Dietary patterns, food groups, and incidence of aortic valve stenosis: A prospective cohort study

Susanna C. Larsson [a,*,1], Alicja Wolk [a,d,1], Magnus Bäck [b,c,1]

[a] Unit of Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
[b] Heart and Vascular Theme – Division of Valvular and Coronary Disease, Karolinska University Hospital, Stockholm, Sweden
[c] Center for Molecular Medicine, Department of Medicine, Karolinska Institutet, Stockholm, Sweden
[d] Department of Surgical Sciences, Uppsala University, Uppsala, Sweden

ABSTRACT

Background: The role of diet in the development of aortic valve stenosis (AVS) is unknown. We therefore examined the associations of two dietary patterns, including a modified Dietary Approaches to Stop Hypertension (mDASH) diet and a modified Mediterranean (mMED) diet, and the food items included in these dietary patterns with incidence of aortic valve stenosis (AVS) in a population-based cohort study.
Methods: The study cohort comprised 74,401 Swedish adults (54% men) who were free of cardiovascular disease at the time of completion of a baseline questionnaire about habitual diet and other risk factors for chronic diseases. Participants were followed-up through linkage with nationwide registers on hospitalization and causes of death.
Results: During 1,132,617 person-years (mean 15.2 years) of follow-up, 1338 incident AVS cases (801 in men and 537 in women) were ascertained. We found no significant associations of the mDASH and mMED dietary patterns or the food groups and beverages included in these diets (i.e., fruit, vegetables, legumes and nuts, whole grains, fish, low-fat dairy foods, full-fat dairy foods, red and processed meat, and sweetened beverages) with risk of AVS. The hazard ratios (95% confidence interval) of AVS per one standard deviation increase in the mDASH and mMED diet scores were respectively 1.02 (0.96–1.07) and 1.00 (0.95–1.06).
Conclusion: This study found no evidence that diet plays a role in the development of AVS.

© 2018 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Aortic valve stenosis (AVS) is a common disease, with a prevalence reaching nearly 10% in populations over age 80 years [1]. The established risk factors for AVS are few, but mounting evidence indicates that cardiometabolic risk factors, such as obesity [2–4], diabetes [2,3,5,6], hypertension [2,3,5,7], and dyslipidemia [5,8–12], increase the risk of AVS. Diet influences cardiometabolic risk factors [13–15] and thus may be implicated in the development of AVS. A healthy diet rich in fruit, vegetables, legumes, low-fat dairy foods, and fish and reduced in red meat, processed meat, and foods rich in added sugars has been shown to be associated with reduced risk of major cardiovascular diseases, including coronary heart disease, heart failure, and stroke

[14,16–19]. However, whether a healthy diet influences the risk of AVS is unknown.

The aim of this study was to investigate the associations of two healthy dietary patterns, including the Dietary Approaches to Stop Hypertension diet and the Mediterranean diet, with incidence of AVS in a population-based cohort of Swedish adults. Furthermore, we examined whether individual food groups and beverages included in these two dietary patterns were associated with risk of AVS.

2. Methods

2.1. Study population

Data for this study was available from the Swedish Infrastructure for Medical Population-based Life-course Environmental Research (SIMPLER) database. SIMPLER consists of data from the Cohort of Swedish Men, a cohort of 48,850 Swedish men aged 45–79 at enrolment in the late autumn of 1997, and from the Swedish Mammography Cohort, a cohort of 39,227 Swedish women aged 49–83 years in 1997. For this study, we excluded participants with an erroneous or a missing personal identification number ($n = 540$); those who died ($n = 81$) or had diagnosis of cancer ($n = 4403$) or cardiovascular disease (AVS, ischemic heart disease, heart failure, or ischemic stroke; $n = 7796$) prior to 1 January 1998; and those with implausibly high or low total energy intake, probably

* Corresponding author at: Unit of Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, 17177 Stockholm, Sweden.
E-mail address: susanna.larsson@ki.se (S.C. Larsson).
[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

reflecting careless completion of the food-frequency questionnaire ($n = 856$). This left 74,401 individuals (39,926 men and 34,475 women) for the present analysis. The Regional Ethical Review Board at Karolinska Institutet in Stockholm, Sweden, approved the study.

2.2. Assessment of diet and other exposures

At baseline in 1997, participants provided information on educational attainment, habitual diet, alcohol consumption, smoking status and history, weight, height and history of diabetes, hypertension, and hypercholesterolemia. Diet was assessed using a validated food frequency questionnaire [20]. Participants were asked to indicate their average consumption of 96 food items over the past year. For most items, eight predefined frequency categories ranging from never to ≥3 times/week were provided. For commonly consumed foods (e.g., milk, bread, and sweetened beverages), participants were asked to indicate their exact consumption per day or per week. We constructed two healthy dietary patterns based on modified versions of the Dietary Approaches to Stop Hypertension (mDASH) and Mediterranean (mMED) diets, as described in detail previously [18,21]. The dietary patterns were slightly modified to better match the Swedish diet. In the present study, the mDASH diet included fruits, vegetables, legumes and nuts, whole grains, and low-fat dairy foods, which were considered healthy foods, as well as red meat and processed meat and sweetened beverages, which were considered less healthy foods. Like the mDASH diet, the mMED diet consisted of fruits, vegetables, legumes and nuts, and whole grains. It further included fish, olive oil use and low to moderate alcohol consumption as beneficial components, and full-fat dairy foods and red meat and processed meat as less healthy foods. We grouped participants into sex-specific quintiles according to their consumption of each food group. For the healthy food groups, participants were assigned a score from 1 to 5 from being in the lowest to the highest quintile. Scores were reversed for the less healthy foods. The scores were summed to create mDASH and mMED diet scores, with higher scores indicating higher adherence to these healthy dietary patterns.

2.3. Ascertainment of AVS cases and follow-up

The personal identification number assigned to each Swedish resident was used for linkage of participants to the Swedish National Patient Register and Swedish Cause of Death Register. Incident cases of AVS were identified using the International Classification of Diseases 10th revision codes I35.0 and I35.2. Participants were followed up from January 1, 1998 until the date of diagnosis of AVS, date of death, or December 31, 2014, whichever was earlier.

2.4. Statistical analysis

Analyses were conducted using Cox proportional hazards regression models, with age as the time scale and stratified by sex. All multivariable models included adjustment for education (less than high school, high school, or university), total energy intake (continuous), alcohol consumption (never drinker, former drinker, or current drinker of <1, 1–6, 7–14, 14–21, and >21 drinks/week) (only in analyses of the mDASH diet and food groups since the mMED diet included alcohol intake), and smoking (never, former <20 pack-years, former ≥20 pack-years, current <20 pack-years, or current ≥20 pack-years). In a second (main) multivariable model, we further adjusted for potential intermediates, including body mass index (weight divided by the square of height; <22.5, 22.5–24.9, 25.0–29.9, or ≥30 kg/m²) and a history of diabetes, hypertension, and hypercholesterolemia. Adjustment for physical activity (exercise and walking/bicycling) did not alter the results. Physical activity was therefore not included in the final multivariable models.

The main results are presented per one standard deviation increment of the mDASH and mMED dietary patterns and food groups. In secondary analyses, we categorized participants into quintiles according to the mDASH and mMED diet scores. In a sensitivity analysis, we excluded participants with a history of diabetes, hypertension, or hypercholesterolemia at baseline who may have changed their dietary behaviors. To correct for multiple testing, we imposed a Bonferroni-corrected significance threshold of 0.005 (i.e., 0.05/11 dietary factors examined). All analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC).

3. Results

Participants with high adherence to the mDASH and mMED dietary patterns were slightly leaner, were more likely to have a postsecondary

Table 1
Baseline characteristics by quintiles of the mDASH and mMED dietary patterns.

Characteristic[a]	mDASH dietary pattern					mMED dietary pattern				
	Q1 ($n = 16,809$)	Q2 ($n = 15,029$)	Q3 ($n = 12,794$)	Q2 ($n = 16,628$)	Q5 ($n = 13,141$)	Q1 ($n = 15,444$)	Q2 ($n = 16,617$)	Q3 ($n = 14,450$)	Q2 ($n = 14,164$)	Q5 ($n = 13,726$)
Age, years	60.5 ± 9.6	59.9 ± 9.4	60.2 ± 9.4	60.1 ± 9.2	60.3 ± 9.1	60.5 ± 9.8	60.5 ± 9.5	60.4 ± 9.3	59.9 ± 9.2	59.6 ± 8.9
Body mass index, kg/m²	25.5 ± 3.9	25.5 ± 3.7	25.4 ± 3.6	25.3 ± 3.5	25.1 ± 3.4	25.5 ± 3.9	25.5 ± 3.7	25.4 ± 3.7	25.3 ± 3.5	25.2 ± 3.5
Postsecondary education, %	12.2	15.1	18.1	21.3	26.7	11.0	14.6	18.1	21.8	27.9
Current smoker %	31.1	26.7	23.8	20.8	17.8	32.7	26.1	23.0	20.7	18.1
History of diabetes, %	4.1	4.4	5.0	5.8	6.6	4.4	4.9	5.9	5.4	6.0
History of hypertension, %	21.2	21.2	21.2	21.1	20.6	20.3	21.3	21.0	21.3	21.6
History of hypercholesterolemia, %	9.4	10.3	10.8	11.3	11.5	9.1	10.3	10.0	11.4	12.5
Food groups and beverages										
Fruit, servings/day[b,c]	1.0 ± 0.8	1.3 ± 1.0	1.7 ± 1.1	2.1 ± 1.3	2.8 ± 1.5	0.9 ± 0.7	1.3 ± 1.0	1.8 ± 1.2	2.1 ± 1.3	2.7 ± 1.5
Vegetables, servings/day[b,c]	1.7 ± 1.2	2.2 ± 1.4	2.8 ± 1.7	3.4 ± 1.8	4.4 ± 2.3	1.5 ± 1.0	2.2 ± 1.3	2.9 ± 1.7	3.5 ± 1.9	4.4 ± 2.2
Legumes and nuts, servings/day[b,c]	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.2	0.2 ± 0.2	0.2 ± 0.3	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.2	0.2 ± 0.2	0.2 ± 0.3
Whole grains, servings/day[b,c]	2.3 ± 1.7	3.1 ± 2.0	3.6 ± 2.1	4.1 ± 2.2	5.0 ± 2.3	2.5 ± 1.9	3.3 ± 2.1	3.7 ± 2.1	4.1 ± 2.3	4.6 ± 2.3
Fish, servings/day[c]	0.2 ± 0.3	0.3 ± 0.3	0.3 ± 0.3	0.3 ± 0.3	0.3 ± 0.3	0.2 ± 0.2	0.2 ± 0.3	0.3 ± 0.3	0.3 ± 0.3	0.4 ± 0.3
Low-fat dairy, servings/day[b]	0.8 ± 1.2	1.2 ± 1.6	1.6 ± 1.7	2.1 ± 2.0	2.9 ± 2.4	1.3 ± 1.7	1.5 ± 1.8	1.7 ± 1.9	1.8 ± 2.0	2.2 ± 2.3
Full-fat dairy, servings/day[c]	3.7 ± 2.6	3.8 ± 2.6	3.7 ± 2.5	3.7 ± 2.6	3.5 ± 2.6	4.5 ± 2.8	3.8 ± 2.6	3.6 ± 2.5	3.4 ± 2.5	2.9 ± 2.3
Red and processed meat, servings/day[b,c]	1.3 ± 0.8	1.2 ± 0.8	1.2 ± 0.7	1.2 ± 0.8	1.0 ± 0.7	1.3 ± 0.8	1.2 ± 0.7	1.2 ± 0.8	1.2 ± 0.8	1.0 ± 0.8
Sweetened beverages, glasses/day[b]	1.0 ± 1.4	0.6 ± 1.1	0.5 ± 1.0	0.3 ± 0.8	0.2 ± 0.5	0.6 ± 1.2	0.6 ± 1.3	0.5 ± 1.0	0.5 ± 1.0	0.4 ± 1.0
Alcohol intake, drinks/week[c,d]	6.1 ± 12.7	6.7 ± 10.3	6.0 ± 8.1	6.2 ± 10.0	5.7 ± 7.6	6.5 ± 12.9	6.1 ± 10.4	5.6 ± 9.6	6.3 ± 8.3	6.2 ± 8.1
Olive oil use, %[c]	13.8	18.2	22.6	25.9	33.9	1.7	7.4	16.8	29.8	61.8
Macronutrients[e]										
Total fat, g/day	74.2 ± 12.5	71.2 ± 11.5	69.5 ± 10.9	67.2 ± 10.7	63.3 ± 10.6	76.4 ± 12.0	71.3 ± 10.9	69.1 ± 10.6	66.3 ± 10.4	62.2 ± 10.5
Carbohydrates, g/day	77.0 ± 33.7	79.7 ± 31.1	81.2 ± 29.1	82.7 ± 28.3	85.5 ± 27.7	234.3 ± 31.8	244.9 ± 29.4	249.2 ± 28.7	254.4 ± 28.2	262.0 ± 28.1
Protein, g/day	242.4 ± 12.8	244.8 ± 12.2	247.7 ± 12.1	251.2 ± 12.1	258.2 ± 12.5	80.7 ± 13.1	80.4 ± 12.7	81.2 ± 12.5	81.0 ± 12.3	82.0 ± 12.7

[a] Age-standardized to the age distribution of the study population at baseline. Values are means ± standard deviation if not otherwise indicated.
[b] Component of the mDASH diet.
[c] Component of the mMED diet.
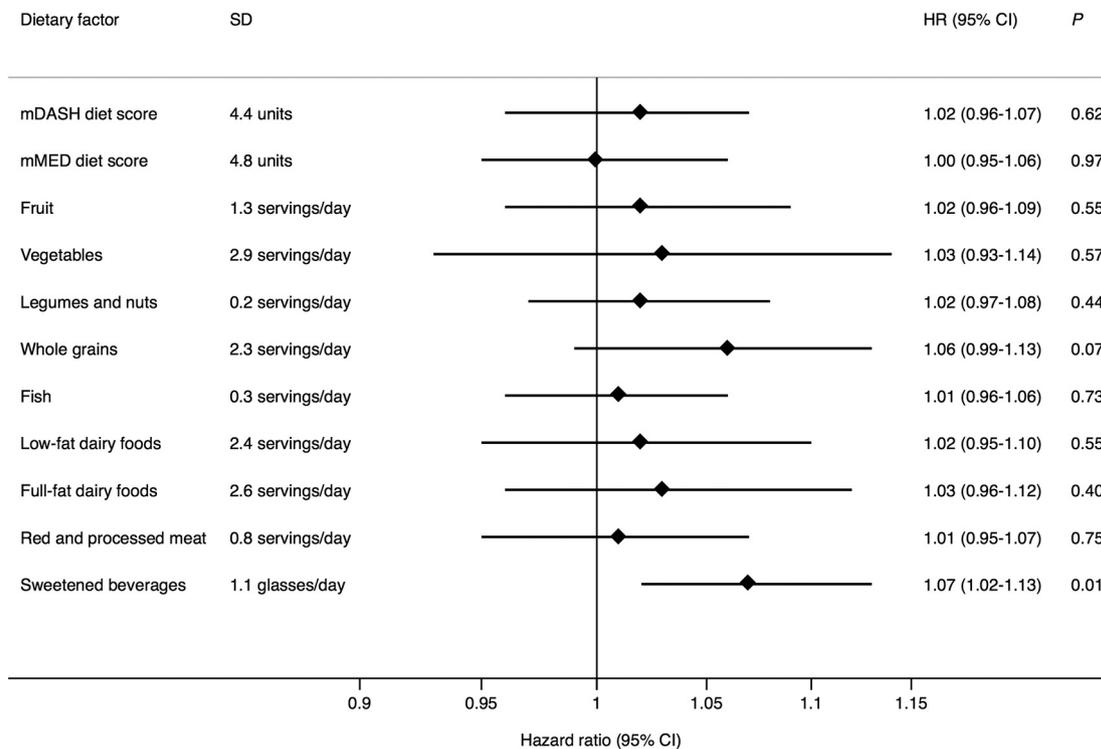[d] Among current drinkers.
[e] Adjusted for total energy intake.

Dietary factor	SD		HR (95% CI)	P
mDASH diet score	4.4 units		1.02 (0.96-1.07)	0.62
mMED diet score	4.8 units		1.00 (0.95-1.06)	0.97
Fruit	1.3 servings/day		1.02 (0.96-1.09)	0.55
Vegetables	2.9 servings/day		1.03 (0.93-1.14)	0.57
Legumes and nuts	0.2 servings/day		1.02 (0.97-1.08)	0.44
Whole grains	2.3 servings/day		1.06 (0.99-1.13)	0.07
Fish	0.3 servings/day		1.01 (0.96-1.06)	0.73
Low-fat dairy foods	2.4 servings/day		1.02 (0.95-1.10)	0.55
Full-fat dairy foods	2.6 servings/day		1.03 (0.96-1.12)	0.40
Red and processed meat	0.8 servings/day		1.01 (0.95-1.07)	0.75
Sweetened beverages	1.1 glasses/day		1.07 (1.02-1.13)	0.01

Hazard ratio (95% CI)

Fig. 1. Hazard ratios of aortic valve stenosis per one standard deviation increase in the mDASH and mMED dietary patterns and the food groups among 74,401 Swedish adults, 1998–2014. Hazard ratios were derived from Cox proportional hazards regression models with age as the time scale, stratified by sex, and adjusted for education (less than high school, high school or university), total energy intake (continuous), alcohol consumption (never drinker, former drinker, or current drinker of <1, 1–6, 7–14, 14–21, and >21 drinks/week) (only for the mDASH diet and food groups since the mMED diet included alcohol intake), smoking (never, former <20 pack-years, former ≥20 pack-years, current <20 pack-years, or current ≥20 pack-years), body mass index (<22.5, 22.5–24.9, 25.0–29.9, or ≥30 kg/m^2), and history of diabetes, hypertension, and hypercholesterolemia. The food groups were mutually adjusted through inclusion in the same model. HR, hazard ratio; CI, confidence interval; mDASH, modified Dietary Approaches to Stop Hypertension; mMED, modified Mediterranean; SD, standard deviation.

education and a history of diabetes and hypercholesterolemia, and were less likely to be current smoker compared with those with low adherence to these dietary patterns (Table 1). Participants with high adherence to the mDASH dietary pattern were somewhat less likely to have a history of hypertension, whereas those with high adherence to the mMED dietary pattern were more likely to have a history of hypertension compared with low adherence to each of these dietary patterns (Table 1). High adherence to the two healthy dietary patterns was associated with lower total fat intake and higher carbohydrate and protein intake (Table 1).

During 1,132,617 person-years (mean 15.2 years) of follow-up, 1338 incident AVS cases (801 in men and 537 in women) were ascertained. The mDASH and mMED dietary patterns were not significantly associated with incidence of AVS (Fig. 1 and Table 2). The hazard ratios (95% confidence interval) per one standard deviation increment of the mDASH and mMED dietary patterns were respectively 1.02 (0.96–1.07) and 1.00 (0.95–1.06) (Fig. 1). In a sensitivity analysis excluding participants with a history of diabetes, hypertension, or hypercholesterolemia at baseline, the corresponding hazard ratios (95% confidence interval) were 0.96 (0.89–1.03) for the mDASH diet and 0.94 (0.87–1.02) for the mMED diet.

Table 2
Hazard ratios of aortic valve stenosis by quintiles of the mDASH and mMED dietary patterns among 74,401 Swedish adults, 1998–2014.

Dietary pattern	No. of cases	Person-years	Age- and sex-adjusted HR (95% CI)	Multivariable HR (95% CI)[a]	Multivariable HR (95% CI)[a,b]
mDASH					
Q1	289	250,805	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2	293	227,612	1.10 (0.93–1.30)	1.13 (0.96–1.33)	1.13 (0.96–1.33)
Q3	217	195,446	0.95 (0.79–1.13)	0.99 (0.83–1.19)	0.98 (0.82–1.17)
Q4	308	255,898	1.03 (0.87–1.20)	1.11 (0.94–1.31)	1.10 (0.93–1.30)
Q5	231	202,856	0.96 (0.81–1.14)	1.08 (0.90–1.29)	1.06 (0.89–1.27)
mMED					
Q1	293	228,948	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2	292	250,845	0.90 (0.77–1.06)	0.93 (0.79–1.09)	0.92 (0.78–1.08)
Q3	253	221,230	0.92 (0.78–1.09)	0.97 (0.82–1.15)	0.96 (0.81–1.14)
Q4	260	217,810	0.96 (0.81–1.14)	1.03 (0.87–1.23)	1.02 (0.86–1.21)
Q5	240	213,784	0.92 (0.77–1.09)	1.02 (0.86–1.22)	1.00 (0.84–1.20)

HR, hazard ratio; CI, confidence interval; mDASH, modified Dietary Approaches to Stop Hypertension; mMED, modified Mediterranean; Q, quintile.

[a] Hazard ratios were derived from Cox proportional hazards regression models with age as the time scale, stratified by sex, and adjusted for education (less than high school, high school or university), total energy intake (continuous), alcohol consumption (never drinker, former drinker, or current drinker of <1, 1–6, 7–14, 14–21, and >21 drinks/week) (only for the mDASH diet and food groups since the mMED diet included alcohol intake), and smoking (never, former <20 pack-years, former ≥20 pack-years, current <20 pack-years, or current ≥20 pack-years).

[b] Further adjusted for body mass index (<22.5, 22.5–24.9, 25.0–29.9, or ≥30 kg/m^2) and history of diabetes, hypertension, and hypercholesterolemia.

Among the food groups included in the mDASH and mMED dietary patterns, sweetened beverage consumption was weakly positively associated with AVS risk ($P = 0.01$) (Fig. 1) but the P value did not achieve the Bonferroni-corrected statistical significance threshold ($P < 0.005$) imposed to adjust for multiple testing. Furthermore, in a post-hoc analysis in which participants were grouped into quintiles of sweetened beverage consumption, no significant association was observed in any quintile (hazard ratio for the highest versus lowest quintile, 1.13; 95% confidence interval 0.95–1.33). The other food groups (Fig. 1) and olive oil use (hazard ratio 0.97; 95% confidence interval 0.84–1.12) were not associated with AVS risk.

4. Discussion

Findings from this large cohort of Swedish adults provide no evidence that diet plays a role in the development of AVS. Specifically, we observed no associations of overall healthy dietary patterns or major foods groups and sweetened beverages with risk of AVS.

In previous studies based on data from this cohort, we have observed inverse associations of the mDASH and mMED dietary patterns with risk of myocardial infarction, heart failure, and stroke [18,19] as well as with all-cause mortality [22,23]. Furthermore, we have observed that fruit, vegetables, low-fat dairy foods, and fish consumption is inversely associated with risk of myocardial infarction, heart failure, stroke, and all-cause mortality whereas high intakes of red meat, processed meat and sweetened beverages are associated with increased risk of these diseases and mortality [24–34]. Components in these foods could possibly influence the risk of AVS by decreasing oxidation and atherogenicity of low-density lipoprotein cholesterol (antioxidant nutrients and phytochemicals in fruit, vegetables, whole grains, legumes, nuts, and olive oil) [35–37]; by reducing blood pressure (antioxidants and minerals in fruit, vegetables, nuts, olive oil, and low-fat dairy foods) [13,38,39] or inflammation (long-chain omega-3 polyunsaturated fatty acids in fish) [40]; by increasing blood pressure (sodium in for example processed meat) [41]; or by inducing postprandial hyperglycemia, hyperinsulinemia, and obesity (sucrose in sugar-sweetened beverages) [14]. Experimental studies in mice have shown that high-fat diets induce aortic valve disease [42,43]. The mDASH and mMED diets were inversely associated with dietary fat intake in this study but none of the dietary patterns or any of the examined food groups were associated with incidence of AVS. In previous studies assessing the risk factors for AVS in this study population we observed no association with nut consumption specifically [44], but found an inverse association with light alcohol consumption [45]. To the best of our knowledge, no other epidemiologic study has assessed the association of any dietary pattern or specific foods or food groups with risk of AVS.

Important strengths of this study include the large number of incident AVS cases and the objective ascertainment of cases through linkage to nationwide population-based registers. A limitation is the use of a self-administered food-frequency questionnaire to assess dietary intake. In addition, only a baseline measurement of diet was used and participants may have changed their diet during follow-up. Thus, some degree of measurement error was inevitable. Nevertheless, the validity of the dietary questionnaire is reasonably good [20] and we have previously observed associations between diet and many other chronic diseases and mortality in this study population (e.g., [18,19,21–34]). This suggests that this dietary questionnaire can detect associations between diet and disease in this study population and that the lack of associations of the healthy dietary patterns and major foods groups with AVS likely represent a true lack of association. However, we cannot rule out that we may have overlooked a weak association. Another limitation is the observational design. We therefore cannot entirely rule out the possibility that the lack of association between diet and AVS is due to residual confounding. Another potential shortcoming is that despite high validity of the diagnoses in the Swedish National Patient Register [46],

AVS incidence may be slightly underestimated. The generalizability of our results to individuals not seeking specialist care is thus unknown.

In conclusion, this study found no evidence that diet plays a role in the development of AVS. Since this is, to the best of our knowledge, the first epidemiologic study evaluating the association between diet and AVS risk, further large cohort studies on dietary patterns, foods, and specific dietary factors (e.g., nutrients and other bioactive dietary compounds) in relation to incidence of AVS may be warranted.

Conflict of interest

The authors have no conflicts of interest to declare.

References

[1] G.W. Eveborn, H. Schirmer, G. Heggelund, P. Lunde, K. Rasmussen, The evolving epidemiology of valvular aortic stenosis. The Tromso study, Heart 99 (2013) 396–400.
[2] A. Martinsson, G. Ostling, M. Persson, K. Sundquist, C. Andersson, O. Melander, et al., Carotid plaque, intima-media thickness, and incident aortic stenosis: a prospective cohort study, Arterioscler. Thromb. Vasc. Biol. 34 (2014) 2343–2348.
[3] G.W. Eveborn, H. Schirmer, P. Lunde, G. Heggelund, J.B. Hansen, K. Rasmussen, Assessment of risk factors for developing incident aortic stenosis: the Tromso Study, Eur. J. Epidemiol. 29 (2014) 567–575.
[4] S.C. Larsson, A. Wolk, N. Håkansson, M. Bäck, Overall and abdominal obesity and incident aortic valve stenosis: two prospective cohort studies, Eur. Heart J. 38 (2017) 2192–2197.
[5] A.T. Yan, A. Koh, K.K. Chan, H. Guo, D.A. Alter, P.C. Austin, et al., Association between cardiovascular risk factors and aortic stenosis: the CANHEART aortic stenosis study, J. Am. Coll. Cardiol. 69 (2017) 1523–1532.
[6] S.C. Larsson, A. Wallin, N. Hakansson, O. Stackelberg, M. Back, A. Wolk, Type 1 and type 2 diabetes mellitus and incidence of seven cardiovascular diseases, Int. J. Cardiol. 262 (2018) 66–70.
[7] B.F. Stewart, D. Siscovick, B.K. Lind, J.M. Gardin, J.S. Gottdiener, V.E. Smith, et al., Clinical factors associated with calcific aortic valve disease. Cardiovascular Health Study, J. Am. Coll. Cardiol. 29 (1997) 630–634.
[8] G. Thanassoulis, C.Y. Campbell, D.S. Owens, J.G. Smith, A.V. Smith, G.M. Peloso, et al., Genetic associations with valvular calcification and aortic stenosis, N. Engl. J. Med. 368 (2013) 503–512.
[9] J.G. Smith, K. Luk, C.A. Schulz, J.C. Engert, R. Do, G. Hindy, et al., Association of low-density lipoprotein cholesterol-related genetic variants with aortic valve calcium and incident aortic stenosis, JAMA 312 (2014) 1764–1771.
[10] A. Langsted, B.G. Nordestgaard, M. Benn, A. Tybjaerg-Hansen, P.R. Kamstrup, PCSK9 R46L loss-of-function mutation reduces lipoprotein(a), LDL cholesterol, and risk of aortic valve stenosis, J. Clin. Endocrinol. Metab. 101 (2016) 3281–3287.
[11] P.R. Kamstrup, A. Tybjaerg-Hansen, B.G. Nordestgaard, Elevated lipoprotein(a) and risk of aortic valve stenosis in the general population, J. Am. Coll. Cardiol. 63 (2014) 470–477.
[12] B.J. Arsenault, S.M. Boekholdt, M.P. Dube, E. Rheaume, N.J. Wareham, K.T. Khaw, et al., Lipoprotein(a) levels, genotype, and incident aortic valve stenosis: a prospective Mendelian randomization study and replication in a case-control cohort, Circ. Cardiovasc. Genet. 7 (2014) 304–310.
[13] L.J. Appel, T.J. Moore, E. Obarzanek, W.M. Vollmer, L.P. Svetkey, F.M. Sacks, et al., A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group, N. Engl. J. Med. 336 (1997) 1117–1124.
[14] D. Mozaffarian, Dietary and policy priorities for cardiovascular disease, diabetes, and obesity: a comprehensive review, Circulation 133 (2016) 187–225.
[15] M. Domenech, P. Roman, J. Lapetra, F.J. Garcia de la Corte, A. Sala-Vila, R. de la Torre, et al., Mediterranean diet reduces 24-hour ambulatory blood pressure, blood glucose, and lipids: one-year randomized, clinical trial, Hypertension 64 (2014) 69–76.
[16] A. Bechthold, H. Boeing, C. Schwedhelm, G. Hoffmann, S. Knuppel, K. Iqbal, et al., Food groups and risk of coronary heart disease, stroke and heart failure: a systematic review and dose-response meta-analysis of prospective studies, Crit. Rev. Food Sci. Nutr. (2017) 1–20.
[17] S.C. Larsson, Dietary approaches for stroke prevention, Stroke 48 (2017) 2905–2911.
[18] S.C. Larsson, A. Wallin, A. Wolk, Dietary approaches to stop hypertension diet and incidence of stroke: results from 2 prospective cohorts, Stroke 47 (2016) 986–990.

[19] T.G. Tektonidis, A. Akesson, B. Gigante, A. Wolk, S.C. Larsson, A Mediterranean diet and risk of myocardial infarction, heart failure and stroke: a population-based cohort study, Atherosclerosis 243 (2015) 93–98.

[20] M. Messerer, S.E. Johansson, A. Wolk, The validity of questionnaire-based micronutrient intake estimates is increased by including dietary supplement use in Swedish men, J. Nutr. 134 (2004) 1800–1805.

[21] S.C. Larsson, N. Hakansson, A. Wolk, Healthy dietary patterns and incidence of biliary tract and gallbladder cancer in a prospective study of women and men, Eur. J. Cancer 70 (2017) 42–47.

[22] S.C. Larsson, J. Kaluza, A. Wolk, Combined impact of healthy lifestyle factors on lifespan: two prospective cohorts, J. Intern. Med. 282 (2017) 209–219.

[23] A. Bellavia, T.G. Tektonidis, N. Orsini, A. Wolk, S.C. Larsson, Quantifying the benefits of Mediterranean diet in terms of survival, Eur. J. Epidemiol. 31 (2016) 527–530.

[24] A. Bellavia, S.C. Larsson, A. Wolk, Fish consumption and all-cause mortality in a cohort of Swedish men and women, J. Intern. Med. 281 (2017) 86–95.

[25] S.C. Larsson, J. Virtamo, A. Wolk, Red meat consumption and risk of stroke in Swedish men, Am. J. Clin. Nutr. 94 (2011) 417–421.

[26] S.C. Larsson, J. Virtamo, A. Wolk, Red meat consumption and risk of stroke in Swedish women, Stroke 42 (2011) 324–329.

[27] S.C. Larsson, J. Virtamo, A. Wolk, Fish consumption and risk of stroke in Swedish women, Am. J. Clin. Nutr. 93 (2011) 487–493.

[28] S.C. Larsson, J. Virtamo, A. Wolk, Total and specific fruit and vegetable consumption and risk of stroke: a prospective study, Atherosclerosis 227 (2013) 147–152.

[29] J. Kaluza, A. Akesson, A. Wolk, Long-term processed and unprocessed red meat consumption and risk of heart failure: a prospective cohort study of women, Int. J. Cardiol. 193 (2015) 42–46.

[30] S. Rautiainen, E.B. Levitan, M.A. Mittleman, A. Wolk, Fruit and vegetable intake and rate of heart failure: a population-based prospective cohort of women, Eur. J. Heart Fail. 17 (2015) 20–26.

[31] O. Stackelberg, M. Bjorck, S.C. Larsson, N. Orsini, A. Wolk, Fruit and vegetable consumption with risk of abdominal aortic aneurysm, Circulation 128 (2013) 795–802.

[32] S.C. Larsson, J. Virtamo, A. Wolk, Dairy consumption and risk of stroke in Swedish women and men, Stroke 43 (2012) 1775–1780.

[33] S.C. Larsson, A. Akesson, A. Wolk, Sweetened beverage consumption is associated with increased risk of stroke in women and men, J. Nutr. 144 (2014) 856–860.

[34] I. Rahman, A. Wolk, S.C. Larsson, The relationship between sweetened beverage consumption and risk of heart failure in men, Heart 101 (2015) 1961–1965.

[35] Y.J. Kim, Y.H. Ahn, Y. Lim, J.Y. Kim, J. Kim, O. Kwon, Daily nutritional dose supplementation with antioxidant nutrients and phytochemicals improves DNA and LDL stability: a double-blind, randomized, and placebo-controlled trial, Nutrients 5 (2013) 5218–5232.

[36] A. Hernaez, O. Castaner, A. Goday, E. Ros, X. Pinto, R. Estruch, et al., The Mediterranean Diet decreases LDL atherogenicity in high cardiovascular risk individuals: a randomized controlled trial, Mol. Nutr. Food Res. 61 (2017).

[37] A. Sureda, M.D. Bibiloni, M. Martorell, P. Buil-Cosiales, A. Marti, A. Pons, et al., Mediterranean diets supplemented with virgin olive oil and nuts enhance plasmatic antioxidant capabilities and decrease xanthine oxidase activity in people with metabolic syndrome: the PREDIMED study, Mol. Nutr. Food Res. 60 (2016) 2654–2664.

[38] C.E. Storniolo, R. Casillas, M. Bullo, O. Castaner, E. Ros, G.T. Saez, et al., A Mediterranean diet supplemented with extra virgin olive oil or nuts improves endothelial markers involved in blood pressure control in hypertensive women, Eur. J. Nutr. 56 (2017) 89–97.

[39] R. Casas, E. Sacanella, M. Urpi-Sarda, G. Chiva-Blanch, E. Ros, M.A. Martinez-Gonzalez, et al., The effects of the Mediterranean diet on biomarkers of vascular wall inflammation and plaque vulnerability in subjects with high risk for cardiovascular disease. A randomized trial, PLoS One 9 (2014), e100084.

[40] K. He, K. Liu, M.L. Daviglus, N.S. Jenny, E. Mayer-Davis, R. Jiang, et al., Associations of dietary long-chain n−3 polyunsaturated fatty acids and fish with biomarkers of inflammation and endothelial activation (from the Multi-Ethnic Study of Atherosclerosis [MESA]), Am. J. Cardiol. 103 (2009) 1238–1243.

[41] F.M. Sacks, L.P. Svetkey, W.M. Vollmer, L.J. Appel, G.A. Bray, D. Harsha, et al., Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group, N. Engl. J. Med. 344 (2001) 3–10.

[42] B. Hofmann, Y. Yakobus, M. Indrasari, N. Nass, A.N. Santos, F.B. Kraus, et al., RAGE influences the development of aortic valve stenosis in mice on a high fat diet, Exp. Gerontol. 59 (2014) 13–20.

[43] M.C. Drolet, E. Roussel, Y. Deshaies, J. Couet, M. Arsenault, A high fat/high carbohydrate diet induces aortic valve disease in C57BL/6J mice, J. Am. Coll. Cardiol. 47 (2006) 850–855.

[44] S.C. Larsson, N. Drca, M. Bjorck, A. Back, A. Wolk, Nut consumption and incidence of seven cardiovascular diseases, Heart 104 (2018) 1615–1620.

[45] S.C. Larsson, A. Wolk, M. Back, Alcohol consumption, cigarette smoking and incidence of aortic valve stenosis, J. Intern. Med. 282 (2017) 332–339.

[46] J.F. Ludvigsson, E. Andersson, A. Ekbom, M. Feychting, J.L. Kim, C. Reuterwall, et al., External review and validation of the Swedish national inpatient register, BMC Public Health 11 (2011) 450.