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Left-Sided Degenerative Valvular Heart Disease in Type 1 and Type 2 Diabetes

Running title: *Rawshani et al.; Valvular heart disease in patients with diabetes*

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Abstract

Background: The role of diabetes in the development of valvular heart disease and particularly the relation with risk factor control, has not been extensively studied.
Methods: We included 715,143 patients with diabetes registered in the Swedish National Diabetes Register and compared them with 2,732,333 matched controls randomly selected from the general population. Trends were analyzed with incidence rates and Cox regression, which was also used to assess diabetes as a risk factor compared to controls, and, second, separately in patients with diabetes according to the presence of five risk factors.
Results: Incidence for valvular outcomes is increasing among patients with diabetes and the general population. In type 2 diabetes, systolic blood pressure, body mass index and renal function was associated with valvular lesions. Hazard ratios for patients with type 2 diabetes who had nearly all risk factors within target rages, compared with controls, were as follows: aortic stenosis 1.34 (95% CI, 1.31 to 1.38), aortic regurgitation 0.67 (95% CI, 0.64 to 0.70), mitral stenosis 1.95 (95% CI, 1.76 to 2.20), and for mitral regurgitation 0.82 (95% CI, 0.79 to 0.85). Hazard ratios for patients with type 1 diabetes and nearly optimal risk factor control, were as follows: aortic stenosis 2.01 (95% CI, 1.58 to 2.56), aortic regurgitation 0.63 (95% CI, 0.43 to 0.94) and mitral stenosis 3.47 (95% CI, 1.37 to 8.84). Excess risk in patients with type 2 diabetes for stenotic lesions showed hazard ratio for aortic stenosis 1.62 (95% CI, 1.59 to 1.65), mitral stenosis 2.28 (95% CI, 2.08 to 2.50), type 1 diabetes showed 2.59 (95% CI, 2.21 to 3.05) and 11.43 (95% CI, 6.18 to 21.15), respectively. Risk for aortic- and mitral regurgitation was lower in type 2 diabetes; 0.81 (95% CI, 0.78 to 0.84) and 0.95 (95% CI, 0.92 to 0.98), respectively.
Conclusions: Individuals with type 1 and 2 diabetes have greater risk for stenotic lesions, whereas risk for valvular regurgitation was lower in type 2 diabetes. Patients with well-controlled cardiovascular risk factors continued to display higher risk for valvular stenosis, without a clear stepwise decrease in risk between various degrees of risk factor control.

Keywords: Aortic valvular disease, mitral valvular disease, diabetes mellitus, risk factors, epidemiology

Non-standard Abbreviations and Acronyms

Multiple imputation by chained equations (MICE)
Body mass index (BMI)
Glycated hemoglobin levels (HbA1c)
Systolic blood pressure (SBP)
Diastolic blood pressure (DBP)
Low-density lipoprotein cholesterol (LDL-C)
High-density lipoprotein cholesterol (HDL-C)
Estimated glomerular filtration rate (eGFR)
The Swedish National Diabetes Registry (NDR)
The International Classification of Disease (ICD)

Clinical Perspective

What is new?

- In this analysis of Swedish nationwide registry data, patients with type 2 diabetes displayed a significantly higher excess risk of aortic and mitral stenosis, whereas excess risk for valvular regurgitation was lower among patients with diabetes, compared to controls.
- Patients with diabetes versus controls with most cardiovascular risk factors (i.e., glycated hemoglobin, systolic blood pressure, low-density lipoprotein cholesterol, smoking and estimated glomerular filtration rate) within guideline target ranges, continued to display higher risk of stenotic lesions.
- Patients with diabetes, displayed a significantly lower risk for valvular regurgitation, virtually regardless of multifactorial risk factor control, except for mitral regurgitation in type 1 diabetes.

What are the clinical implications?

- Achievement of current evidence-based target levels of five selected risk factors is associated with lower excess risk of valvular lesions, and if these associations are causal, their control may eliminate the excess risk of aortic stenosis in patients with type 2 diabetes.
- Systolic blood pressure, kidney function and BMI were strongly associated with increased prevalence of valvular lesions.
- In general, diabetes was associated with higher risk for left-sided valvular stenotic lesions, but significantly lower risk for valvular regurgitation, warranting further clinical and basic research.

Introduction

Diabetes mellitus, heart failure and atherosclerotic conditions have all experienced considerable advances with regards to the understanding of these conditions, treatment and outcomes.(1-4) By contrast, the pathobiology, and potential treatment, of left-sided degenerative valvular heart disease remain largely unexplored. Degenerative valvular heart disease is the leading form of valvular heart lesions in the Western world, with aortic- and mitral valvular disease being the most common lesions. Increasing life-expectancy, obesity prevalence and accumulation of cardiovascular risk factors are the most likely explanations for continued increase in left-sided degenerative valvular disease, despite substantial reductions globally in the prevalence of rheumatic heart disease.(5-9), Presumably, this epidemiological transition in middle- and low-income countries will result in a shift from rheumatic to degenerative valvular disease.(6)

Risk factors for diabetes and atherosclerosis overlap significantly with predictors of aortic- and mitral valve disease.(10) Hyperglycaemia has also been proposed as a mediator that may accelerate the progression of degenerative valvular disease through complex mechanisms involving valvular protein glycation, inflammation, osteogenic differentiation, coagulation activation and even alterations in circulating proteins that regulate valvular calcification.(11-15) The notion that degenerative valvular disease is a passive, degenerative process has been largely replaced by the view that disease initiation and progression is an active biological process, characterized by inflammation, lipid deposition, calcification,(16) and a strong association with coronary atherosclerosis. Potentially, diabetes may not only accelerate the atherosclerotic process, but also degenerative valvular heart disease, (10) with patients with diabetes reported to have a higher risk of mitral valve disease,(17, 18) and aortic stenosis ranging from 35% to 49% higher risk.(19, 20)

In this nationwide observational study, we set out to investigate the long-term trends (2001 through 2019) were investigated for left-sided degenerative valvular heart disease, in a large cohort of patients with type 1 and type 2 diabetes from the Swedish National Diabetes Registry, compared with controls from the general population matched on age, sex and county of residence. Furthermore, we examined excess risk for valvular lesions in patients with diabetes, risk associated with multifactorial risk factor control and optimal levels for selected cardiovascular risk factors were examined, in patients with and without diabetes, separately.

Methods

Because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to the Swedish National Diabetes registry, the Swedish National Board of health and Welfare, the Swedish Central Bureau of Statistics and permission from the Swedish Ethical Review Authority. Authors had full access to all the data in the study, first- and last authors take responsibility for its integrity and the data analysis.

Study design and support

The regional Ethics Review Board Gothenburg approved the study (2020-04796). All patients provided informed consent before inclusion in the registry. Information on the characteristics of study participants and other relevant information are provided in Table 1. The Swedish Association of Local Authorities and Regions and other non-profit agencies supported the study; no industry support was provided.

Data sources and study cohort

The Swedish National Diabetes Registry (NDR) has been described previously.(2, 21) The distinction between type 1 diabetes and type 2 diabetes is based on the epidemiological

definition and the physician's clinical judgement. Patients with at least one entry in the registry between Jan 1st 2001 to Dec 31st 2019, were included in the study.

At baseline, (first entry in the register), each person with diabetes was matched for age, sex and county of residence with five controls without diabetes who were randomly selected from the Swedish population register by Statistics Sweden. Study participants with prespecified baseline comorbidities were thereafter excluded from the final cohort. Exclusion criteria are presented in Figure S1 (supplementary material).

Outcomes

Four different valvular outcomes were assessed: aortic stenosis, aortic regurgitation, mitral stenosis and mitral regurgitation. Outcomes were retrieved from hospital inpatient- and outpatient discharge records with the use of codes from the International Classification of Disease (ICD) version 9 and 10. The specific codes are listed in Table S1. Patients were followed until an event occurred or until December 31, 2019.

Statistical analyses

Incidence rates were assessed using direct standardization and expressed as the number of events per 100,000 person-years of observation. The study period (2001–2019) was divided into 2-year intervals, with the exception of the final period that was a 3-year period (2017–2019). The incidence was standardized to the age- and sex-distribution observed in the initial time period. Numerators were the number of first events in a particular time period, while denominators were the number of persons at risk during the same time period. Changes in risk over time were assessed using Cox regression. These trends were calculated by stratification on the first- and last time periods (i.e., 2001-2006 versus 2013-2019). The regression models included age, sex and socioeconomic variables (ethnicity, marital status, income and education). The Cox model that estimates changes in risk over time between first- and last time period, in patients with diabetes compared with controls, includes an

interaction term between *category* (i.e., patient with diabetes or control) and *time-period* (i.e., first- and last time periods), in addition, this model does not include socioeconomic variables.

Cox regression models were constructed for all outcomes, which included baseline values to examine the risk association of cardiometabolic risk factors. Data on cardiometabolic risk factors were only available for individuals with diabetes. Age, glycated hemoglobin (HbA1c), body mass index (BMI), systolic- and diastolic blood pressure, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, estimated glomerular filtration rate and duration of diabetes (eGFR), were modelled using restricted cubic splines with 3 knots. Adjustment was made for these variables, as well as sex, smoking, physical activity, socioeconomic variables, comorbidities and pharmacological treatment.

For the analyses of multifactorial risk factor control, the risk of each outcome was estimated among patients with diabetes, according to the number of risk factors within target ranges on the basis of guideline-recommended target levels. The following five risk factors were considered (cut-offs in parentheses): HbA1c (≥ 7.0% [≥ 53 mmol/mol]), systolic and diastolic blood pressure (either ≥ 130 mmHg systolic or ≥ 80 diastolic), albuminuria, (presence of microalbuminuria or macroalbuminuria), smoking (being a “current smoker” at study entry) and LDL-C (≥ 2.5 mmol/L [97 mg per deciliter]). Adjustment for duration of diabetes was done by assigning matched controls to a duration of zero years and patients with diabetes had their duration of diabetes centralized around the grand mean. In order to obtain maximum statistical power in regression models, patients with multifactorial risk factor control were categorized into three groups of risk factor control.

In addition, the optimal levels for five selected risk factors were assessed – i.e., the level associated with the lowest risk – of HbA1c, systolic blood pressure (SBP), low-density lipoprotein cholesterol (LDL-C), BMI and eGFR. The evidence-based target level was set as

reference for each risk factor. Furthermore, logistic regression was performed to assess the relationship between diabetes and combined valvular disease.

Missing data (around 5–10%) was handled using multiple imputation by chained equations (MICE). Distributions and means were analyzed before and after imputation without observing any significant differences. Given the exploratory nature of this study, we used regular 95% confidence intervals and emphasize on patterns and associations in the data, with no adjustments for computing multiple confidence intervals. A comprehensive discussion of statistical methods and model construction has been presented in the supplementary material (expanded methods). Calculations were performed in R Studio version 4.0.3 (R Foundation for Statistical Computing).

Results

Study population

In all, 36,211 patients with type 1 diabetes, 166,125 of their controls, 678,932 patients with type 2 diabetes, and 2,566,208 of their controls, were included in the study. Mean age was 32 years for type 1, and 64 years for type 2 diabetes (Table 1). Cardiovascular comorbidities were roughly twice as common in people with diabetes. Use of anticoagulants, statins and anti-thrombotic medications were also more common in people with diabetes. Median follow-up for type 1 diabetes was 10.4 years and 7.4 years for type 2 diabetes. The number of recorded events for the entire case-control cohort were as follows; 48,461 cases of aortic stenosis, 20,291 cases of aortic regurgitation, 1,970 cases of mitral stenosis and 23,316 cases of mitral regurgitation.

Incidence and change in risk of valvular outcomes

Incidence rates for most outcomes were relatively high in the first time period. However, these rates decreased considerably between the first- and second time period. Thereafter, we observed a gradual increase in incidence for most outcomes was observed.

The incidence rate of aortic stenosis (per 100,000 person-years) was 241.4 for type 2 diabetes and 138.7 for controls, in the final time period, respectively. Hazard ratios for individuals with type 2 diabetes during the first time period were 1.64 (95% CI, 1.60–1.69) and 1.53 (95% CI, 1.45–1.61) during the last time period (Fig 1 Panel A). There was no significant change in risk for aortic stenosis between patients with type 2 diabetes and matched controls, during the first and last time periods, HR 0.99 (95% CI, 0.94–1.06). Type 1 diabetes was not associated with a significant excess risk for aortic stenosis in the final time period 1.60 (95% CI, 0.67–3.84), compared with controls (Fig 1 Panel B).

Incidence rates of aortic regurgitation increased parallelly in patients with type 1 and type 2 diabetes, and their matched controls. Cox model that assesses change in risk between patients with diabetes and controls, showed that patients with type 2 diabetes displayed a 17% greater relative risk reduction over time, compared to matched controls, for aortic regurgitation (HR 1.17 (95% CI, 1.06–1.30). In type 2 diabetes, results from Cox regression revealed that diabetes was associated with lower risk for aortic regurgitation (Fig 1 Panel C and Panel D). Incidence rates for mitral stenosis were greater in patients with diabetes, compared with controls, particularly in type 1 diabetes, albeit results from the Cox model did not show a significant change in excess risk between the first and last time periods (Fig 1 Panel E and Panel F). The number of events and person-years for each time period and outcome are presented in Table S3-S6. These tables also include information on crude- and standardized incidence rates. Also, Cox models were constructed to assess the change in risk between the first- and last time period, in patients with diabetes and controls, respectively (Table S7).

Cardiometabolic risk factors and valvular outcomes

In patients with type 2 diabetes, higher SBP, elevated BMI and eGFR were associated with higher risk for aortic stenosis, whereas higher HbA1c was associated with slightly lower risk. In the fully adjusted model, LDL-C levels were significantly associated with aortic stenosis. (Fig 2 Panel A). Higher SBP was associated with higher risk for aortic regurgitation, mitral stenosis and mitral regurgitation. (Fig 2 Panel B–D). Higher BMI was associated with lower risk of mitral regurgitation, while lower eGFR was associated with higher risk (Fig 2 Panel D)

Figure 3 shows the association between cardiometabolic risk factors and valvular outcomes in people with type 1 diabetes. Development of aortic stenosis was not significantly associated with any risk factor. It is noted, however, that there are suggested positive trends for HbA1c, LDL-C and U-shaped associations with eGFR (Fig 3 Panel A). For aortic regurgitation, a suggestion of positive associations is noted for HbA1c, SBP and eGFR, albeit none being significant (Fig 3 Panel B). For mitral regurgitation, we note positive associations are suggested for increasing BMI and LDL-C, although also not significant, whereas increasing SBP was associated with higher risk (Fig 3 Panel D). The results from regression models constructed to assess the associations between age at baseline, age at diagnosis of diabetes and duration of diabetes with valvular lesions in patients with diabetes are presented in Figure S2, Figure S3 and Figure S4.

Multifactorial risk factor control

Figure 4, panels A through D presents adjusted hazard ratios for all outcomes, compared with controls and number of risk factors withing target range. For aortic stenosis in type 2 diabetes, results show a gradual increase in hazard ratios for each additional risk factors not within target range. The hazard ratio for type 2 diabetes with 0–1 risk factors out of target range at baseline, as compared with controls, was 1.34 (95% CI 1.31 to 1.38). Hazard ratio

for having 4–5 risk factors out of target range, as compared with controls, was 1.69 (95% CI 1.61 to 1.77) (Fig 4 Panel A). In contrast, type 2 diabetes displayed a significantly lower risk for aortic and mitral valvular regurgitation, irrespective of number of risk factors at target.

Patients with type 1 diabetes had higher risk for aortic stenosis, regardless of number of risk factors within target range (Fig 4 Panel B). For aortic regurgitation, participants with type 2 diabetes were at lower risk of, compared with controls. The hazard ratio for aortic regurgitation for type 2 diabetes, with nearly optimal risk factor control, compared with controls, was 0.67 (95% CI 0.64 to 0.70) (Fig 4 Panel C). In type 1 diabetes, having 0-1 risk factors were associated with lower risk for aortic regurgitation, HR 0.63 (95% CI, 0.43 to 0.94) (Fig 4 Panel D).

For mitral stenosis, participants with diabetes were consistently at higher risk, compared with controls, even with most risk factors within target range (Fig 4 Panel E and Panel F).

For mitral regurgitation, participants with type 2 diabetes were at lower risk than controls. The hazard ratio for type 2 diabetes with none of the risk factors at baseline, as compared with controls, was 0.82 (95% CI 0.79 to 0.85) (Fig 4 Panel G). Type 1 diabetes and multifactorial risk factor control was not associated with significant association for mitral regurgitation (Fig 4 Panel H).

Overall excess risk for valvular outcomes

Adjusted for age, sex and socioeconomic variables, the HRs for aortic stenosis for patients with type 2 and type 1 diabetes were 1.62 (95% CI, 1.59–1.65) and 2.59 (95% CI, 2.21–3.05), respectively; hazard ratios of aortic regurgitation were 0.81 (95% CI, 0.78–0.84) and 0.85 (95% CI, 0.65–1.11), respectively (Fig 5 Panel A–D). For mitral stenosis, HRs for type 2 and type 1 diabetes were 2.28 (95% CI, 2.08–2.50) and 11.43 (95% CI, 6.18–21.15), respectively,

and for mitral regurgitation, 0.95 (95% CI, 0.92–0.98) and 1.38 (95% CI, 1.09–1.70), respectively (Fig 5 Panel E – H).

Combined valvular disease

The relationship between diabetes and combined valvular disease was assessed, using logistic regression. These models included adjustment for age, sex and socioeconomic variables. Compared with matched controls, patients with type 2 and type 1 diabetes displayed greater odds ratio for combined valvular disease, OR 1.38 (95% CI, 1.29 to 1.47) and OR 2.38 (95% CI, 1.53 to 3.68), respectively (Table 2). See Table S1 and Figure S1 for definition of combined valvular disease and information about number events included in the model.

Degenerative mitral valvular disease

We constructed sensitivity analyses to assess risk for degenerative mitral valvular heart disease, considering the elevated risk for mitral stenosis in patients with diabetes, particularly type 1 diabetes. Figure S5 displays excess risk for degenerative mitral valvular disease among patients with diabetes, compared with controls. These results support our findings regarding the excess risk for mitral stenosis. Hazard ratio for degenerative valvular disease in type 2 diabetes was HR 2.27 (95% CI, 1.98–2.61) and in type 1 diabetes HR 21.72 (95% CI, 6.33–74.5).

Discussion

This nationwide observational study of 36,211 patients with type 1 diabetes, 678,932 patients with type 2 diabetes, and 2,732,333 controls from the general population, demonstrates that aortic and mitral valve disease are prevalent conditions in people with and without diabetes. The present findings show that diabetes mellitus is associated with higher risk for left-sided stenotic lesions, whereas risk for left-sided valvular regurgitation was generally lower among

patients with diabetes, suggesting a diverse pathological processes for the development of valvular leaflet- and annulus fibrosis and calcification, between patients with- and without diabetes.

In type 2 diabetes, a 1.62-fold higher risk of aortic stenosis and 2.28-fold higher risk of mitral stenosis were observed, while the risks of aortic- and mitral regurgitation were 19% and 5% lower, respectively, compared with controls. Type 1 diabetes was associated with 2.59-fold, 11.43-fold and 1.38-fold higher risk of aortic stenosis, mitral stenosis and mitral regurgitation, respectively, and no association with risk for aortic regurgitation. Patients with diabetes and optimal multifactorial cardiovascular risk factor control had higher risk compared with controls for left-sided valve stenotic lesions, whereas risk was for valvular regurgitation was continuously lower for individuals with diabetes, irrespective of risk factor control.

Patients with type 2 diabetes and optimal multifactorial cardiovascular risk factor control had lower risk for valvular regurgitation. The difference in excess risk between diabetes and controls decreased incrementally with worsening cardiovascular risk factor control. Nevertheless poor cardiovascular risk factor control remained statistically associated with lower risk for valvular regurgitation. In type 1 diabetes, poor cardiovascular risk factor control was associated with higher risk for valvular regurgitation. While HbA1c is an overall predictor of diabetes-related complications, it does not appear to be a convincing risk factor for any aortic valvular disease. However, lower baseline levels HbA1c, than targeted by contemporary guidelines was associated with significantly lower risk for aortic- and mitral stenosis, while higher levels for HbA1c were associated with higher risk for mitral regurgitation. Systolic blood pressure, BMI, LDL-C and eGFR were positively associated with most valvular lesions.

Previous research on the incidence of valvular heart disease in the Swedish general population, reveals similar changes in trends, during the overlapping time periods of the present study.(8, 9) In addition, reports on trends for cardiovascular outcomes in people with and without diabetes, using the same study population as this study, although with shorter follow-up period (2, 21), demonstrated declining rates for acute myocardial infarction, coronary heart disease, stroke and heart failure. In contrast, this study shows increasing incidence and risk over time for valvular stenosis and regurgitation, still, incidence rates for cardiovascular disease and heart failure still exceeds degenerative valvular heart disease. This pattern is also true for the general population. On the contrary to cardiovascular disease and heart failure, there are no causal treatments for the progression of valvular heart disease; active monitoring and surgical or percutaneous valve replacement is currently the only long-term treatments that modify outcomes.(22-24) Moreover, in the standardized incidence analyses, the initial time period displayed high rates for several outcomes. This is presumably due to patients with diabetes in the Swedish National Diabetes Register that were included in the registry between 1996–2000, which were patients that generally have more comorbidities or poor risk factor control, compared to patients with diabetes that were registered in subsequent years, which included more primary care and outpatient clinics.

There may be several explanations for the rising incidence and risk observed for left-sided valvular stenotic lesions in patients with diabetes, as well as the lower risk for valvular regurgitation. Traditional risk factors for coronary atherosclerosis such as old age, active smoking, elevated blood pressure, dyslipidemia, obesity, family history and kidney function, have also been implicated as risk factors for aortic valve stenosis, while factors for mitral stenosis are less well characterized.(17, 25-30) Results from previous studies also indicate dyglycemia as an important predictor for valvular stenosis, presumably by means of increased production of advanced glycation end products and oxidative stress, resulting in

inflammation and calcification.(14) The greater risk for valvular stenotic lesions in patients with diabetes is most likely related to abovementioned risk factors, which are more prevalent and pronounced in diabetes, resulting in aortic- and mitral leaflet calcification. In contrast, a similar process with inflammation and calcification in valvular commissures, in combination with, valvular annular calcification as a result of calcium deposition on either apoptotic- or necrotic interstitial cells or calcified extracellular matrix(31-33), could counteract the dilation in valvular annular rings and subsequent primary valvular regurgitation.(34, 35) These concepts are substantiated by the sensitivity analysis of combined valvular disease, which displayed greater risk for combined left-sided valvular disease in patients with diabetes, presumably due to stenotic lesions that precipitates secondary valvular regurgitation. The present results for stenotic lesions and combined valvular disease are comparable, whereas, primary valvular regurgitation demonstrated an opposite risk association in patients with diabetes.

Women with diabetes had significantly lower risk for valvular lesions, with the exception of mitral stenosis. Previous epidemiological research suggests that mitral stenosis is more common in women and associated with higher mortality, regardless of ethnic background, (36, 37) presumably due to rheumatic heart disease. However, epidemiological reports from the Swedish patient registry shows that a majority of the women that were diagnosed with mitral stenosis did not have a known history of rheumatic heart disease, and the prevalence of rheumatic fever in Sweden is extremely low, (8, 9) suggesting that other etiologies may be the most important cause of mitral stenosis. Sensitivity analyses showed that diabetes was associated with significantly higher risk for degenerative valvular disease, particularly in those with type 1 diabetes where hazard ratio was 21.72 (95% CI, 6.33–74.5).

The present findings demonstrate a transition in the spectrum of valvular heart disease, with an increase in age-degenerative left-sided valvular disease, in addition to

recognizing a range of potential etiologies between cardiometabolic risk factors, diabetes and valvular disease, which merit further investigation. The potential effect of multifactorial cardiovascular risk factor control maybe important for valvular disease, however our findings does not indicate a gradual decline in excess risk for those with multifactorial risk factor control, a similar pattern was observed for valvular regurgitation, however, with a lower risk association, compared to controls. The association for stenotic- and regurgitative valvular lesions in patients with diabetes, suggests that diabetes and cardiometabolic factors influence valvular leaflet- and annular areas differently, and that diabetes is associated with an accelerated degenerative process for cardiac valves.

Limitations

There is no option to differentiate rheumatic and non-rheumatic valvular disease. However, the former is uncommon in Sweden, so this is predominantly a study of non-rheumatic valvular heart disease. Cardiometabolic data on controls is not available, making it impossible to study how this associate with valvular heart disease in the general population, or to examine to what extent such risk factors explain the association between diabetes and valvular heart disease. Using baseline values for risk factors, may be considered as a limitation as baseline values, for some patients, will not be representative of follow-up. However, index values are preferred due to their advantage from a clinical point of view. The present results are dependent on model assumptions and could change slightly with different approaches to analyses of the data. No distinction was made between patients with all or some cardiovascular risk factors within target range between those treated to target verses with de novo levels. No adjustments were made for multiple testing; therefore p-values can be only interpreted as exploratory or suggestive. Residual confounding is impossible to fully overcome. Finally, we do not have information on lipoprotein (a) levels, which is increasingly appreciated as a driver of calcific valvular disease.

Conclusion

This study adds to the notion that cardiovascular disease epidemiology is shifting with less cardiovascular disease and more valvular heart disease. Patients with diabetes are at higher risk than those without diabetes for left sided valvular stenosis, whereas risk for valvular regurgitation was lower, compared with matched controls. Patients with type 1 diabetes are at very high risk of developing mitral stenosis (11.43-fold).

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Disclosures

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Supplemental Materials

Expanded methods

Table S1 – S7

Figure S1 -S5

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Table 1. Baseline Characteristics for Patients with Type 1 Diabetes and Type 2 Diabetes, Along with Matched Controls From the General Population.

	All diabetes patients	All matched controls	Type 1 diabetes	T1D matched controls	Type 2 diabetes	T2D matched controls
Number of study participants	715143	2732333	36211	166125	678932	2566208
Gender = Women (%)	314393 (44.0)	1306535 (47.8)	15783 (43.6)	73830 (44.4)	298610 (44.0)	1232705 (48.0)
Age (mean (SD))	62.77 (14.52)	60.48 (14.91)	32.65 (15.38)	30.55 (13.40)	64.38 (12.59)	62.41 (12.78)
Age-categories (%)						
<45	73508 (10.3)	361159 (13.2)	26841 (78.5)	131010 (84.0)	44662 (7.0)	220053 (9.2)
45-54	92945 (13.0)	425401 (15.6)	3086 (9.0)	12598 (8.1)	89859 (14.1)	412803 (17.2)
55-64	211147 (29.5)	853418 (31.2)	2472 (7.2)	7975 (5.1)	168733 (26.4)	674427 (28.2)
65-74	188051 (26.3)	636361 (23.3)	1165 (3.4)	2997 (1.9)	186886 (29.2)	633364 (26.4)
>75	149492 (20.9)	455994 (16.7)	642 (1.9)	1449 (0.9)	148850 (23.3)	454545 (19.0)
Education (%)						
Pre-secondary education ≤ 9 years	315219 (44.1)	974753 (35.7)	15439 (42.6)	68791 (41.4)	299780 (44.2)	905962 (35.3)
Secondary education >9 to 12 years	279986 (39.2)	1063249 (38.9)	14187 (39.2)	63606 (38.3)	265799 (39.1)	999643 (39.0)
Post-secondary education ≥ 12 years	119938 (16.8)	694331 (25.4)	6585 (18.2)	33728 (20.3)	113353 (16.7)	660603 (25.7)
Marital status (%)						
Married	345576 (48.3)	1316605 (48.2)	7535 (20.8)	31220 (18.8)	338041 (49.8)	1285385 (50.1)
Ethnicity = Scandinavia (%)	602119 (84.2)	2447022 (89.6)	33114 (91.4)	149590 (90.0)	569005 (83.8)	2297432 (89.5)
Income family (Quartiles) (%)						
Quartile 1	215889 (30.2)	646047 (23.6)	9002 (24.9)	34847 (21.0)	206887 (30.5)	611200 (23.8)
Quartile 2	200714 (28.1)	661547 (24.2)	7631 (21.1)	34408 (20.7)	193083 (28.4)	627139 (24.4)
Quartile 3	170935 (23.9)	690544 (25.3)	9289 (25.7)	44419 (26.7)	161646 (23.8)	646125 (25.2)
Quartile 4	127605 (17.8)	734195 (26.9)	10289 (28.4)	52451 (31.6)	117316 (17.3)	681744 (26.6)

Income (Quartiles) (%)						
Quartile 1	212283 (29.7)	650101 (23.8)	18958 (52.4)	83807 (50.4)	193325 (28.5)	566294 (22.1)
Quartile 2	210001 (29.4)	652155 (23.9)	7244 (20.0)	29484 (17.7)	202757 (29.9)	622671 (24.3)
Quartile 3	164971 (23.1)	696411 (25.5)	6760 (18.7)	34267 (20.6)	158211 (23.3)	662144 (25.8)
Quartile 4	127888 (17.9)	733665 (26.9)	3249 (9.0)	18567 (11.2)	124639 (18.4)	715098 (27.9)
Coronary heart disease = Yes (%)	118580 (16.6)	212639 (7.8)	1790 (4.9)	3447 (2.1)	116790 (17.2)	209192 (8.2)
Acute myocardial infarction = Yes (%)	55743 (7.8)	92639 (3.4)	716 (2.0)	1284 (0.8)	55027 (8.1)	91355 (3.6)
Stroke = Yes (%)	45180 (6.3)	95569 (3.5)	913 (2.5)	943 (0.6)	44267 (6.5)	94626 (3.7)
Heart failure = Yes (%)	42190 (5.9)	66694 (2.4)	479 (1.3)	361 (0.2)	41711 (6.1)	66333 (2.6)
Atrial fibrillation = Yes (%)	54134 (7.6)	116853 (4.3)	326 (0.9)	662 (0.4)	53808 (7.9)	116191 (4.5)
Hypertension = Yes (%)	202885 (28.4)	340341 (12.5)	2627 (7.3)	1815 (1.1)	200258 (29.5)	338526 (13.2)
Peripherial arterial disease = Yes (%)	14731 (2.1)	23445 (0.9)	406 (1.1)	123 (0.1)	14325 (2.1)	23322 (0.9)
Chronic obstructive pulmonary disease = Yes (%)	20338 (2.8)	52756 (1.9)	119 (0.3)	306 (0.2)	20219 (3.0)	52450 (2.0)
Dementia = Yes (%)	4956 (0.7)	28470 (1.0)	48 (0.1)	90 (0.1)	4908 (0.7)	28380 (1.1)
Alcoholism = Yes (%)	19455 (2.7)	65062 (2.4)	1339 (3.7)	4069 (2.4)	18116 (2.7)	60993 (2.4)
End-stage renal disease = Yes (%)	17932 (2.5)	24156 (0.9)	1618 (4.5)	254 (0.2)	16314 (2.4)	23902 (0.9)
Cancer = Yes (%)	75558 (10.6)	272436 (10.0)	9724 (26.9)	2041 (1.2)	74887 (11.0)	270395 (10.5)
Antihypertensive medication = Yes (%)	406934 (56.9)	924959 (33.9)	10327 (28.5)	17858 (10.7)	397210 (58.5)	907101 (35.3)
Statins = Yes (%)	344091 (48.1)	438984 (16.1)	897 (2.5)	6651 (4.0)	333764 (49.2)	432333 (16.8)
Anti-coagulant medication = Yes (%)	81217 (11.4)	216878 (7.9)	3504 (9.7)	3404 (2.0)	80320 (11.8)	213474 (8.3)
Antithrombotic medication = Yes (%)	161226 (22.5)	311154 (11.4)	2627 (7.3)	4172 (2.5)	157722 (23.2)	306982 (12.0)
Imputed baseline values for individuals with diabetes						

Insulin method = 2 (%)			5890 (16.3)		2862 (0.4)	
Age of onset of disease (mean (SD))			18.76 (12.41)		60.45 (13.34)	
Duration of diabetes (mean (SD))			13.66 (13.40)		3.95 (6.28)	
Glycated hemoglobin (HbA1c) (mean (SD)) *			65.50 (18.55)		55.02 (16.95)	
Smoker = Yes (%)			5575 (15.4)		112516 (16.6)	
Albuminuria (%)						
No albuminuria			31436 (86.8)		535798 (78.9)	
Normalized value			105 (0.3)		2980 (0.4)	
Microalbuminuria (3–30)			3007 (8.3)		96721 (14.2)	
Macroalbuminuria (>30)			1663 (4.6)		43433 (6.4)	
eGFR (mean (SD))			114.94 (57.29)		83.68 (28.32)	
Retinopathy = Yes (%)			11966 (33.0)		121895 (18.0)	
Systolic blood pressure (mean (SD))			123.72 (15.95)		137.96 (17.65)	
Diastolic blood pressure (mean (SD))			73.04 (9.23)		79.14 (10.13)	
Total cholesterol (mean (SD))			4.74 (1.09)		5.06 (1.17)	
High-density lipoprotein cholesterol (mean (SD))			1.61 (0.52)		1.27 (0.43)	
Triglycerides (mean (SD))			1.34 (1.28)		2.03 (1.52)	
LDL-cholesterol (mean (SD))			2.59 (0.91)		2.93 (1.00)	
S-creatinine (mean (SD))			73.12 (43.84)		78.96 (29.80)	
Body mass index (mean (SD))			25.07 (4.21)		30.24 (5.67)	
Physical activity (%)						
Never			4135 (11.4)		105128 (15.5)	
< 1 time/week			5113 (14.1)		94526 (13.9)	

1–2 time/week			7694 (21.2)		137079 (20.2)	
3–5 time/week			9767 (27.0)		145800 (21.5)	
5 time/week			9502 (26.2)		196399 (28.9)	

Controls are individuals, matched for age, sex and county, who were randomly selected from the general population.
* Concentrations of glycated hemoglobin are based on values from the International Federation of Clinical Chemistry.
† Glomerular filtration rate was estimated using the Modification of Diet in Renal Disease Study Equation.

Table 2. Odds ratio for combined valvular disease in patients with diabetes, compared to controls.

	Type 1 case-control cohort	**Type 2 case-control cohort**
Characteristic	OR* (95% CI†)	OR* (95% CI†)
Diabetes	2.38 (1.53 to 3.68)	1.38 (1.29 to 1.47)
Age	1.05 (1.04 to 1.07)	1.03 (1.03 to 1.04)
Sex		
Women	0.89 (0.57 to 1.37)	0.77 (0.72 to 0.82)
Income		
Quartile 2	1.35 (0.81 to 2.28)	0.88 (0.82 to 0.95)
Quartile 3	0.73 (0.37 to 1.38)	0.64 (0.58 to 0.70)
Quartile 4	0.83 (0.40 to 1.63)	0.54 (0.49 to 0.59)
Ethnicity		
Scandinavia	2.67 (1.00 to 10.9)	1.34 (1.20 to 1.49)
Marital status		
Married	1.63 (1.03 to 2.61)	1.33 (1.26 to 1.41)
* OR = Odds Ratio, † CI = Confidence interval		

Figure Legends

Figure 1. Standardized incidence rates and adjusted hazard ratio for degenerative valvular heart disease among patients with type 1 and type 2 diabetes, as well as, matched controls from general population. Legend: Controls were matched for age, sex, and county. I bars represent 95% confidence intervals. Cox regression was used to estimate risk between patients with diabetes and controls. Models were adjusted for age, sex and socioeconomic variables. To estimate change in risk between first- and last time periods, in patients with diabetes compared with controls, we used an interaction term denoting category (patients with diabetes or control)*time-period.

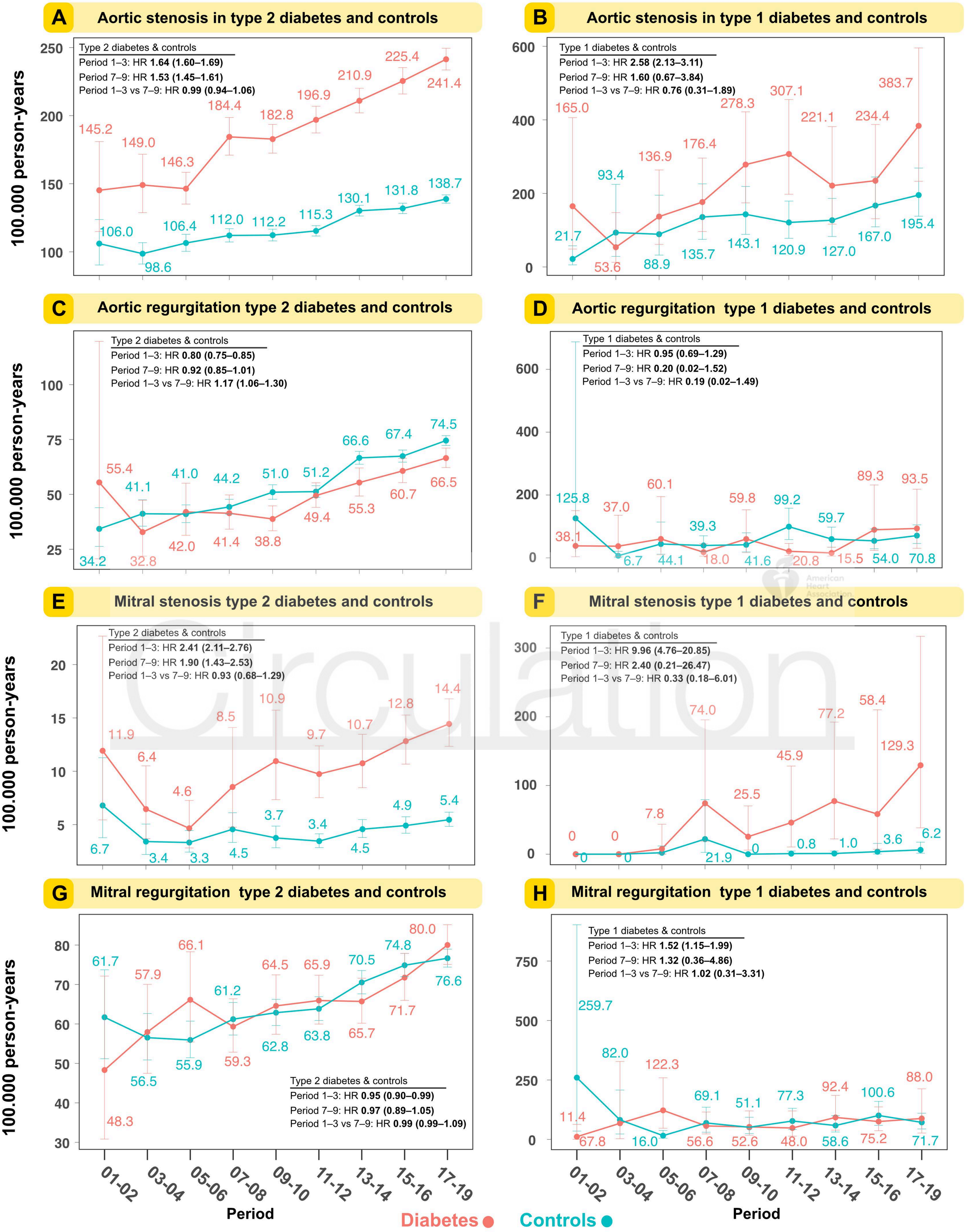
Figure 2. Association between levels of cardiometabolic risk factors for degenerative valvular heart disease in patients with type 2 diabetes. Legend: We constructed a Cox model for each outcome and applied a prediction function to assess the relationship between selected risk factors and outcomes (Panel A to Panel D). The dark lines indicate the hazard function and the shaded areas 95% confidence intervals. Continuous variables were modeled with restricted cubic splines. The following cut-of levels were used for risk factors: glycated hemoglobin (≥ 7.0% [≥ 53 mmol/mol]), SBP (≥ 130 mmHg), LDL–C (≥ 2.5 mmol/L [97 mg per deciliter]), BMI ≥ 25 kg/m2 and eGFR ≥ 90 mL/min/1.73m2. 25th – 75th denotes the 25 percentile to 75 percentile range.

Figure 3. Association between levels of cardiometabolic risk factors for degenerative valvular heart disease in patients with type 1 diabetes. Legend: We constructed a Cox model for each outcome and applied a prediction function to assess the relationship between selected risk factors and outcomes (Panel A to Panel D). The dark lines indicate the hazard

function and the shaded areas 95% confidence intervals. Continuous variables were modeled with restricted cubic splines. The following cut-of levels were used for risk factors: glycated hemoglobin (≥ 7.0% [≥ 53 mmol/mol]), SBP (≥ 130 mmHg), LDL–C (≥ 2.5 mmol/L [97 mg per deciliter]), BMI ≥ 25 kg/m2 and eGFR ≥ 90 mL/min/1.73m2. 25th – 75th denotes the 25 percentile to 75 percentile range.

Figure 4: Adjusted hazard ratios for outcomes, according to number of risk factor variables outside target range among patients with type 1 and type 2 diabetes, as compared to matched controls. Legend: Hazard ratios shows the excess risk of each outcome among patients with diabetes, compared to matched controls from the general population, according to number of risk factors (scale, none to five) that were outside therapeutic ranges.

Figure 5: Excess risk for degenerative valvular heart disease among patients with type 1 and type 2 diabetes, as compared to matched controls. Legend: Excess risk for valvular lesions was assessed with Cox regression models for patients with diabetes and their matched controls.



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Legend: Controls were matched for age, sex, and county. I bars represent 95% confidence intervals. Cox regression was used to estimate risk between patients with diabetes and controls. To estimate change in risk between first- and last time periods, in patients with diabetes compared with controls, we used an interaction term denoting *category* (patients with diabetes or control)**time-period*.

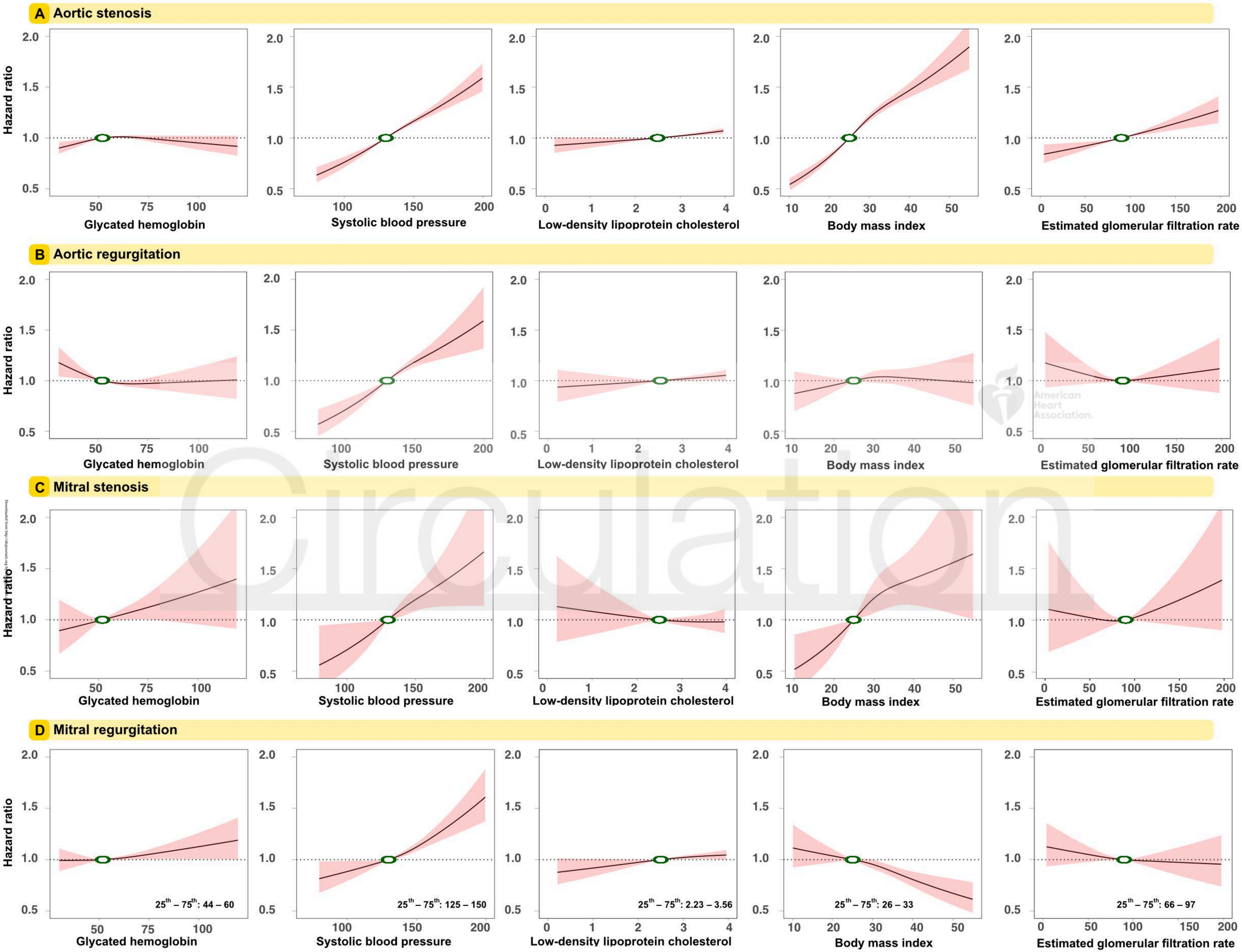


Figure 2. Association between levels of cardiometabolic risk factors for degenerative valvular heart disease in patients with type 2 diabetes. Legend: We constructed a Cox model for each outcome and applied a prediction function to assess the relationship between selected risk factors and outcomes (Panel A to Panel D). The dark lines indicate the hazard function and the shaded areas 95% confidence intervals. Continuous variables were modeled with restricted cubic splines. The following cut-of levels were used for risk factors: glycated hemoglobin (≥ 7.0% [≥ 53 mmol/mol]), SBP (≥ 130 mmHg), LDL–C (≥ 2.5 mmol/L [97 mg per deciliter]), BMI ≥ 25 kg/m2 and eGFR ≥ 90 mL/min/1.73m2. 25th – 75th denotes the 25 percentile to 75 percentile range.

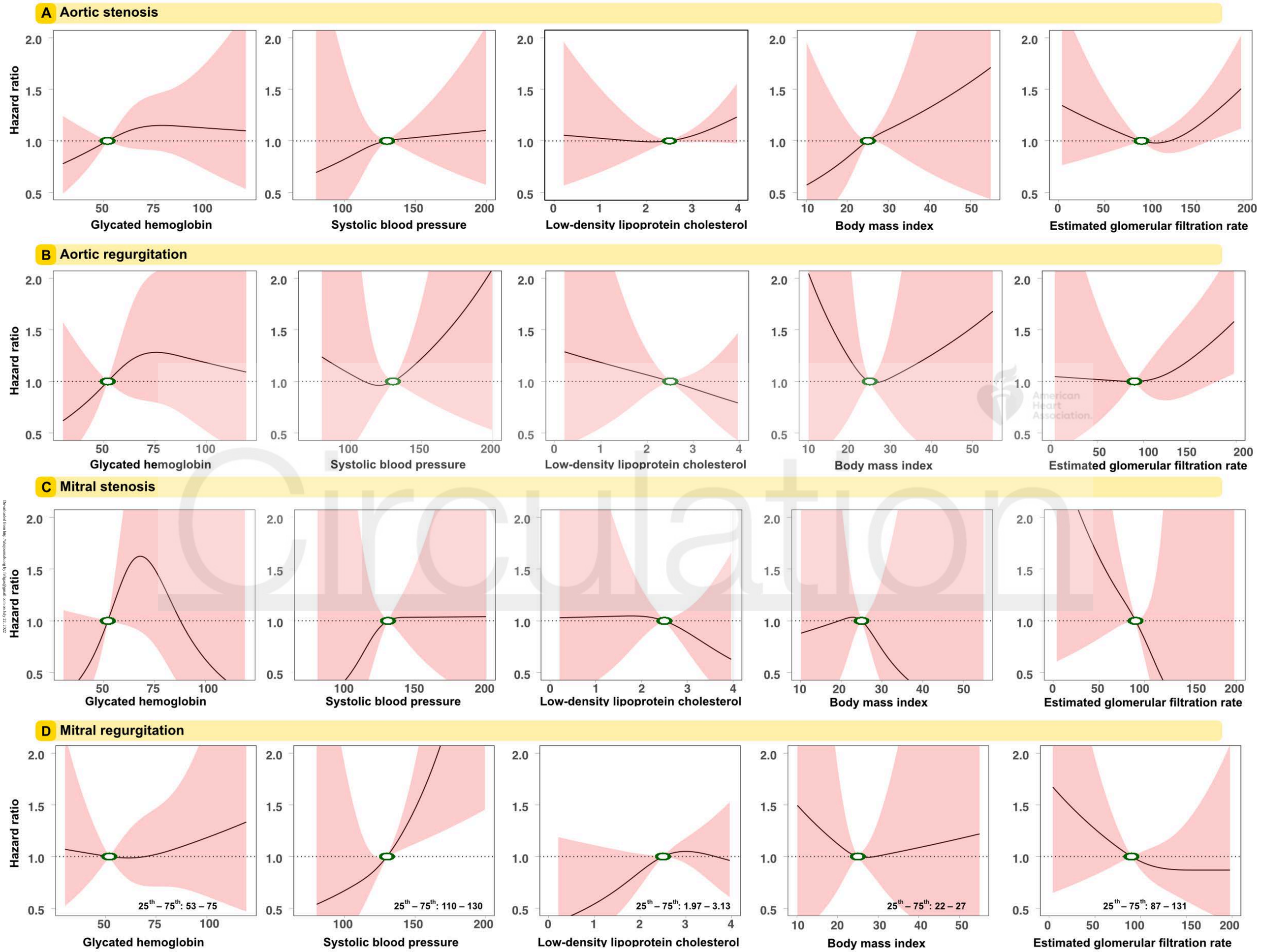
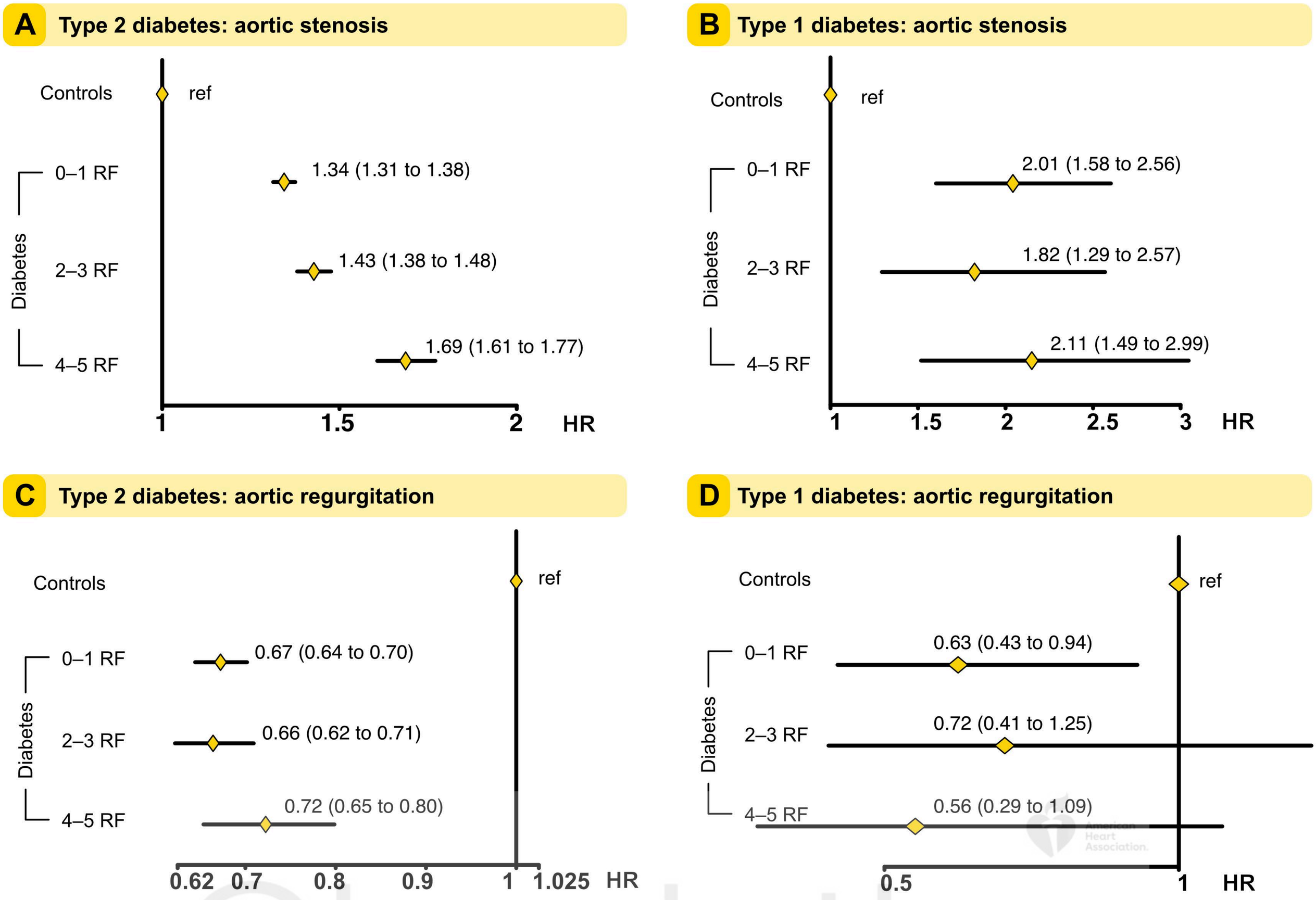


Figure 3. Association between levels of cardiometabolic risk factors for degenerative valvular heart disease in patients with type 1 diabetes. Legend: We constructed a Cox model for each outcome and applied a prediction function to assess the relationship between selected risk factors and outcomes (Panel A to Panel D). The dark lines indicate the hazard function and the shaded areas 95% confidence intervals. Continuous variables were modeled with restricted cubic splines. The following cut-of levels were used for risk factors: glycated hemoglobin (≥ 7.0% [≥ 53 mmol/mol]), SBP (≥ 130 mmHg), LDL–C (≥ 2.5 mmol/L [97 mg per deciliter]), BMI ≥ 25 kg/m2 and eGFR ≥ 90 mL/min/1.73m2. 25th – 75th denotes the 25 percentile to 75 percentile range.



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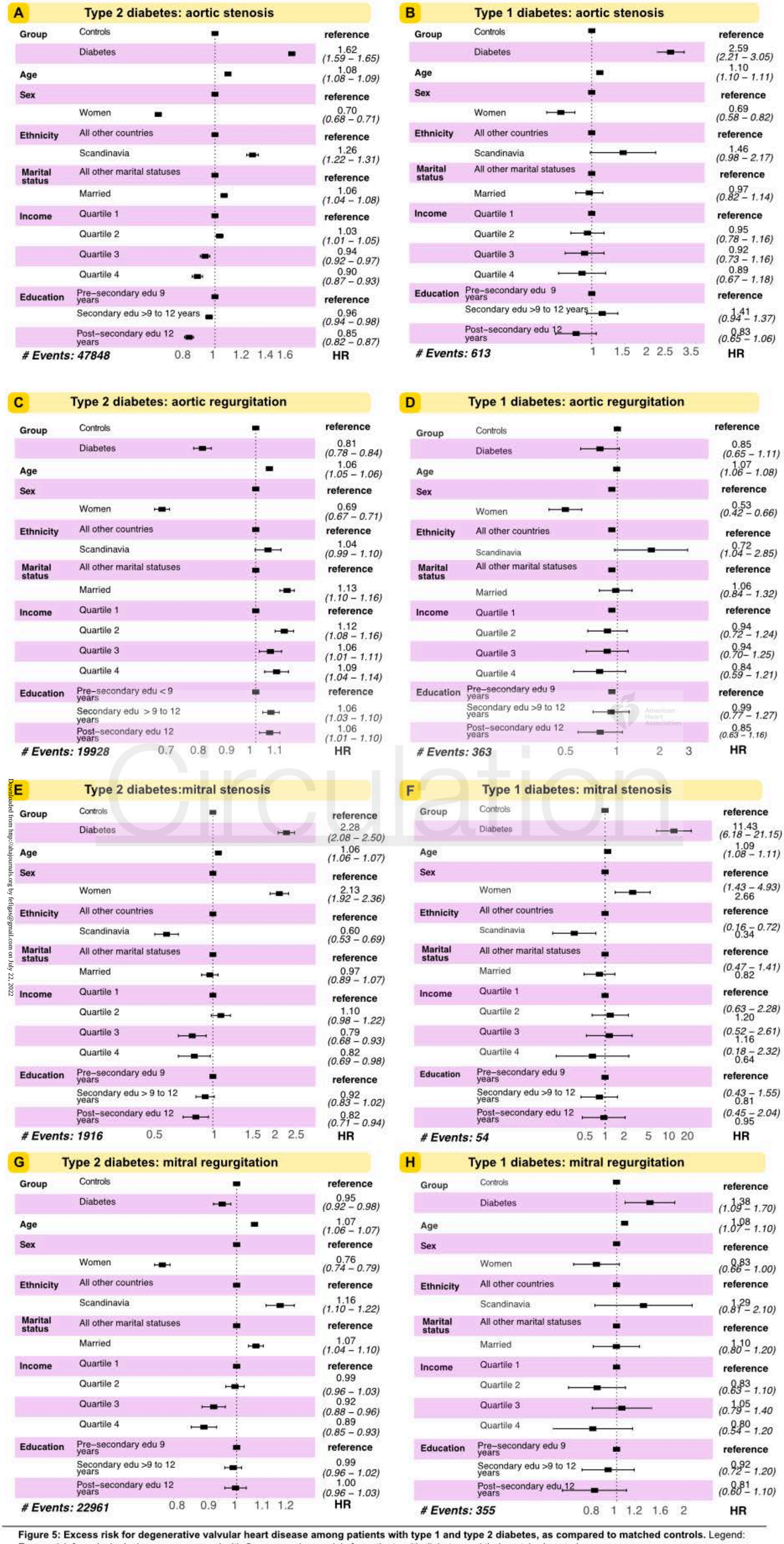

Figure 5: Excess risk for degenerative valvular heart disease among patients with type 1 and type 2 diabetes, as compared to matched controls. Legend: Excess risk for valvular lesions was assessed with Cox regression models for patients with diabetes and their matched controls.