Title

Association Between Omega-3 Fatty Acid Levels and Aortic Valve Calcium (from the Multi-Ethnic Study of Atherosclerosis)

Authors

Pisaniello, Anthony D

Alfaddagh, Abdulhamied

Tibuakuu, Martin

et al.

Publication Date

2022-12-01

DOI

10.1016/j.amjcard.2022.08.026

Peer reviewed

HHS Public Access

Author manuscript

Am J Cardiol. Author manuscript; available in PMC 2024 December 22.

Published in final edited form as:

Am J Cardiol. 2022 December 01; 184: 104–110. doi:10.1016/j.amjcard.2022.08.026.

Association Between Omega-3 Fatty Acid Levels and Aortic Valve Calcium (from the Multi-Ethnic Study of Atherosclerosis)

Anthony D. Pisaniello, MBBS, PhD[a,b], **Abdulhamied Alfaddagh, MD, MHS**[a], **Martin Tibuakuu, MD, MPH**[a], **Seamus P. Whelton, MD, MPH**[a], **Matthew J. Czarny, MD**[a], **Michael J. Blaha, MD, MPH**[a], **Michael Y. Tsai, PhD**[c], **Matthew J. Budoff, MD**[d], **Steven Shea, MD, MS**[e,f], **Matthew A. Allison, MD, MPH**[g], **Wendy S. Post, MD, MS**[a,*]

[a]Division of Cardiology, Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland

[b]Discipline of Medicine, The University of Adelaide, Adelaide, Australia

[c]Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, Minnesota

[d]Division of Medicine, Lundquist Institute at Harbor-UCLA, Torrance, California

[e]Department of Medicine and, The University of California, San Diego, California

[f]Department ofEpidemiology, Columbia University, New York, New York

[g]Department of Family Medicine and Public Health, The University of California, San Diego, California.

Abstract

Calcific aortic valve disease, a condition of chronic inflammation, is associated with increased cardiovascular events and all-cause mortality. Omega-3 fatty acids (O3FAs) reduce both acute and chronic inflammation, but their associations with aortic valve calcium (AVC) have not been studied. The Multi-Ethnic Study of Atherosclerosis is a prospective cohort study of 6,814 adults without clinical cardiovascular disease. Plasma fatty acid levels and cardiac computed tomography (CT) scans were performed at baseline, and CT scans were performed at subsequent clinical visits over a median 9-year period. We assessed whether plasma levels of O3FAs and their species correlate with the presence, severity, and progression of AVC measured by CT in Multi-Ethnic Study of Atherosclerosis. The mean age of the 6,510 included participants with baseline fatty acid levels, AVC, and covariate data was 62.1 ± 10.2 years, and 47.1% of the participants were male. Race distribution was 38.6% White, 27.2% Black, 22.1% Hispanic/Latino, and 12.1% Chinese. Among the 6,510 participants, 5,884 had a subsequent CT scan, and 3,304 had a third CT scan with AVC measurements. At baseline, 862 participants (13.2%) had prevalent AVC (Agatston score >0), and were more likely to be of older age, male, of the White race, have a lower education level, and have co-morbidities that are associated with a higher risk for AVC. Plasma

*Corresponding author: fax: +1 410-614-9190. wpost@jhmi.edu (W.S. Post).

Disclosures

The authors have no conflicts of interest to declare.

tertiles of eicosapentaenoic acid, docosahexaenoic acid, and total O3FA were not associated with prevalent AVC at baseline, incident AVC, or change in AVC. In conclusion, plasma levels of O3FAs in subjects not routinely supplemented with O3FAs are not useful for predicting the presence or development of AVC. Whether high plasma O3FA levels, achievable by high-dose O3FA over-the-counter supplementation or pharmacotherapy, is associated with AVC requires further investigation.

Calcific aortic valve stenosis (AS), the most prevalent valvular heart disease in the developed world,[1] is characterized by fibrosis and calcification of the valve apparatus, resulting in impaired leaflet mobility, and when severe, reduced forward flow. The development of aortic valve calcium (AVC) is progressive and independently associated with increased cardiovascular events and all-cause mortality, even without valvular stenosis.[2] Untreated severe symptomatic calcific AS has a mean survival of only 2 years.[3] The original mechanistic hypothesis of a cumulative “wear and tear” effect causing aortic valve calcification and ultimately stenosis, has been refined to one of chronic inflammation.[4] Despite the availability of numerous therapies that target inflammation, none have been shown to retard the progression of calcific AS.[5] However, omega-3 fatty acids (O3FAs) have been shown to reduce both acute and chronic inflammation through multiple mechanisms,[6,7] and there is evidence that eicosapentaenoic acid (EPA) may reduce arterial calcification.[8] Furthermore, in population studies, blood O3FA levels are inversely associated with both coronary artery[9] and abdominal aortic calcification.[10] Notably, the association between blood omega-3 levels, including the relative effects of EPA compared with docosahexaenoic acid (DHA) on aortic valve calcification, has not previously been studied. In a previous study, using data from the Multi-Ethnic Study of Atherosclerosis (MESA), no significant association was found between plasma levels of the omega-9 fatty acid oleic acid, and aortic valve calcification.[11] Therefore, this study aimed to determine whether plasma O3FA levels correlate with the presence, severity, and progression of AVC in the MESA. Furthermore, we sought to determine whether these associations differ between EPA and DHA. Our hypothesis was that higher plasma O3FA levels associate with less aortic valve calcification in a dose-dependent manner, with EPA levels having a stronger association than DHA levels.

Methods

The MESA was a prospective cohort study of 6,814 adults between 45 and 84 years of age recruited from 6 sites in the United States. A full description of the study design and recruitment process has been reported previously.[12] Recruitment targeted 4 racial/ethnic groups (White, Black, Hispanic/Latino, and Chinese). Participants had no history of clinical cardiovascular disease at baseline. Each participating MESA site obtained Institutional Review Board approval, and each participant provided written, informed consent before enrollment. We included MESA participants with baseline O3FA measurements and AVC measured in Agatston Units using computed tomography (CT).

At baseline, participant demographic, anthropometric measurements, and fasting blood samples were obtained. O3FAs were extracted from frozen plasma samples using a chloroform/methanol extraction method and thin layer chromatography. Fatty acids were

then transformed into methyl esters and quantified using gas chromatography.[13] Each fatty acid was quantified as a percentage of total fatty acids. Total O3FA content was calculated as the sum of EPA, DHA, and docosapentaenoic acid for each participant.

Full details on the CT scan methods used to measure AVC have previously been published.[14,15] In summary, a CT scan of the chest was performed with either an electrocardiographic-triggered electron-beam (at 80% of the RR interval) CT scanner, or a prospectively electrocardiographic-triggered (at 50% of the RR interval) multidetector CT scanner that acquired 4 simultaneous 2.5-mm slices for each cardiac cycle in a sequential or axial scan mode. Certified technologists scanned all participants twice over phantoms of known physical calcium concentration. AVC was phantom-adjusted and quantified in Hounsfield Units using the Agatston scoring method.[16] Each scan was independently interpreted.

All MESA participants underwent a cardiac CT at examination 1 from 2000 to 2002. A random half of returning participants underwent repeat cardiac CT from 2002 to 2004 (examination 2) and the second half did so from 2004 to 2005 (examination 3; combined n = 6,058 in examinations 2 and 3).[17] From 2010 to 2012, a total of 3,410 participants completed an additional CT scan at examination 5. These scans were read for AVC (n = 6,812 at baseline, n = 5,884 at examinations 2/3, n = 3,304 at examination 5)[18] at the core laboratory at the Los Angeles Biomedical Research Institute at Harbor-UCLA (University of California Los Angeles) Medical Center by experienced readers who were blinded to clinical information. Prevalent baseline AVC was defined as AVC > 0 at examination 1. Incident AVC was defined as the development of AVC > 0 in those with AVC = 0 at baseline. The change in AVC was defined as the difference between the most recent AVC measurement and the baseline AVC.

When comparing the incidence and progression of AVC stratified by tertiles of O3FA levels, the differences between groups at baseline and known risk factors for AVC formed the basis for the adjustments in the statistical analysis. Other factors that may introduce variability and bias, that is, the site of enrollment and CT scanner type, were corrected for, although the equivalence of AVC quantification across CT scanner types has previously been demonstrated.[19] Moreover, the interobserver, interscan, and intraobserver variability of AVC in the MESA is low.[14]

Participants were grouped and compared according to tertiles of EPA, DHA, and total O3FAs. Values of EPA, DHA, and total O3FAs were also examined as continuous variables after log transformation. Data that were normally distributed were expressed as mean (SD), or otherwise median (interquartile range). Proportions were compared using the chi-square test, and continuous variables were compared using the Student's t test (if normally distributed) or Mann-Whitney U test (if not normally distributed). The associations between plasma O3FA levels and AVC measures were estimated by Poisson regression, and those between plasma O3FA levels and the progression of AVC per year were estimated using linear regression, both with adjustment using serial models. Both unadjusted and multivariable-adjusted estimates were presented. Model 1 adjusted for age, race/ethnicity, gender, MESA field center, education levels, CT scan model, and time between scans.

Model 2 adjusted for the variables included in model 1 plus moderate and vigorous physical activity level (log-transformed metabolic equivalent of task-min/week), body mass index, smoking status, systolic blood pressure, diabetes mellitus status (diabetes mellitus was defined based on a single fasting blood glucose measurement ≥126 mg/100 ml (7.0 mmol/L)[20] or the use of diabetes medications), total cholesterol level, high-density lipoprotein cholesterol level, use of antihypertensive medications, use of lipid-lowering medications, and estimated glomerular filtration rate. We also included an exploratory model (model 3) which adjusted for factors included in model 2 plus lipoprotein(a) level and high-sensitivity C-reactive protein level. A 2-sided $p < 0.05$ was considered statistically significant. All analyses were performed using Stata version 16 (StataCorp LLC, College Station, Texas).

Results

A total of 6,510 participants with baseline AVC, plasma O3FA levels, and complete covariate data for models 1 and 2 were included in the analysis. A flowchart of participants is shown in Figure 1. The mean ± SD age was 62.1 ± 10.2 years, 47.1% of the participants were male, 38.6% were White, 27.2% were Black, 22.1% were Hispanic/Latino, and 12.1% were Chinese.

Table 1 shows the baseline characteristics of the study population stratified by baseline AVC. At baseline, 862 participants (13.2%) had AVC > 0. Those with AVC > 0 were more likely to be older, male, non-Hispanic White, have a lower level of education, a history of diabetes and smoking, have higher systolic blood pressures, lower levels of moderate and vigorous physical activity, lower levels of high-density lipoprotein cholesterol level, higher levels of triglycerides and lipoprotein(a), and lower estimated glomerular filtration rates. They were also more likely to be taking lipid-lowering and antihypertensive medications. Baseline O3FA levels were similar in those with and without AVC.

Higher tertiles of EPA, DHA, and total O3FAs were not associated with the presence of AVC at baseline. These findings were consistent after adjustment for covariates specified in models 1 and 2 (Table 2). Similar findings were observed when examining log-transformed O3FA variables, and when further adjusting for lipoprotein(a) and high-sensitivity C-reactive protein levels (model 3).

The median time between baseline and follow-up CT scans was 9.0 (interquartile range 2.2 to 9.6) years. Among the 4,982 participants with no AVC at baseline, and a follow-up AVC measurement, 377 (7.6%) developed AVC. They were more likely to be older, male, have a history of diabetes or smoking, have a higher body mass index, have a lower estimated glomerular filtration rate, and be taking antihypertensive and lipid-lowering agents (Table 3). They also had higher triglyceride and lipoprotein(a) levels. Baseline plasma EPA levels were higher in those who developed AVC.

Higher tertiles of EPA, DHA, and total O3FA levels were not associated with incident AVC. These findings were consistent after adjustment for covariates specified in models 1 and 2 (Table 4). Similarly, there were no significant associations between tertiles of EPA, DHA, and total O3FA levels at baseline and the change in AVC in those with AVC =

0 at baseline. These findings were consistent after adjustment for covariates specified in models 1 and 2 (Table 5). These findings were consistent when log-transformed O3FA levels were examined, and when further adjusted for lipoprotein(a) and high-sensitivity C-reactive protein levels (model 3).

Discussion

This study sought to establish whether plasma O3FA levels, and in particular, EPA compared with DHA levels, predict the prevalence and progression of AVC. The development of AVC has multiple established risk factors, with the predominant mechanistic contributor being chronic inflammation. Since O3FAs have anti-inflammatory properties, it is plausible that higher plasma O3FA levels may associate with less AVC.

The MESA enrolled individuals without clinical cardiovascular disease. We studied those who had plasma fatty acid levels measured at baseline, and AVC measured on CT scans performed at baseline and subsequent visits. Plasma O3FA levels were typical of healthy adults not supplemented with O3FAs.[21] Moreover, participants with the highest tertile of plasma O3FA levels had lower plasma O3FA levels than what has been observed with high-dose omega-3 supplementation.[22]

Tertiles of plasma O3FA levels did not correlate with the presence or absence of AVC, including after adjusting for covariates in models 1 to 3. Furthermore, baseline tertiles of plasma O3FAs did not correlate with the incidence of AVC, nor the change in AVC over time, including after adjusting for covariates. Our results are similar to a cross-sectional analysis from MESA showing no association between blood omega-9 fatty acid levels and the presence of AVC.[11] The lack of a significant association suggests that circulating O3FAs may not be directly relevant to procalcific mechanistic pathways in the aortic valve. This does not refute the finding of Plunde et al,[23] that the expression of a single nucleotide polymorphism within the fatty acid desaturase 1 gene, which encodes a rate-limiting enzyme for O3FA and omega-6 fatty acid metabolism, is associated with calcified aortic valve tissue. Alternatively, the plasma O3FA levels in the participants studied may be insufficient to demonstrate an anti-calcific association. Conceivably, high circulating O3FA levels could retard the calcification process, which was not demonstrated in the present study that included individuals who were not routinely supplemented with O3FAs. The mechanisms by which this could occur, based on the current understanding of the pathogenesis of AVC, include reduction of lipoprotein deposition, chronic inflammation, and osteoblastic transition of valve interstitial cells.[24] Furthermore, in one study, the content of O3FA metabolites in aortic valve tissue was shown to associate inversely with the degree of calcification present. Artiach et al[25] demonstrated that in excised, severely stenosed, and calcified human aortic valves, specialized pro-resolving lipid mediators derived from both EPA and DHA were at their lowest tissue concentrations at sites of calcification. In that study, a greater association was observed with the EPA-derived mediator resolvin E1 compared with the DHA-derived mediator resolvin D3, and furthermore, resolvin E1 had anticalcifying effects on valvular interstitial cells.

Agents that reduce chronic inflammation are prime candidates for an investigation into the prevention and attenuation of AVC, the precursor to calcific AS. There are currently no medical therapies shown to slow the progression of this disease, which would be expected to reduce symptoms and the rates of aortic valve interventions, representing a significant unmet need.

This study has several limitations. The observational design predisposes to unmeasured residual confounders. The progression of AVC was assumed to be linear, and the time between the first and last scans varied between individuals. This study did not identify different aortic valve morphologies, such as bicuspid aortic valve, and their effects on AVC. This study did not consider time-varying covariates. Plasma O3FA levels measured from participants at baseline were assumed to be unchanged throughout the study period. It has previously been demonstrated that plasma O3FA levels measured at one time point reasonably predict levels measured many years later.[26] This study included participants who were not routinely supplemented with O3FAs. The associations between O3FA levels and AVC in this setting do not reflect those of persons supplemented with either over-the-counter or prescription O3FAs who typically achieve high blood and tissue O3FA levels, or those of persons who have diets very rich in O3FAs. A prospective, randomized controlled trial of O3FA supplementation at an appropriate dose, ideally with a variety of O3FA formulations, would be required to demonstrate the effect of O3FAs on AVC.

In conclusion, in this large, ethnically diverse prospective study, plasma O3FA levels were not found to be associated with the presence or development of AVC. Hence, the measurement of plasma O3FA levels acquired through diet in persons not routinely consuming O3FA supplements is not useful for identifying those who are at the highest risk of having or developing AVC. Whether high plasma O3FA levels, achievable by high-dose O3FA supplementation, may be associated with AVC requires further investigation.

Acknowledgment

The authors thank the other investigators, the staff, and the participants of the Multi-Ethnic Study of Atherosclerosis study for their valuable contributions. A full list of participating Multi-Ethnic Study of Atherosclerosis investigators and institutions can be found at http://www.mesa-nhlbi.org.

The Multi-Ethnic Study of Atherosclerosis was supported by R01 HL071739 and contracts 75N92020D00001, HHSN268201500003I, N01-HC-95159, 75N92020D00005, N01-HC-95160, 75N92020D00002, N01-HC-95161, 75N92020D00003, N01-HC-95162, 75N92020D00006, N01-HC-95163, 75N92020D00004, N01-HC-95164, 75N92020D00007, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168 and N01-HC-95169 from the National Heart, Lung, and Blood Institute (Bethesda, Maryland), and by grants UL1-TR-000040, UL1-TR-001079, and UL1-TR-001420 from the National Center for Advancing Translational Sciences (Bethesda, Maryland).

References

1. Carabello BA, Paulus WJ. Aortic stenosis. Lancet 2009;373:956–966. [PubMed: 19232707]
2. Otto CM, Lind BK, Kitzman DW, Gersh BJ, Siscovick DS. Association of aortic-valve sclerosis with cardiovascular mortality and morbidity in the elderly. N Engl J Med 1999;341:142–147. [PubMed: 10403851]
3. Horstkotte D, Loogen F. The natural history of aortic valve stenosis. Eur Heart J 1988;9(suppl E):57–64.

4. Sverdlov AL, Ngo DT, Chapman MJ, Ali OA, Chirkov YY, Horowitz JD. Pathogenesis of aortic stenosis: not just a matter of wear and tear. Am J Cardiovasc Dis 2011;1:185–199. [PubMed: 22254198]

5. Marquis-Gravel G, Redfors B, Leon MB, Généreux P. Medical treatment of aortic stenosis. Circulation 2016;134:1766–1784. [PubMed: 27895025]

6. Calder PC. Marine omega-3 fatty acids and inflammatory processes: effects, mechanisms and clinical relevance. Biochim biophys acta 2015;1851:469–484. [PubMed: 25149823]

7. Pisaniello AD, Psaltis PJ, King PM, Liu G, Gibson RA, Tan JTM, Duong M, Nguyen T, Bursill CA, Worthley MI, Nicholls SJ, Di Bartolo BA. Omega-3 fatty acids ameliorate vascular inflammation: a rationale for their atheroprotective effects. Atherosclerosis 2021;324:27–37. [PubMed: 33812168]

8. Kanai S, Uto K, Honda K, Hagiwara N, Oda H. Eicosapentaenoic acid reduces warfarin-induced arterial calcification in rats. Atherosclerosis 2011;215:43–51. [PubMed: 21193197]

9. Sekikawa A, Mahajan H, Kadowaki S, Hisamatsu T, Miyagawa N, Fujiyoshi A, Kadota A, Maegawa H, Murata K, Miura K, Edmundowicz D, Ueshima H, Research Group SESSA. Association of blood levels of marine omega-3 fatty acids with coronary calcification and calcium density in Japanese men. Eur J Clin Nutr 2019;73:783–792. [PubMed: 30050076]

10. Shang X, Sanders KM, Scott D, Khan B, Hodge A, Khan N, English DR, Giles GG, Ebeling PR. Dietary alpha-linolenic acid and total omega-3 fatty acids are inversely associated with abdominal aortic calcification in older women, but not in older men. J Nutr 2015;145:1778–1786. [PubMed: 26041673]

11. Steffen BT, Duprez D, Szklo M, Guan W, Tsai MY. Circulating oleic acid levels are related to greater risks of cardiovascular events and all-cause mortality: the Multi-Ethnic Study of Atherosclerosis. J Clin Lipidol 2018;12:1404–1412. [PubMed: 30201531]

12. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, Greenland P, Jacob DR Jr, Kronmal R, Liu K, Nelson JC, O'Leary D, Saad MF, Shea S, Szklo M, Tracy RP. Multi-Ethnic Study of Atherosclerosis: objectives and design. Am J Epidemiol 2002;156:871–881. [PubMed: 12397006]

13. Cao J, Schwichtenberg KA, Hanson NQ, Tsai MY. Incorporation and clearance of omega-3 fatty acids in erythrocyte membranes and plasma phospholipids. Clin Chem 2006;52:2265–2272. [PubMed: 17053155]

14. Budoff MJ, Takasu J, Katz R, Mao S, Shavelle DM, O'Brien KD, Blumenthal RS, Carr JJ, Kronmal R. Reproducibility of CT measurements of aortic valve calcification, mitral annulus calcification, and aortic wall calcification in the multi-ethnic study of atherosclerosis. Acad Radiol 2006;13:166–172. [PubMed: 16428051]

15. Nasir K, Katz R, Al-Mallah M, Takasu J, Shavelle DM, Carr JJ, Kronmal R, Blumenthal RS, O'Brien K, Budoff MJ. Relationship of aortic valve calcification with coronary artery calcium severity: the Multi-Ethnic Study of Atherosclerosis (MESA). J Cardiovasc Comput Tomogr 2010;4:41–46. [PubMed: 20159627]

16. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Jr Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990;15:827–832. [PubMed: 2407762]

17. Linefsky JP, O'Brien KD, Katz R, de Boer IH, Barasch E, Jenny NS, Siscovick DS, Kestenbaum B. Association of serum phosphate levels with aortic valve sclerosis and annular calcification: the cardiovascular health study. J Am Coll Cardiol 2011;58:291–297. [PubMed: 21737022]

18. Massera D, Buzkova P, Bortnick AE, Owens DS, Mao S, Li D, De Boer IH, Kestenbaum BR, Budoff MJ, Kizer JR. Bone mineral density and long-term progression of aortic valve and mitral annular calcification: the Multi-Ethnic Study of Atherosclerosis. Atherosclerosis 2021;335:126–134. [PubMed: 34511241]

19. Budoff MJ, Katz R, Wong ND, Nasir K, Mao SS, Takasu J, Kronmal R, Detrano RC, Shavelle DM, Blumenthal RS, O'Brien KD, Carr JJ. Effect of scanner type on the reproducibility of extracoronary measures of calcification: the multi-ethnic study of atherosclerosis. Acad Radiol 2007;14:1043–1049. [PubMed: 17707311]

20. Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R, Kitzmiller J, Knowler WC, Lebovitz H, Lernmark A, Nathan D, Palmer J, Rizza R, Saudek C, Shaw J, Steffes M, Stern

M, Tuomilehto J, Zimmet P. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 2003;26:3160–3167. [PubMed: 14578255]

21. Stark KD, Van Elswyk ME, Higgins MR, Weatherford CA, Salem N Jr. Global survey of the omega-3 fatty acids, docosahexaenoic acid and eicosapentaenoic acid in the blood stream of healthy adults. Prog Lipid Res 2016;63:132–152. [PubMed: 27216485]
22. Nicholls SJ, Lincoff AM, Garcia M, Bash D, Ballantyne CM, Barter PJ, Davidson MH, Kastelein JJP, Koenig W, McGuire DK, Mozaffarian D, Ridker PM, Ray KK, Katona BG, Himmelmann A, Loss LE, Rensfeldt M, Lundström T, Agrawal R, Menon V, Wolski K, Nissen SE. Effect of high-dose omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: the STRENGTH randomized clinical trial. JAMA 2020;324:2268–2280. [PubMed: 33190147]
23. Plunde O, Larsson SC, Artiach G, Thanassoulis G, Carracedo M, Franco-Cereceda A, Eriksson P, Bäck M. FADS1 (fatty acid desaturase 1) genotype associates with aortic valve FADS mRNA expression, fatty acid content and calcification. Circ Genom Precis Med 2020;13: e002710. [PubMed: 32397743]
24. Lindman BR, Clavel MA, Mathieu P, Iung B, Lancellotti P, Otto CM, Pibarot P. Calcific aortic stenosis. Nat Rev Dis Primers 2016;2:16006. [PubMed: 27188578]
25. Artiach G, Carracedo M, Plunde O, Wheelock CE, Thul S, Sjövall P, Franco-Cereceda A, Laguna-Fernandez A, Arnardottir H, Bäck M. Omega-3 polyunsaturated fatty acids decrease aortic valve disease through the Resolvin E1 and ChemR23 Axis. Circulation 2020;142:776–789. [PubMed: 32506925]
26. Lai HT, de Oliveira Otto MC, Lemaitre RN, McKnight B, Song X, King IB, Chaves PH, Odden MC, Newman AB, Siscovick DS, Mozaffarian D. Serial circulating omega 3 polyunsaturated fatty acids and healthy ageing among older adults in the cardiovascular health study: prospective cohort study. BMJ (Clin Res Ed) 2018;363:k4067.

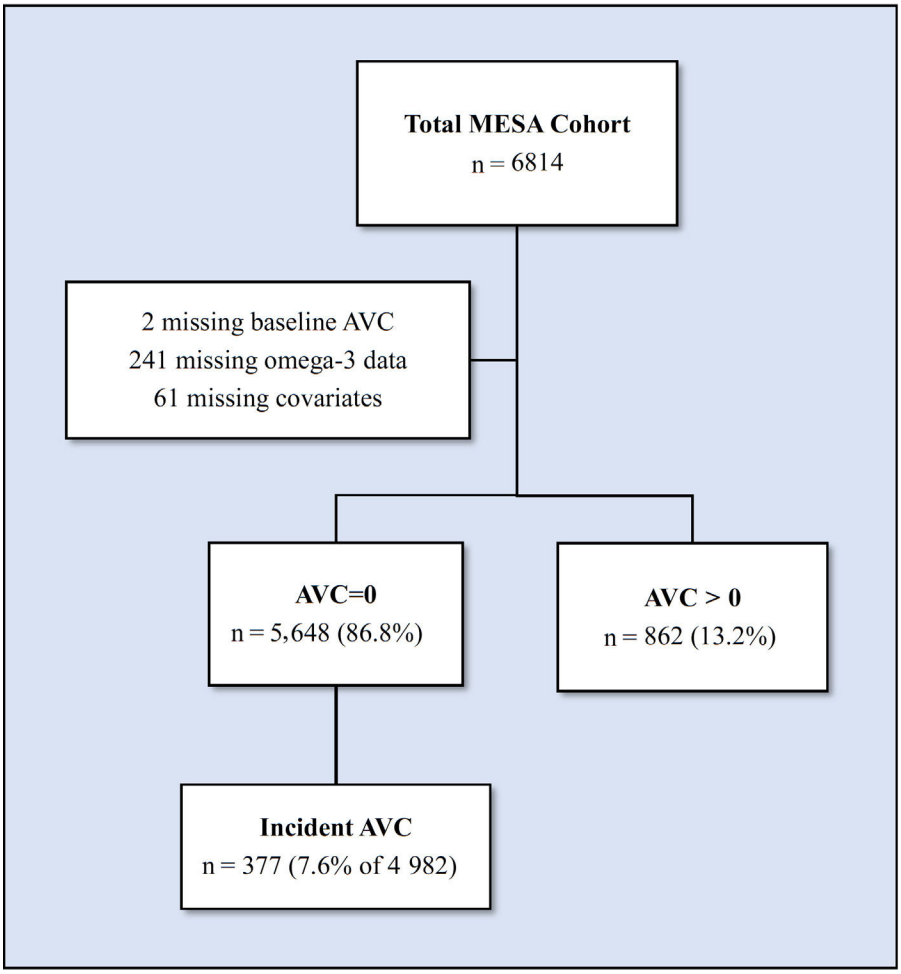

Figure 1.
Flowchart of study participants.

Table 1

Baseline characteristics in participants with and without aortic valve calcium at baseline

Characteristic	Aortic valve calcium		P-value
	Not present (n = 5648)	Present (n = 862)	
Age (years), mean±SD	60.8±9.9	70.5±8.1	<0.001
Male	2547 (45.1%)	519 (60.2%)	<0.001
White	2118 (37.5%)	394 (45.7%)	<0.001
Chinese	726 (12.9%)	63 (7.3%)	<0.001
Black	1556 (27.5%)	215 (24.9%)	0.109
Hispanic/Latino	1248 (22.1%)	190 (22.0%)	0.97
Education			<0.001
Less than high school	984 (17.4%)	198 (23.0%)	
High school or vocational school	2338 (41.4%)	367 (42.6%)	
College, graduate or professional school	2326 (41.2%)	297 (34.5%)	
Systolic BP (mmHg), mean±SD	125.2±21.1	134.9±22.2	<0.001
Body mass index (kg/m^2), mean±SD	28.3±5.5	28.5±4.9	0.21
Diabetes mellitus	641 (11.3%)	172 (20.0%)	<0.001
Smoking status			<0.001
Never	2901 (51.4%)	375 (43.5%)	
Former	1987 (35.2%)	398 (46.2%)	
Current	760 (13.5%)	89 (10.3%)	
Moderate and vigorous physical activity (MET-min/wk), median [IQR]	4136 [2025, 7725]	3450 [1598, 6570]	<0.001
Total cholesterol (mg/dl), mean±SD	194.0±35.2	195.0±38.2	0.43
HDL cholesterol (mg/dl), mean±SD	51.3±14.9	49.2±14.3	<0.001
Triglycerides (mg/dl), median [IQR]	110.0 [77.0, 159.0]	120.00 [82.00, 172.00]	<0.001
Lipoprotein(a) (mg/dl), median [IQR]	20.0 [9.9, 42.5]	25.0 [11.0, 61.3]	<0.001
eGFR (mL/min/1.73m^2), mean±SD	79.2±16.0	70.6±16.5	<0.001
CRP (mg/l), median [IQR]	1.9 [0.8, 4.3]	2.1 [1.0, 4.1]	0.054
Taking lipid-lowering medications	829 (14.7%)	221 (25.6%)	<0.001
Taking antihypertensive medications	1730 (30.6%)	426 (49.4%)	<0.001
Total omega 3 (%), median [IQR]	5.34 [4.31, 6.81]	5.23 [4.33, 6.59]	0.28

Characteristic	Aortic valve calcium		P-value
	Not present (n = 5648)	Present (n = 862)	
EPA (%), median [IQR]	0.67 [0.48, 1.00]	0.66 [0.48, 0.97]	0.42
DHA (%), median [IQR]	3.60 [2.71, 4.70]	3.53 [2.75, 4.58]	0.36
DPA (%), median [IQR]	0.91 [0.78, 1.05]	0.89 [0.76, 1.05]	0.10

BP = blood pressure; CRP = C-reactive protein; DHA = docosahexaenoic acid; DPA = docosapentaenoic acid; eGFR = estimated glomerular filtration rate; EPA = eicosapentaenoic acid; HDL = high-density lipoprotein; MET = metabolic equivalent of task.

Table 2

Univariate and multivariate adjusted associations between the percentage of omega-3 fatty acid levels in plasma and prevalent aortic valve calcium at baseline

	Unadjusted PR (95% CI)	Model 1* PR (95% CI)	Model 2† PR (95% CI)	Model 3‡ PR (95% CI)
Plasma EPA %				
Lowest tertile	Ref	Ref	Ref	Ref
Middle tertile	1.00 (0.86, 1.16)	1.08 (0.92, 1.27)	1.03 (0.88, 1.21)	1.08 (0.91, 1.28)
Highest tertile	0.91 (0.78, 1.06)	0.94 (0.79, 1.12)	0.90 (0.76, 1.07)	0.93 (0.77, 1.12)
Log EPA	0.93 (0.73, 1.17)	1.04 (0.79, 1.36)	0.98 (0.74, 1.29)	1.01 (0.75, 1.35)
Plasma DHA %				
Lowest tertile	Ref	Ref	Ref	Ref
Middle tertile	1.03 (0.89, 1.19)	1.08 (0.92, 1.27)	1.06 (0.90, 1.24)	1.01 (0.85, 1.20)
Highest tertile	0.91 (0.78, 1.06)	0.99 (0.83, 1.19)	0.96 (0.80, 1.15)	0.94 (0.77, 1.14)
Log DHA	0.89 (0.63, 1.27)	1.07 (0.68, 1.68)	0.96 (0.61, 1.51)	0.86 (0.52, 1.40)
Plasma total omega-3 %				
Lowest tertile	Ref	Ref	Ref	Ref
Middle tertile	1.07 (0.92, 1.25)	1.03 (0.87, 1.21)	1.00 (0.85, 1.17)	0.98 (0.82, 1.17)
Highest tertile	0.95 (0.81, 1.11)	1.04 (0.86, 1.24)	1.01 (0.84, 1.21)	1.00 (0.83, 1.21)
Log total O3FA	0.82 (0.54, 1.23)	0.98 (0.59, 1.62)	0.89 (0.54, 1.48)	0.86 (0.50, 1.47)

CI = confident interval; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; O3FA = omega-3 fatty acids ; PR = prevalence ratio.

*Model 1 = age, race, sex, education level, site, baseline CT scanner model, and time between scans.

†Model 2 = Model 1 + physical activity level, body mass index, smoking status, systolic blood pressure, diabetes status, total cholesterol, high-density lipoprotein cholesterol, triglyceride level, lipid-lowering medication use, antihypertensive medication use, and estimated glomerular filtration rate.

‡Model 3 = Model 2 + lipoprotein(a) and high-sensitivity C-reactive protein.

Table 3

Baseline characteristics of participants with no aortic valve calcium at baseline, according to follow-up aortic valve calcium

Characteristic	Incident aortic valve calcium		P-value
	No(n = 4605)	Yes(n = 377)	
Age (years), mean±SD	60.2±9.8	65.2±8.9	<0.001
Male	2054 (44.6%)	212 (56.2%)	<0.001
Race/ethnicity			0.015
White	1757 (38.2%)	161 (42.7%)	
Chinese	608 (13.2%)	29 (7.7%)	
Black	1234 (26.8%)	106 (28.1%)	
Hispanic/Latino	1006 (21.8%)	81 (21.5%)	
Education			0.68
Less than high school	739 (16.0%)	67 (17.8%)	
High school or vocational school	1903 (41.3%)	153 (40.6%)	
College, graduate or professional school	1963 (42.6%)	157(41.6%)	
Systolic BP (mmHg), mean±SD	124.1±20.5	131.1±21.8	<0.001
Body mass index (kg/m^2), mean±SD	28.2±5.5	29.0±5.2	0.008
Diabetes mellitus	480 (10.4%)	53 (14.1%)	0.028
Smoking status			0.029
Never	2390 (51.9%)	186 (49.3%)	
Former	1606 (34.9%)	154 (40.8%)	
Current	609 (13.2%)	37 (9.8%)	
Moderate and vigorous physical activity (MET-min/wk), median [IQR]	4238 [2100, 7793]	4268 [2025, 7808]	0.74
Total cholesterol (mg/dl), mean±SD	194.3±35.1	193.3±33.4	0.58
HDL cholesterol (mg/dl), mean±SD	51.4±14.8	50.1±14.9	0.10
Triglycerides (mg/dl), median [IQR]	109.0 [77.0, 159.0]	117.0 [82.0, 163.0]	0.048
Lipoprotein(a) (mg/dl), median [IQR]	19.9 [9.9, 41.0]	25.8 [10.9, 56.5]	<0.001
eGFR (mL/min/1.73m^2), mean±SD	79.6±15.6	75.2±15.8	<0.001
CRP (mg/l), median [IQR]	1.8 [0.8, 4.2]	2.0 [1.0, 4.0]	0.28
Taking lipid-lowering medications	649 (14.1%)	92 (24.4%)	<0.001
Taking anti-hypertensive medications	1350 (29.3%)	144 (38.2%)	<0.001
Taking fish oil supplements	148 (4.0%)	12 (3.2%)	0.44
Total omega 3 (%), median [IQR]	5.32 [4.31, 6.83]	5.44 [4.52, 6.80]	0.12
EPA (%), median [IQR]	0.67 [0.48, 0.99]	0.73 [0.52, 1.06]	0.007
DHA (%), median [IQR]	3.61 [2.71,4.71]	3.65 [2.87, 4.61]	0.24
DPA (%), median [IQR]	0.91 [0.77, 1.05]	0.92 [0.81, 1.05]	0.13

BP = blood pressure; CRP = C-reactive protein;; DHA = docosahexaenoic acid; DPA = docosapentaenoic acid; eGFR = estimated glomerular filtration rate; EPA = eicosapentaenoic acid; HDL = high-density lipoprotein; MET = metabolic equivalent of task.

Table 4

Univariable and multivariable-adjusted associations between the percentage of omega-3 fatty acids in plasma and incident aortic valve calcium

	Unadjusted IR (95% CI)	Model 1* IR (95% CI)	Model 2† IR (95% CI)	Model 3‡ IR (95% CI)
Plasma EPA level %				
Lowest tertile	Ref	Ref	Ref	Ref
Middle tertile	1.26 (0.98, 1.61)	1.24 (0.97, 1.58)	1.17 (0.92, 1.49)	1.07 (0.81, 1.40)
Highest tertile	1.27 (0.99, 1.62)	1.16 (0.90, 1.49)	1.09 (0.85, 1.40)	1.07 (0.82, 1.41)
Log EPA	1.49 (1.08, 2.06)	1.31 (0.94, 1.84)	1.25 (0.87, 1.78)	1.18 (0.79, 1.75)
Plasma DHA level %				
Lowest tertile	Ref	Ref	Ref	Ref
Middle tertile	1.29 (1.01, 1.64)	1.14 (0.89, 1.46)	1.15 (0.90, 1.47)	1.07 (0.81, 1.40)
Highest tertile	1.15 (0.90, 1.48)	1.00 (0.76, 1.31)	1.00 (0.77, 1.32)	0.96 (0.71, 1.30)
Log DHA	1.53 (0.89, 2.61)	1.17 (0.62, 2.19)	1.14 (0.59, 2.18)	0.93 (0.46, 1.89)
Plasma total O3FA level %				
Lowest tertile	Ref	Ref	Ref	Ref
Middle tertile	1.32 (1.04, 1.69)	1.12 (0.88, 1.43)	1.11 (0.87, 1.41)	1.02 (0.78, 1.34)
Highest tertile	1.16 (0.90, 1.48)	0.99 (0.76, 1.29)	0.98 (0.75, 1.28)	0.93 (0.70, 1.25)
Log total O3FA	1.70 (0.95, 3.06)	1.25 (0.64, 2.44)	1.21 (0.60, 2.42)	0.97 (0.45, 2.09)

DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; IR = incidence ratio; O3FA = omega-3 fatty acids.

*Model 1 = age, race, sex, education level, site, baseline CT scanner model, and time between scans.

†Model 2 = Model 1 + physical activity level, body mass index, smoking status, systolic blood pressure, diabetes status, total cholesterol, high-density lipoprotein cholesterol, triglyceride level, lipid-lowering medication use, antihypertensive medication use, and estimated glomerular filtration rate.

‡Model 3 = Model 2 + lipoprotein(a) and high-sensitivity C-reactive protein.

Table 5

Univariate and multivariate adjusted associations between the percentage of omega-3 fatty acids in plasma and progression of aortic valve calcium (Agatston Units per year)

	Unadjusted AU/yr (95% CI)	Model 1* AU/yr (95% CI)	Model 2† AU/yr (95% CI)	Model 3‡ AU/yr (95% CI)
Plasma EPA level %				
Lowest tertile	Ref	Ref	Ref	Ref
Middle tertile	−2.49 (−6.66, 1.68)	−2.29 (−6.51, 1.94)	−2.18 (−6.42, 2.06)	−2.71 (−7.00, 1.58)
Highest tertile	0.82 (−3.40, 5.04)	1.05 (−3.37, 5.47)	1.41 (−3.08, 5.91)	0.81 (−3.77, 5.39)
Log EPA	3.12 (−3.25, 9.48)	3.39 (−3.33, 10.10)	4.12 (−2.76, 11.00)	3.50 (−3.48, 10.48)
Plasma DHA level %				
Lowest tertile	Ref	Ref	Ref	Ref
Middle tertile	−2.80 (−6.98, 1.39)	−3.14 (−7.50, 1.23)	−3.09 (−7.51, 1.33)	−3.18 (−7.64, 1.29)
Highest tertile	−0.23 (−4.42, 3.97)	−0.40 (−4.97, 4.17)	−0.14 (−5.01, 4.73)	−0.04 (−5.00, 4.93)
Log DHA	−0.06 (−10.07, 9.95)	−0.39 (−11.43, 10.65)	0.14 (−11.78, 12.06)	0.36 (−11.81, 12.54)
Plasma Total O3FA level %				
Lowest tertile	Ref	Ref	Ref	Ref
Middle tertile	−2.41 (−6.59, 1.76)	−2.44 (−6.77, 1.90)	−2.39 (−6.79, 2.00)	−2.41 (−6.83, 2.02)
Highest tertile	0.10 (−4.11, 4.31)	0.21 (−4.35, 4.77)	0.52 (−4.29, 5.32)	0.55 (−4.34, 5.44)
Log Total O3FA	3.12 (−9.18, 13.41)	3.27 (−10.03, 14.56)	3.43 (−9.67, 16.53)	3.69 (−9.65, 17.03)

AU/yr = Agatston Units per year; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; O3FA = omega-3 fatty acids.

*Model 1 = age, race, sex, education level, site, baseline CT scanner model, and time between scans.

†Model 2 = Model 1 + physical activity level, body mass index, smoking status, systolic blood pressure, diabetes status, total cholesterol, high-density lipoprotein cholesterol, triglyceride level, lipid-lowering medication use, antihypertensive medication use, and estimated glomerular filtration rate.

‡Model 3 = Model 2 + lipoprotein(a) and high-sensitivity C-reactive protein.