and predialysis increased by 41% (99% CI 12.0% to 78.1%) and by 45% (99% CI 39.1% to 51.6%), respectively. Inversely, age-standardised proportions of dialysis and pre-dialysis among non-AS patients decreased by 63% (99% CI 55.8% to 68.7%) and by 32% (99% CI 29.9% to 34.6%), respectively, during the same study period. In patients with and without AS, age-standardised annual proportions of males in predialysis were significantly higher than females in most of the study period. Patients with AS on dialysis and predialysis were younger than their respective controls (dialysis: 29.6% vs 45.1% had ≥80 years, predialysis: 60.8% vs 72.7% had ≥80 years).

Conclusions Over time, the proportion of patients with CKD increased significantly and remained consistently higher in incident AS individuals compared with controls. Our results highlight the need to investigate whether interventions targeting CKD risk factors may influence AS incidence in the future.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Aortic stenosis (AS) is the most common valvular heart disease in developed countries.
⇒ Mineral and bone disorders in chronic kidney disease (CKD) have been identified as key mechanisms involved in the pathophysiology of AS.
⇒ On a population level, little is known about CKD among people with AS, and how this has changed over the last decades.

WHAT THIS STUDY ADDS

⇒ This study is the first to provide insight into the epidemiology and temporal trends of AS with comorbid CKD at a population level.
⇒ Between 2000 and 2016, the proportion of patients with comorbid CKD increased significantly and remained consistently higher in incident AS individuals compared with controls with no AS.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ This study shows the important relationship between AS and CKD.
⇒ Our results highlight the need to investigate whether interventions targeting CKD risk factors may influence AS, as this valvular heart disease has the potential to become a major health issue over the coming years.

INTRODUCTION

Aortic stenosis (AS) is the most common valvular heart disease (VHD) in developed countries with an estimated prevalence of 0.4% in the general population.[1] The burden of AS is expected to rise due to the ageing of the population and the increased prevalence of cardiometabolic risk factors.[2]

AS is characterised by progressive fibrocalcific remodelling of the aortic valve leaflets that causes an obstruction to left ventricular outflow.[1] In recent years, mineral imbalance and bone metabolism dysregulation in chronic kidney disease (CKD) have been identified as key mechanisms in the pathophysiology of AS.[3] AS occurs 10–20 years earlier in patients with CKD than in the general population, and its progression is up to 10 times faster in patients treated with long-term hemodialysis.[4 5] However, there are few data on the epidemiology and concomitant

evolution of these two conditions, AS and CKD, and little is known about the burden of AS among patients who are not yet on maintenance dialysis.[3 6]

The main objectives of this study were thus: (1) to investigate temporal trends of comorbid CKD status and severity among incident AS adults from Quebec (Canada) between 2000 and 2016 and, (2) to compare the burden of comorbid CKD status and severity between this AS population with a matched control population. We hypothesised that (1) AS and comorbid CKD are increasingly concomitant over time, and (2) the presence of comorbid CKD is higher among AS population than in the control population, essentially because CKD has been identified as a risk factor for the development and progression of AS.

METHODS

Data sources

This population-based nested case-control study was conducted using the Quebec Integrated Chronic Disease Surveillance System (QICDSS) which links five administrative databases, starting in 1 January 1996.[7] The key for linking data is the personal health insurance number. QICDSS is updated annually and contains information related to the management of the public health insurance plans covering all healthcare services used by the population (medical consultations, hospitalisations, drug use) and information on deaths. In 2016, these data were available for the vast majority of the Quebec population which represented approximately 98% of Quebecers (8.2 million).[8]

For this study, the health insurance registry, the hospital discharge and the physician claims databases were used. The health insurance registry contains demographic and geographical information. Hospitalisations' data provide hospital admissions (date of admission, length of stay, etc). Diagnosis codes were based on the *International Classification of Diseases, ninth Revision* (ICD-9) up to 31 March 2006 and the *10th Revision, with Canadian enhancement* (ICD-10-CA) thereafter which can include 16 and 26 diagnoses, respectively. Lastly, the physician claims database centralises information related to physician fee-for-service billings which include the most relevant ICD-9 diagnosis code and related service rendered.[7]

Study period

The study period was from fiscal years 2000–2001 (2000) to 2016–2017 (2016), although the QICDSS starts in January 1996, to allow a minimum of 4 years run-in period for the differentiation of prevalent and incident cases of AS at the beginning of the study.

Identification of AS cases and controls

From 2000 to 2016, incident cases of AS (AS cohort) were identified through the hospital discharge database using primary or secondary diagnosis in patients ≥20 years (see online supplemental table 1). This identification method was consistent with prior studies.[9–11] The date on which patients received their first AS diagnosis (incident cases) was defined as the index date. To create a control cohort (non-AS cohort), we randomly paired patients with AS in a one-to-five ratios with people from the general population of the same age (±3 years), sex, and fiscal year. Each control was assigned the index date of their corresponding case. This allowed us to create three subgroups (dialysis, predialysis, and non-CKD) using CKD-related codes within the same 2 years prior to this index date in the patient with AS and his controls. Based on a previously validated algorithm (sensitivity, 93.05%; specificity, 99.97%; positive predictive value, 94.38%; negative predictive value, 99.98%), all patients who had prior kidney transplant before the index date were excluded.[12]

Identification of CKD

Three subgroups were considered in the AS cohort and the non-AS cohort: (1) dialysis, (2) predialysis, and (3) non-CKD. Based on validated algorithm, the dialysis subgroup needed to have at least two outpatient physician billing codes ≥90 days apart associated with any visit or supervision for dialysis in the 2 years prior to the index date (codes during the index date were excluded) (see online supplemental table S2).[13 14] The predialysis subgroup needed at least one hospital diagnosis code in any field related to CKD, or at least two physician billing diagnostic codes ≥30 days apart of CKD in the 2 years prior to the index date (codes during the index date were excluded) (see online supplemental table S3).[15 16] To be included in the dialysis or predialysis subgroups, the aforementioned case definitions needed to have at least one of their respective codes appearing within the previous year of the index date. Finally, individuals that did not meet the case definitions presented above were included in the non-CKD subgroup.

Identification of comorbidities

We used the combined comorbidity index of Charlson and Elixhauser to define the characteristics of the study population (see online supplemental table S4).[17] This combined index includes 32 comorbidities, in which, for this study, *Renal Disease* codes and those related to AS were withdrawn. As for predialysis subgroup, we considered patients to have a comorbidity if there was at least one hospital diagnosis code recorded in any fields at the index date or in the 2 years prior to the index date, or two physician claims diagnosis codes ≥30 days apart recorded in the 2 years prior to the index date; with at least one of these claims appearing within 1 year of the index date.[15]

Statistical analysis

Characteristics of individuals were summarised according to AS status, CKD and non-CKD subgroups using numbers and percentages and means±SD. Statistical significance was estimated with the χ^2 and with the Mann-Whitney U tests for comparison of subjects with and without AS, as well as for pairwise comparison of CKD subgroups between AS and non-AS cohort. To evaluate changes

Table 1 Number and percentage of incident AS and respective controls cohorts according to CKD subgroups from 2000 to 2016

	2000–2016								
	Cohort with incident AS				Cohort without AS				Total (both cohorts)
	Total	Dialysis	Predialysis	Non-CKD	Total	Dialysis	Predialysis	Non-CKD	652 680
No. of patients (%)	108 780 (100.0)	1 203 (1.1)	26 809 (24.6)	80 768 (74.3)	543 900 (100.0)	2 113 (0.4%)	44 136 (8.1)	497 651 (91.5)	

The colour shades represent the three studied groups: Dialysis, Predialysis and Non-CKD.
AS, aortic stenosis; CKD, chronic kidney disease; No., number.

in individuals' characteristics over the study period, we used the Cochrane-Armitage Trend and the Jonckheere-Terpstra tests.

Overall and sex-specific annual proportions were calculated using the total number of individuals identified in each subgroup during the selected fiscal year as the numerator and the total number of incident AS cohort or matched controls as the denominator, respectively, during the same year. For each fiscal year, age-standardised proportions were calculated using the year 2016–2017 as reference. The patient cohort was stratified by fiscal year (1 April to 31 March) of the index date. Relative mean changes of proportions over time were obtained by performing robust Poisson regressions with age group as adjustment variable. Linear relative risks were represented in the figures with a linear curve adjusted for age. Statistical analyses were performed using SAS V.7.1 and a two-sided p value of <0.01 was considered significant.

RESULTS

Between 2000 and 2016, we identified 108 780 patients with incident AS (mean age 76.4±11.7 years, 51.8% females). Among this AS cohort, 28 012 (25.8%) patients with CKD were identified including: 1203 (1.1%) on dialysis and 26 809 (24.6%) in predialysis (table 1). The non-AS control group was composed of 543 900 age-matched, sex-matched and fiscal year-matched patients (mean age 76.2±11.9 years, 51.8% females). In this non-AS cohort, 46 249 (8.5%) patients with CKD were identified including: 2113 (0.4%) on dialysis, 44 136 (8.1%) in predialysis.

Characteristics of AS and control populations

In 2000 and 2016, hypertension (HTN) and cardiac arrhythmias were the most common comorbidities among AS and non-AS cohorts (table 2). In 2000, patients with AS with dialysis were more likely to be diagnosed with HTN and VHD (other than AS) than patients without AS with dialysis AS, while in 2016, they were more likely to be diagnosed with HTN, diabetes, and cardiovascular disease than their respective controls. In 2000, patients with AS with predialysis had significantly more obesity, congestive heart failure (CHF), cardiac arrhythmias, and VHD, while in 2016, they had significantly more cardiac risk factors (HTN, diabetes and obesity) and cardiovascular disease compared with their respective predialysis non-AS controls. There was no significant difference in the combined comorbidity index of Charlson-Elixhauser score between AS and non-AS dialysis subgroups over the study period. In contrast, patients with AS with predialysis had a significantly lower score compared with patients without AS with predialysis in 2000 while this trend reversed in 2016. Between 2000 and 2016, 72 (6.0%), 1756 (6.6%), and 11 359 (14.1%), underwent surgical aortic valve replacement in dialysis, predialysis and patients without CKD, respectively. Finally, <5 (<0.2%), 112 (0.4%), and 229 (0.3%), underwent transcatheter aortic valve implantation in dialysis, predialysis and patients without CKD, respectively, during the same study period.

Evolution of comorbidities over time

Over the study period, there was a significant increase in diabetes, obesity, cardiac arrhythmias and cancer for AS with CKD (dialysis and predialysis) while HTN, peripheral vascular disease, and dementia were increased in predialysis AS population only. Importantly, there were less cerebrovascular disease and CHF among AS with predialysis while VHD decreased for both patients with AS with dialysis and predialysis. In the predialysis control group, cardiovascular diseases decreased with time while cerebrovascular disease, CHF and peripheral vascular disorder decreased among dialysis control population. Finally, the changes observed in the aforementioned comorbidities is reflected by an increase in the combined comorbidity index for patients with AS with CKD while it decreased in the control group.

Age-standardised annual proportions of CKD

Among the incident AS population, the age-standardised annual proportions of dialysis patients showed a global mean relative increase of 41% (99% CI 12.0% to 78.1%) throughout the entire study period (figure 1A). In the non-AS population, the age-standardised annual proportions of dialysis patients showed rather an overall mean relative decrease of 63% (99% CI 55.8% to 68.7%).

In the predialysis AS cohort, a linear increase was observed between 2000 and 2006, followed by inconsistent variations from 2007 to the end of 2016 (figure 1B), ultimately leading to an overall increase of 45% (99% CI

Table 2 Baseline characteristics of incident AS and respective controls cohorts according to CKD subgroups in 2000–2001 and 2016–2017

	2000–2001							2016–2017						
	Cohort with incident AS (n=5874)			Cohort without AS (n=29 370)				Cohort with incident AS (n=8329)			Cohort without AS (n=41 645)			
Patient characteristics	**Dialysis**	**Predialysis**	**Non-CKD**	**Dialysis**	**Predialysis**	**Non-CKD**		**Dialysis**	**Predialysis**	**Non-CKD**	**Dialysis**	**Predialysis**	**Non-CKD**	
No. of patients (%) (% change from 2000 to 2001 to 2016–2017)	**52 (0.9)**	**986 (16.8)**	**4 836 (82.3)**	**169 (0.6)**	**2 353 (8.0)**	**26 848 (91.4)**	**P value***	**93 (1.1) (+22%)**	**2 418 (29.0) (+73%)**	**5 818 (69.9) (−15%)**	**95 (0.2) (−67%)**	**2 750 (6.6) (−18%)**	**38 800 (93.2)(+2%)**	**P value***
Demographics														
Age, years (median, IQR)	72 (63.5–77.5)†	79 (74–85)‡	76 (67–82)§	76 (72–80)	80 (76–85)	76 (67–84)	0.0120	76 (67–82)†¶	84 (76–89)‡¶	77 (69–85)§¶	82 (76–85)¶	86 (82–91)¶	79 (70–86)¶	0.1211
Female sex, n (%)	25 (48.1)	459 (46.6)	2 623 (54.2)	64 (37.9)	1 173 (49.9)	14 298 (53.3)	1.0000	47 (50.5)†	1 219 (50.4)‡	2 923 (50.2)§¶	25 (26.3)¶	1 307 (47.5)¶	19 613 (50.6)¶	1.0000
No. of comorbidities (median, IQR)	9 (7–12)	8 (6–11)‡	6 (3–8)§	8 (5–11)	8 (5–10)	1 (0–4)	<0.0001	11 (7–14)†¶	9 (6–11)‡¶	6 (4–8)§¶	4 (1–9)¶	6 (4–9)¶	1 (0–2)¶	<0.0001
Combined Index of Charlson-Elixhauser Score (median, IQR)	4 (2–7.5)	4 (3–6)‡	3 (1–5)§	5 (2–7)	5 (3–8)	0 (0–3)	<0.0001	6 (3–9)¶	5 (3–8)‡¶	3 (1–5)§¶	2 (0–5)¶	4 (2–7)¶	0 (0–1)¶	<0.0001
Cardiac risk factor, n (%)														
Hypertension	46 (88.5)†	709 (71.9)	2 805 (58.0)§	122 (72.2)	1 634 (69.4)	7 207 (26.8)	<0.0001	87 (93.6)†	2 126 (87.9)‡¶	4 264 (73.3)§¶	61 (64.2)	2 088 (75.9)¶	9 212 (23.7)¶	<0.0001
Diabetes	23 (44.2)	323 (32.8)‡	1 043 (21.6)§	69 (40.8)	888 (37.7)	3 294 (12.3)	<0.0001	64 (68.8)†¶	1 050 (43.4)‡¶	1 665 (28.6)§¶	41 (43.2)	934 (34.0)¶	4613 (11.9)	<0.0001
Obesity	<5 (<9.6)	80 (8.1)‡	366 (7.6)§	5 (3.0)	142 (6.0)	456 (1.7)	<0.0001	15 (16.1)¶	324 (13.4)‡¶	661 (11.4)§¶	10 (10.5)¶	162 (5.9)¶	425 (1.1)¶	<0.0001
Cardiovascular disease, n (%)														
Cerebrovascular disease	12 (23.1)	244 (24.8)	906 (18.7)§	49 (29.0)	632 (26.9)	2 445 (9.1)	<0.0001	21 (22.6)†	361 (14.9)‡¶	664 (11.4)§¶	6 (6.3)¶	354 (12.9)¶	989 (2.6)¶	<0.0001
Congestive heart failure	27 (51.9)	585 (59.3)‡	1 497 (31.0)§	74 (43.8)	1 206 (51.3)	2 242 (8.4)	<0.0001	45 (48.4)†	1 310 (54.2)‡¶	1 518 (26.1)§¶	17 (17.9)¶	722 (26.3)¶	1 006 (2.6)¶	<0.0001
Myocardial infarction	19 (36.5)	325 (33.0)	1 100 (22.8)§	43 (25.4)	722 (30.7)	1 518 (5.7)	<0.0001	41 (44.1)†¶	817 (33.8)‡	1 215 (20.9)§	24 (25.6)¶	533 (19.4)¶	905 (2.3)¶	<0.0001
Cardiac arrhythmias	26 (50.0)	522 (52.9)‡	2 050 (42.4)§	62 (36.7)	952 (40.5)	2 927 (10.9)	<0.0001	56 (60.2)†¶	1 484 (61.4)‡¶	2 670 (45.9)§¶	32 (33.7)	1 104 (40.2)¶	3 290 (8.5)¶	<0.0001
Valvular heart disease, other than AS	19 (36.5)†	455 (46.2)‡	1 912 (39.5)§	17 (10.1)	301 (12.8)	477 (1.8)	<0.0001	30 (32.3)†¶	484 (20.0)‡¶	1 037 (17.8)§¶	6 (6.3)	232 (8.4)¶	396 (1.0)¶	<0.0001
Peripheral vascular disorder	25 (48.1)	295 (29.9)	770 (15.9)§	73 (43.2)	665 (28.3)	1 480 (5.5)	<0.0001	45 (48.4)†	778 (32.2)‡¶	1 239 (21.3)§¶	25 (26.3)¶	559 (20.3)¶	1 097 (2.8)¶	<0.0001
Other conditions, n (%)														
Dementia	<5 (<9.6)	78 (7.9)‡	237 (4.9)§	18 (10.7)	373 (15.9)	2 386 (8.9)	<0.0001	7 (7.5)	366 (15.1)‡¶	529 (9.1)§¶	<5 (<5.3)	762 (27.7)¶	2 601 (6.7)¶	<0.0001
Cancer, with and without metastasis	6 (11.5)	122 (12.4)‡	554 (11.5)§	31 (18.3)	562 (23.9)	4 677 (17.4)	<0.0001	18 (19.4)¶	455 (18.8)¶	910 (15.6)§¶	20 (21.1)	522 (19.0)¶	3 937 (10.2)¶	<0.0001

Continued

Table 2 Continued

Patient characteristics	2000–2001							2016–2017						
	Cohort with incident AS (n=5874)			Cohort without AS (n=29 370)				Cohort with incident AS (n=8329)			Cohort without AS (n=41 645)			
	Dialysis	Predialysis	Non-CKD	Dialysis	Predialysis	Non-CKD	P value*	Dialysis	Predialysis	Non-CKD	Dialysis	Predialysis	Non-CKD	P value*
No. of patients (%) (% change from 2000 to 2001 to 2016–2017)	52 (0.9)	986 (16.8)	4 836 (82.3)	169 (0.6)	2 353 (8.0)	26 848 (91.4)		93 (1.1) (+22%)	2 418 (29.0) (+73%)	5 818 (69.9) (–15%)	95 (0.2) (–67%)	2 750 (6.6) (–18%)	38 800 (93.2)(+2%)	

*Comparison between subjects with AS and without AS globally (including the three subgroups).
†Significant difference (p<0.05), AS dialysis versus non-AS dialysis.
‡Significant difference (p<0.05), AS predialysis versus non-AS predialysis.
§Significant difference (p<0.05), AS non-CKD versus non-AS non-CKD.
¶Significant difference (p<0.05) for time trend for respective subgroup.
AS, aortic stenosis; CKD, chronic kidney disease; No., number.

39.1% to 51.6%). In contrast, an overall mean relative decrease of 32% (99% CI 29.9% to 34.6%) was observed for the predialysis non-AS cohort during the same period.

In the AS cohort without CKD, the age-standardised annual proportions decreased linearly between 2000 and 2006, followed by irregular variations thereafter to the end of the study period (figure 1C), which represented an overall mean relative decrease of 12% (99% CI 10.6% to 13.0%). Conversely, the age-standardised annual proportions of non-AS and non-CKD cohort showed a small mean relative increase of 4% (99% CI 3.6% to 4.3%) between 2000 and 2016 which was statistically significant.

Sex-specific age-standardised annual proportions of CKD

From 2000 to 2016, age-standardised annual proportions of dialysis patients in both, AS and non-AS cohorts were similar between males and females (figure 2A). In the predialysis AS group, the age-standardised annual proportion of males was significantly higher than that of females for most years (figure 2B). This was also the case for predialysis non-AS individuals, and this was true throughout the study period. However, the opposite was observed in non-AS individuals without CKD where females were more frequently represented (figure 2C). In AS group with no CKD, the age-standardised annual proportions of females were significantly higher than males for most years.

Age-specific distribution by CKD subgroup

Globally, in dialysis AS and non-AS populations, the highest proportion of individuals was observed in the 75–79 years group as shown in figure 3A. In dialysis population, the proportion of AS individuals was lower only in those ≥75 years compared with controls (50.4% vs 74.5%). Different patterns were observed for predialysis and non-CKD subgroups. Indeed, proportions of individuals increased almost exponentially to reach the highest point in those ≥85 years (figure 3B,C).

DISCUSSION

In this large population-based case-control study including 652 680 adults from Quebec (Canada), we highlighted the high proportion of individuals affected with CKD in the AS population: 26% versus 9% in the control population between 2000 and 2016. We also demonstrated that age-standardised annual proportions of AS individuals with CKD increased markedly, whereas it decreased in non-AS individuals. These findings support the concepts that: (1) AS and CKD are increasingly diagnosed over time, and (2) the burden of CKD is more important among AS compared with the non-AS population.

Our study specifically reported trends of AS according to the severity of renal disease in a large population. Some cohort studies have previously examined trends of AS but reported CKD only as a baseline characteristic. Badheka *et al* investigated individuals >60 years hospitalised for non-rheumatic aortic valve disorders in the primary discharge diagnosis in the United-States and

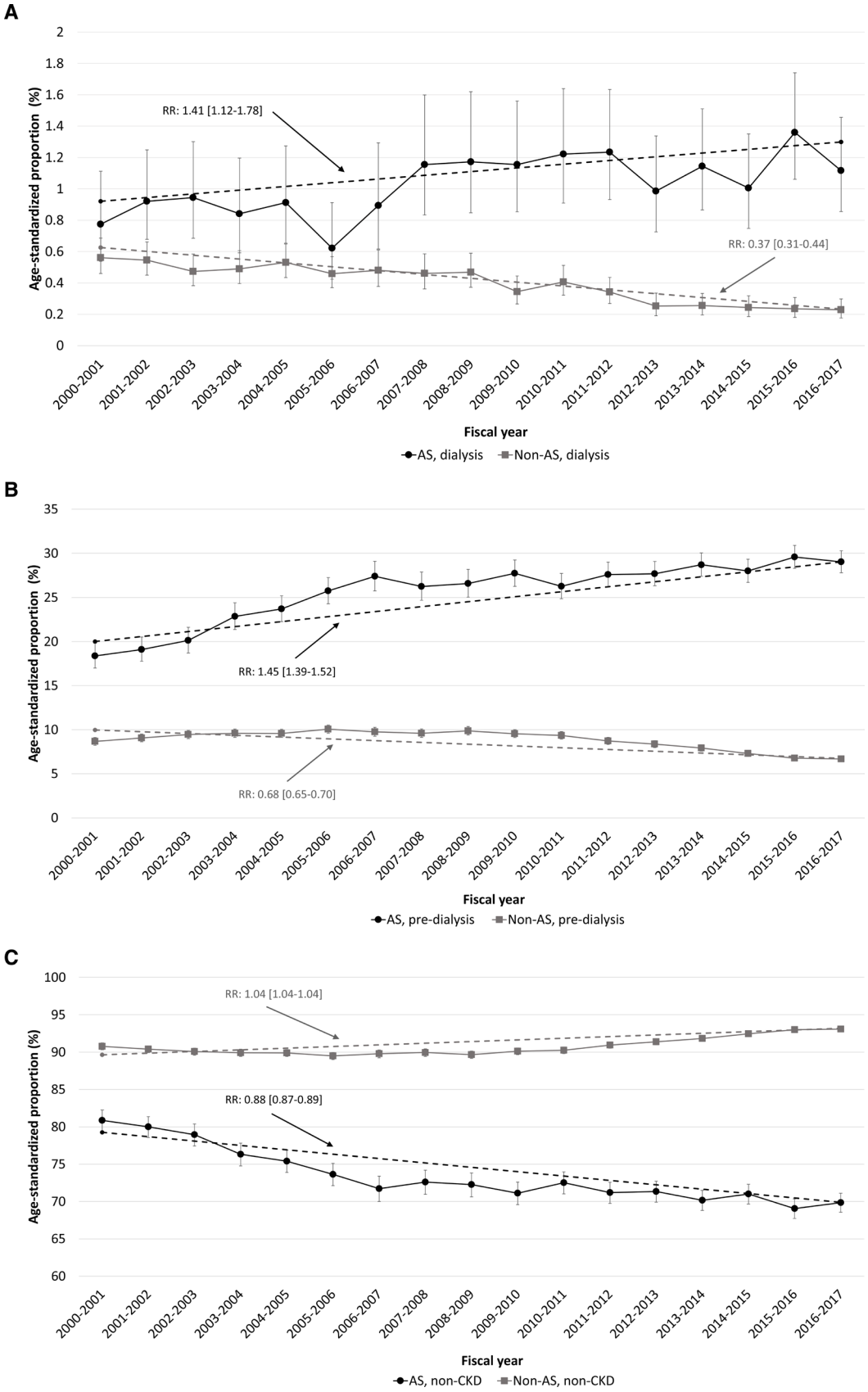

Figure 1 Age-standardised annual proportion of individuals with (A) dialysis, (B) predialysis and (C) non-CKD status, among patients with incident AS aged ≥20 years and controls, Province of Quebec, 2000–2001 to 2016–2017. Trends overtime were obtained by performing robust Poisson regressions and are represented with linear curves adjusted for age. Ninety-nine per cent CI were computed for relative risks (RR) and age-standardised proportions (bars). AS, aortic stenosis; CKD, chronic kidney disease.

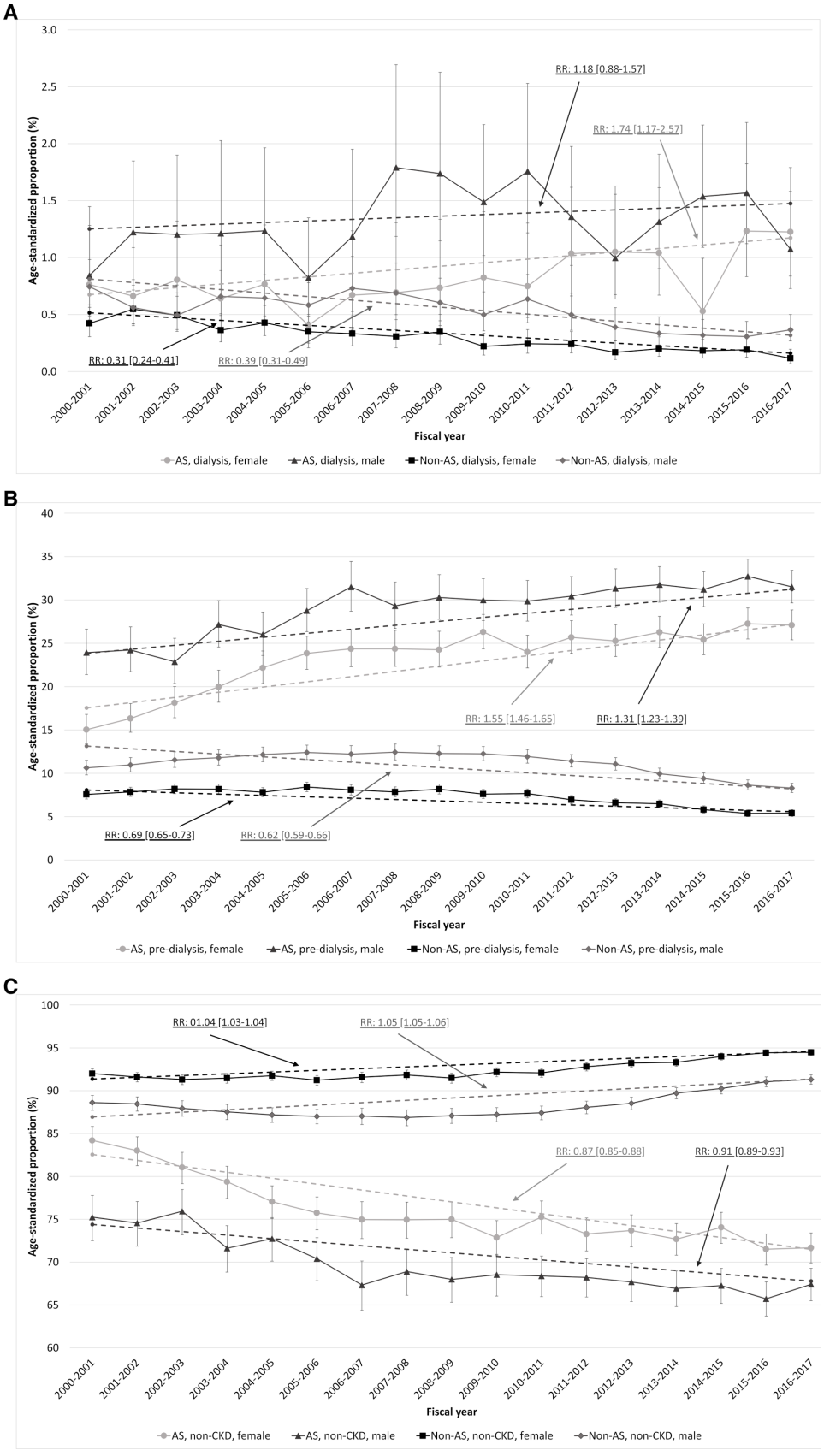

Figure 2 Sex-specific age-standardised annual proportion of individuals with (A) dialysis, (B) predialysis and, (C) non-CKD status, among patients with incident AS aged ≥20 years and controls according to sex, Province of Quebec, 2000–2001 to 2016–2017. Trends overtime were obtained by performing robust Poisson regressions and are represented with linear curves adjusted for age. Ninety-nine per cent CI were computed for relative risks (RR) and age-standardised proportions (bars). AS, aortic stenosis; CKD, chronic kidney disease.

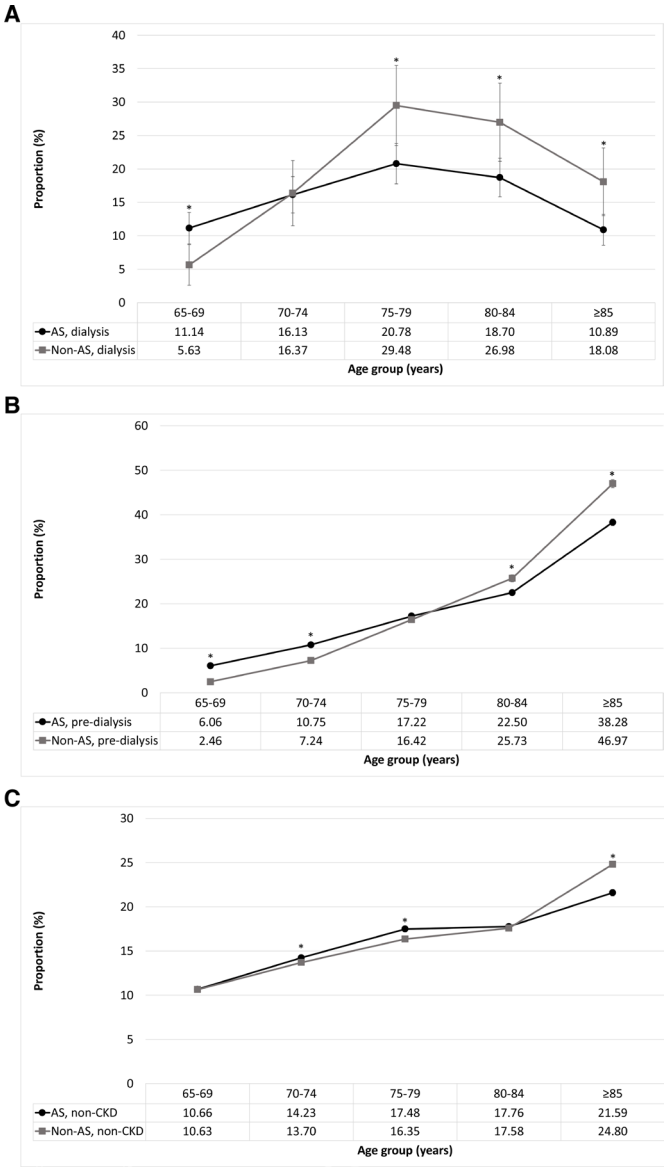

Figure 3 Age group distribution, among patients with incident AS and controls by CKD status (A) dialysis, (B) predialysis and (C) non-CKD aged ≥65 years, Province of Quebec, period from 2000 to 2001 to 2016–2017. Age groups 20–64 years are not shown. *Significant difference (p<0.01) between AS and non-AS cohorts. AS, aortic stenosis; CKD, chronic kidney disease.

renal failure was found among 15.4% of subjects in 2002, to reach 43.3% in 2012.[18] Furthermore, Berry *et al* have reported renal disease in 8.1% of new incident cases of AS, using Scottish national inpatient databases between 1997 and 2005.[10] The lower proportion of renal disease in their cohort may be related to the use of more restrictive diagnosis codes for CKD in contrast to our broader definition, which included codes for hypertensive CKD, chronic nephrotic syndrome, renal osteodystrophy and dialysis. Recently, Roleder *et al* have reported the presence of CKD in 5.5%–7.6% of patients hospitalised for AS between 2006 and 2016, using Poland registry.[19] The lower proportion of patients with CKD could be underestimated due to the Polish regulations, where the reporting of coexisting diseases is not mandatory. Thus, although the estimates vary across studies, our results suggest that CKD remains a highly prevalent coexisting condition in the AS population.

As previously reported, the incidence of AS has increased by 32% between 2006 and 2018 in Quebec.[20] Explanations for this finding could be earlier recognition of AS and better access to specialist care and cardiac imaging for the detection of VHD.[21 22] Furthermore, since mineral and bone disorders in CKD have been identified as a key contributor to the development of AS, the increased incidence of AS could therefore be partly attributable to the increasing burden of CKD.[3 11] Greater availability of laboratory testing for the screening of CKD and possibly changes in billing and coding practices may also explain the increasing burden of AS and CKD in Quebec. Despite improvements in the proportions of comorbid CVD during the study period in both cohorts, HTN and diabetes, which are important risk factors for CKD, increased significantly and remained higher in AS individuals. Further studies are needed to explore whether preventive efforts to better control CKD risk factors improve the epidemiology of AS.

By using an age/sex matched control group, we further demonstrated that the estimated prevalence of CKD in Quebec has significantly decreased in the last decade. This secular pattern is consistent with data from the Canadian population where the prevalence of CKD showed a slight decline between 2010 and 2014 (from 5.34% to 4.65%).[23] Furthermore, the prevalence of CKD has previously been estimated in Quebec at 4.0% between 2009 and 2010, which is lower than our estimation for 2009 at 10.1%.[24] The difference may lie in the mean ages of the previous study cohorts (48.5±17.8[23] and 54±8[24] years compared with 76.2±11.9 years in ours). Since CKD is an age-related disease, its prevalence is thus expected to be higher in an elderly cohort like ours. Also, the use of diagnosis codes is known to overestimate the prevalence of CKD compared with laboratory measurements that were used in their studies.[25]

Finally, the age-standardised annual proportions of males in AS and non-AS patients with predialysis were significantly higher than those observed in females in most of the study period. These findings add to the existing literature that recognise sex-specific differences in diagnosis, recognition and possibly prevalence in CKD.[26 27] Also, our results show that (1) AS individuals with concomitant CKD (predialysis and dialysis) are younger than non-AS individuals with concomitant CKD and that (2) dialysis patients are younger than predialysis patients in both, AS and non-AS populations. These results thus suggest a better survival in patients without AS with concomitant CKD compared with patients with AS with concomitant CKD. It also suggests a better survival in predialysis patients compared with dialysis patients, which is fairly understandable, as these populations have globally a lower rate of comorbidities. However, it is

possible that non-AS individuals are much less identified with CKD than AS individuals, as a result of lower interaction with the healthcare system.

Study strengths and limitations

This is a population-based case-control study reporting the burden of AS and CKD in a large population using continuously, systematically, and rigorously collected healthcare data.[7] In addition, we were able to include nearly all of Quebec's population with diagnosed AS, providing a view on the majority of hospitalised AS over a 17-year period. Finally, we included a control group which allowed us to better define the rising burden of these two increasingly common diseases at a population level.

This study also has limitations. First, to remain consistent with prior studies,[9–11 18 19 28] our AS cohort was based on the hospitalisations database only. This may have captured only sicker patients who require admission, thus raising the potential of detection bias. To minimise this, we also included secondary diagnoses, which allowed to include patients hospitalised for other conditions than AS. Also, the severity of AS is not available, nor the severity of the comorbidities since we do not have access to echo lab data or any other clinical information. Second, the sensitivity and specificity of our predialysis subgroups algorithm were not tested in our study, and we could not have access to laboratory data to estimate CKD stage specific proportion. However, we used a refined version of a widely used algorithm to identify specific comorbidity that has been validated with medical charts.[15 16] As we used validated algorithms to exclude kidney transplant patients and to identify dialysis patients, we believe that the predialysis CKD study group was correctly identified. Also, as the prevalence of CKD in the control group is comparable to rates observed in other European, North American, and Canadian studies,[29–32] this strongly suggests that our algorithm to identify CKD is reliable. Finally, because AS and CKD can be asymptomatic, there could be a misclassification bias that may underestimate the true burden. This underestimation could even be more exaggerated in the presence of dialysis as AS could be occulted unless an echocardiogram is performed. Nonetheless, the existence of nearly 20 years of reliable data and the use of uniform case definitions strengthened the results of this study.

CONCLUSION

Our study provided an insight into the epidemiology and temporal trends of AS with comorbid CKD at a population level. In contrast to what was observed in the control population without AS, individuals with AS tend to have more CKD diagnosed than in past decades. These trends likely reflect inadequate risk factor control in this complex population and may suggest that VHD could be an important complication in patients with CKD. Our results highlight the need to investigate whether interventions targeting CKD risk factors may influence AS. From a public health perspective, our results are also a first step in monitoring the burden of CKD and AS, as AS have the potential to become a major health issue over the years.

Twitter Philippe Pibarot @ppibarot

Contributors Conception and study design: NK, CB, SJ and FM-W. Data acquisition: NK, CB, SJ, DH and FM-W. Data analysis/interpretation: NK, CB, SJ, DH and FM-W. Drafting manuscript: NK. Critical revision of manuscript, final approval of manuscript: all authors. NK and FMW take responsibility for the integrity and accuracy of the data. FMW accepts full responsability for the work, the conduct of the study and controlled the decision to publish. All authors agree to be accountable for all aspects of this manuscript.

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Patient consent for publication Not applicable.

Ethics approval The current study was conducted according to an agreement established between the INSPQ and the government bodies in legal possession of the databases (RAMQ and MSSS) in part of the ministerial plan of multithematic surveillance. This plan has received approval by the Public Health Ethic Committee (ISBN: 978-2-550-58576-3) and the Commission d'accès à l'information du Québec (#1015039).

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ORCID iDs
Nada Khelifi http://orcid.org/0000-0003-3084-4100
Claudia Blais http://orcid.org/0000-0002-5299-9691
Sonia Jean http://orcid.org/0000-0002-8553-5498
Philippe Pibarot http://orcid.org/0000-0002-3607-279X
Fabrice Mac-Way http://orcid.org/0000-0002-6879-9344

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