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Omega-3 Supplement Use, Fish Intake, and Risk of Non-fatal Coronary Artery Disease and Ischemic Stroke in the Million Veteran Program

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Abstract

Background and Aims: Observational and clinical trial evidence suggests an inverse association of omega-3 polyunsaturated fatty acid with coronary artery disease (CAD) mortality, although relationships with non-fatal CAD and stroke are less clear. We investigated whether omega-3 fatty acid supplement use and fish intake were associated with incident non-fatal CAD and ischemic stroke among US Veterans.

Methods: The Million Veteran Program (MVP) is an ongoing nation-wide longitudinal cohort study of US Veterans with self-reported survey, biospecimen, and electronic health record data. Regular use of omega-3 supplements (yes/no) and frequency of fish intake within the past year were assessed using a food frequency questionnaire. Cox proportional hazard models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the associations of omega-3 supplement use and fish intake with incident non-fatal CAD and ischemic stroke, defined from electronic health records using validated algorithms. Multivariable models included demographics, body mass index, education, smoking status, alcohol intake, and exercise frequency.

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Results: Among 197,761 participants with food frequency data (mean age: 66 ± 12 years, 92% men), 21% regularly took omega-3 supplements and median fish intake was 1 (3–5 ounce) serving/week. Over a median follow-up of 2.9 years for non-fatal CAD and 3.3 years for non-fatal ischemic stroke, we observed 6,265 and 4,042 incident cases of non-fatal CAD and non-fatal ischemic stroke, respectively. Omega-3 fatty acid supplement use was independently associated with a lower risk of non-fatal ischemic stroke [HR (95% CI): 0.88 (0.81, 0.95)] but not non-fatal CAD [0.99 (0.93, 1.06)]. Fish intake was not independently associated with non-fatal CAD [1.01 (0.94, 1.09) for 1–3 servings/month, 1.03 (0.98, 1.11) for 1 serving/week, 1.02 (0.93, 1.11) for 2–4 servings/week, and 1.15 (0.98, 1.35) for ≥5 servings/week, reference = <1 serving/month, linear p-trend = 0.09] or non-fatal ischemic stroke [0.92 (0.84, 1.00) for 1–3 servings/month, 0.93 (0.85, 1.02) for 1 serving/week, 0.96 (0.86, 1.07) for 2–4 servings/week, and 1.13 (0.93–1.38) for ≥5 servings/week, linear p-trend = 0.16].

Conclusions: Neither omega-3 supplement use, nor fish intake, was associated with non-fatal CAD among US Veterans. While omega-3 supplement use was associated with lower risk of non-fatal ischemic stroke, fish intake was not. Randomized controlled trials are needed to confirm whether omega-3 supplementation is protective against ischemic stroke in a US population.

Keywords

diet; omega-3 fatty acids; fish; coronary artery disease; stroke; Veterans

Cardiovascular disease is one of the leading causes of death within the US.(1) Evidence from observational studies and randomized controlled trials suggests cardioprotective effects of omega-3 polyunsaturated fatty acids.(2, 3) However, findings vary depending on the cardiovascular endpoint investigated. While most studies indicate an inverse association between omega-3 fatty acids and coronary artery disease (CAD) mortality,(4) there are inconsistent findings for non-fatal CAD and stroke.(5) Data from Japan, where fish intake is greater than in the US, suggest that higher doses of omega-3 fatty acids may be needed to affect non-fatal cardiovascular events.(3, 6) Given current dietary patterns within the US, fish intake alone may not achieve sufficient levels of omega-3 fatty acids to affect non-fatal events. It is possible that among US cohorts who consume modest amounts of fish, omega-3 fatty acid supplement use alone or in combination with fish intake is needed to affect non-fatal CAD events. To our knowledge, the relationships of omega-3 fatty acid supplement use and fish intake with incident non-fatal CAD and stroke have not been investigated within a US population.

We examined the association between omega-3 fatty acid supplement use and incident non-fatal CAD in the Million Veteran Program (MVP). In secondary aims of this study, we evaluated whether dietary fish intake alone or in combination with omega-3 fatty acid supplements was associated with incident non-fatal CAD and/or non-fatal ischemic stroke. We hypothesized that omega-3 fatty acid supplement use would be associated with a lower risk of non-fatal CAD and ischemic stroke, and that fish intake alone would not be associated with these outcomes.

1. Materials and methods

1.1 Study population

The Million Veteran Program (MVP) is an ongoing nation-wide prospective cohort study of US Veterans with self-reported survey, biospecimen, and electronic health record (EHR) data. Detailed description of the MVP study design has been published previously.(7) Participants were active users of the Veterans Health Administration (VHA). A total of 591,184 participants were enrolled between January 2011 and August 2017. Participants who had data from the food frequency questionnaire and who were free of CAD or stroke at the time of the MVP Lifestyle Survey (n=197,761) were included in this analysis. The Veterans Affairs Central Institutional Review Board approved this study and informed consent was obtained from all participants.

1.2 Assessment of omega-3 fatty acid supplement use and fish intake

Omega-3 fatty acid supplement use and frequency of fish intake were measured using a food frequency questionnaire. Supplement use was assessed by asking participants whether there were any supplements they took on a regular basis. A list of several supplements, including omega-3 fatty acids, was provided and participants were instructed to mark all that apply. Dietary habits, including fish intake, were assessed using the following question: “For each food listed, please mark the column indicating how often, on average, you have used the amount specified during the past year.” The amount specified for fish was 3–5 ounces. Possible responses were “never or less than once a month,” “1–3 per month,” “once (1) a week,” “2–4 per week,” “5–6 per week,” “once (1) a day,” “2–3 per day,” “4–5 per day,” and “6+ per day.”

1.3 Incident non-fatal CAD and non-fatal ischemic stroke

Incident non-fatal CAD and non-fatal ischemic stroke were defined using Internal Classification of Disease Ninth and Tenth Revision (ICD9 and ICD10, respectively) codes within the Veterans Affairs (VA) EHR. Non-fatal CAD was defined using ICD9 codes 410.x (acute myocardial infarction), 411.x (other acute and subacute forms of ischemic heart disease), and 413.x (angina pectoris) to 414.x (other forms of ischemic heart disease) and ICD10 codes I20.x to I25.x (ischemic heart disease), excluding I25.2 (old myocardial infarction). Non-fatal ischemic stroke was defined using ICD9 codes 433.x (occlusion and stenosis of precerebral arteries), 434.x (occlusion of cerebral arteries), 436.x (acute, but ill-defined, cerebrovascular disease), and 437.1 (other generalized ischemic cerebrovascular disease) and ICD10 codes I63.x (cerebral infarction), I65.x (occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction), I66.x (occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction), I67.2 (cerebral atherosclerosis), I67.6 (nonpyogenic thrombosis of intracranial venous system), and I67.8 (other specified cerebrovascular diseases).

1.4 Additional variables

Information on age, sex, and race was obtained from the MVP baseline and lifestyle surveys. If date of birth and gender were missing from the surveys, they were obtained from the

electronic health record. Body mass index (BMI, kg/m^2) was calculated from self-reported height and weight. Additional information obtained from the surveys included education, cigarette smoking, alcohol intake, and exercise frequency.

1.5 Statistical analysis

Baseline characteristics (mean, standard deviation, percentage) were reported for participants who did and did not regularly use omega-3 fatty acid supplements. Smoking status and alcohol use were categorized as never, former, and current. Exercise frequency was categorized as <1 time/week, 1 time/week, 2 to 4 times/week, and ≥5 times/week. BMI was categorized using standard cutpoints (<25, 25–30, and ≥30). Education level was categorized as <high school, high school diploma/GED, some college, Associate's degree, Bachelor's degree, Master's degree, or Professional or Doctorate degree. Due to small numbers of responses in the highest fish intake categories, the latter five categories were collapsed to ≥5 per week. Person-time of follow-up was computed from the completion date of the MVP Lifestyle Survey until the first occurrence of non-fatal CAD, non-fatal ischemic stroke, death, or the date when the data was pulled from the electronic health record (August 31, 2017). Cox proportional hazard models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for non-fatal CAD and ischemic stroke according to omega-3 fatty acid supplement use and frequency of fish intake. Sequential models were built with potential confounders based on a priori knowledge. After analyzing unadjusted models for CAD and ischemic stroke, we adjusted for age, sex, and race (Model 1), and then additionally adjusted for BMI, smoking status, alcohol intake, and exercise (Model 2). The quadratic term for age was included in models when significant. Proportional hazards assumptions were tested by examining Schoenfeld residuals and were met. To investigate whether the combined effect of omega-3 supplement use and fish intake differed from the effect of either exposure alone, we examined their interaction in fully adjusted models. We additionally performed a sensitivity analysis excluding participants with <1 year of follow-up. All analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, North Carolina).

2. Results

Among 197,761 MVP participants analyzed, mean age was 66 ± 12 years and 92% were male. Median fish intake was 1 serving per week and 21% of participants regularly took omega-3 fatty acid supplements. Participants who regularly took omega-3 fatty acid supplements had higher educational attainment and were less likely to be current smokers (Table 1). Over a median follow-up of 2.9 years for non-fatal CAD and 3.3 years for non-fatal ischemic stroke, there were 6,265 and 4,042 incident cases of non-fatal CAD and non-fatal ischemic stroke, respectively. Omega-3 supplement use was associated with a lower hazard of non-fatal CAD when adjusting for age, sex, and race [HR (95% CI): 0.93 (0.88, 0.99)], but this association became statistically nonsignificant after additional adjustment for lifestyle factors [HR (95% CI): 0.99 (0.93, 1.06), Table 2]. Compared to non-users, omega-3 fatty acid supplement use was associated with a 12% lower risk of non-fatal ischemic stroke in the fully adjusted model [HR (95% CI): 0.88 (0.81, 0.95), Table 3]. Similar associations were seen when stratified by sex (Tables 2 and 3), but the association of omega-3

supplement use with non-fatal ischemic stroke did not reach statistical significance among women (Table 3).

We found no association between fish intake and non-fatal CAD [fully adjusted HRs (95% CIs): 1.01 (0.94, 1.09) for 1–3 servings/month, 1.03 (0.95, 1.11) for 1 serving/week, 1.02 (0.93, 1.11) for 2–4 servings/week, and 1.15 (0.98, 1.35) for ≥5 servings/week, reference = <1 serving/month, linear p-trend = 0.09) (Supplemental Table 1). Similarly, we did not observe an association between fish intake and non-fatal ischemic stroke when adjusting for demographics and lifestyle factors (HRs (95% CIs): 0.92 (0.84, 1.00) for 1–3 servings/month, 0.93 (0.85, 1.02) for 1 serving/week, 0.96 (0.86, 1.07) for 2–4 servings/week, and 1.13 (0.93–1.38) for ≥5 servings/week, linear p-trend = 0.16) (Supplemental Table 2).

We found no evidence of a multiplicative effect of omega-3 fatty acid supplement use with fish intake on non-fatal CAD (interaction p-value = 0.08) or non-fatal ischemic stroke (interaction p-value = 0.86). Dichotomizing fish consumption to ≥5 servings/week and <5 servings/week yielded similar results (interaction p-value=0.90 for non-fatal CAD; interaction p-value=0.41 for non-fatal ischemic stroke).

The median (inter-quartile range) follow-up time for the sensitivity analysis in which we excluded participants with <1 year of follow-up (16% excluded for CAD and 13% excluded for ischemic stroke) was 3.2 (2.2–4.3) years for CAD and 3.6 (2.4–4.7) years for ischemic stroke. Findings from the sensitivity analysis were consistent with the main analysis (results not shown).

3. Discussion

In this large prospective cohort of US Veterans, omega-3 fatty acid supplement use was independently associated with a lower risk of non-fatal ischemic stroke but not with the incidence of non-fatal CAD. When adjusting for demographics and lifestyle factors, fish intake was not associated with non-fatal CAD or ischemic stroke and we found no significant interaction of omega-3 supplement use and fish intake on CAD or ischemic stroke.

To our knowledge, this is the first US cohort study to investigate the association of omega-3 supplement use and fish consumption with incident non-fatal CAD and stroke among Veterans. Most of the literature on omega-3 intake and CAD has focused on secondary prevention among high-risk patients.(2, 8, 9) Our findings are mostly consistent with the few studies that have investigated the effect of omega-3 supplementation on primary prevention of CAD within subgroup analyses. The Japan EPA lipid intervention study (JELIS), which investigated primary prevention of CAD as a secondary outcome among hypercholesterolaemic patients found that omega-3 supplementation reduced the risk of major coronary events by 18%, but this effect was not statistically significant (95% CI: 0.63, 1.06).(6) Similarly, subgroup analyses from a trial among patients with chronic heart failure without prior myocardial infarction and a trial among patients with dysglycemia without a prior cardiovascular event have shown no significant effects of omega-3 supplementation on

coronary events.(10, 11) These studies did not assess the effects on primary prevention of stroke.

Previous studies on omega-3 supplement use and cardiovascular outcomes have primarily been conducted in non-US populations. Large clinical trials investigating omega-3 supplementation have been performed in Japan, Norway, Italy, and internationally with varied results.(6, 10, 12) Heterogeneity in results may be due, in part, to differences in dietary patterns that influence omega-3 fatty acid intake and metabolism. According to the National Marine Fisheries Service (NMFS), both Japan and Norway had more than twice the estimated per capita consumption of fish and shellfish as the United States.(13) While Italy's per capita consumption was only slightly higher than that of the US, other factors associated with a Mediterranean diet may influence omega-3 intake in the region.(14) Given that these study populations likely had higher levels of dietary omega-3 intake, it may not be appropriate to generalize findings from these studies to a US population.

Regional differences in dietary patterns may be particularly important when synthesizing evidence on the relationship of omega-3 fatty acids with different subtypes of cardiovascular events. Evidence from meta-analyses and systematic reviews suggests that omega-3 fatty acids may be protective against fatal cardiovascular events, while results for non-fatal events are less consistent.(3, 15) Some have suggested that higher doses of omega-3 fatty acids may be needed to protect against non-fatal events,(3) citing epidemiologic and clinical trial data from Japan where fish consumption is very high.(6, 16) Given that fish intake tends to be lower among US populations, we hypothesized that omega-3 supplement use, but not fish intake alone, would be associated with fewer non-fatal events. Our results suggest that this hypothesis may be true for non-fatal ischemic stroke, but not CAD.

Previous studies have shown inconsistent findings on the effects of omega-3 intake on stroke.(15) These discrepancies may be due, in part, to the fact that many of these studies did not investigate ischemic and hemorrhagic stroke separately. It has been hypothesized that the antiplatelet aggregation property of omega-3 fatty acids may be responsible for a protective effect on ischemic stroke but not hemorrhagic stroke.(17, 18) This is supported by our finding that omega-3 supplement use was associated with a lower incidence of non-fatal ischemic stroke. Due to few events, we were unable to examine associations with hemorrhagic stroke.

To our knowledge, only one other study has investigated the association of fish consumption with stroke in a US Veteran population. An observational study of US twins Veterans found that dietary fish and seafood consumption were not associated with stroke;(19) however, they did not investigate ischemic and hemorrhagic stroke separately. In addition, they did not investigate omega-3 supplement use or assess the relationship of fish and seafood consumption with CAD.

Our study has both strengths and limitations. Given the use of a detailed food frequency questionnaire, we were able to assess the associations of both omega-3 supplement use and fish intake together in a single cohort, whereas many other studies have been limited to investigating either supplement use or dietary fish intake alone. We investigated a large

cohort of US Veterans with data linked to an electronic health record. The large number of events that occurred over the 3-year follow up period allowed us to investigate specific subtypes of cardiovascular events, namely non-fatal incident CAD and non-fatal incident ischemic stroke. Limitations of this study include a lack of information on omega-3 supplement dose. A study from the US Department of Agriculture concluded that the most common amounts of omega-3 fatty acids in supplements were 180 mg for eicosapentaenoic acid (EPA) and 120 mg for docosahexaenoic acid (DHA).(14) They also presented evidence from chemical analysis that the EPA and DHA content mostly reflected the amount specified on the label.(14) A dose of 250 mg has been recommended for the prevention of CAD death,(3, 20) but more work is needed to investigate the optimal dose for preventing non-fatal events, particularly for ischemic stroke in a population with low fish consumption. We also did not have information of the type of fish consumed or the method used to cook fish. Omega-3 fatty acid levels from fish vary based on the type of fish consumed, with fatty fish, such as salmon, containing higher levels than leaner fish such as cod or tilapia.(21) Moreover, there is evidence that the benefit conferred from fish intake depends on the method used to prepare the fish. Data from the Cardiovascular Health Study has shown that while baked and broiled fish were associated with a lower risk of ischemic heart disease death, fried fish and fish sandwiches were associated with higher risk.(22) Future work is needed to investigate information on trends in type of fish meals consumed within this population. We assessed omega-3 supplement use and fish consumption through self-report, therefore some recall bias and misclassification may have occurred. Participants who took omega-3 supplements as part of a multivitamin complex may not have accurately reported omega-3 supplement use, potentially leading to misclassification bias. In addition, we did not include prescription data for omega-3 supplements in our analysis. While we expect that prescription omega-3 supplements would be captured through the self-report questionnaire, it is possible that were not, leading to some misclassification. However, the number of participants who were prescribed omega-3 supplements prior to the MVP Lifestyle Survey was small (n=24). We currently do not have nutrient data, and were therefore unable to adjust for total energy intake within this study. This may have contributed to some measurement error for fish intake. Given few fatal and hemorrhagic stroke events, we were unable to investigate these outcomes. We do not have information on acute CAD or stroke events that occurred in non-VA hospitals, although VA patient records would likely include coding for the event once they returned to the VA for care. Our study population of US Veterans was predominantly male. While men and women had a similar magnitude of association between omega-3 supplement use and non-fatal ischemic stroke in our subgroup analysis, the association did not reach statistical significance in women, likely due to limited statistical power. We adjusted for a number of lifestyle factors, including smoking, alcohol consumption, and exercise, however, we cannot rule out residual confounding in our results, given the observational design of our study. Randomized controlled trials are needed to confirm our results.

In conclusion, our findings show that omega-3 supplement use is associated with a lower risk of non-fatal ischemic stroke, but not non-fatal CAD among US Veterans. Fish intake was not independently associated with non-fatal ischemic stroke or CAD. Future

randomized controlled trials are needed to confirm whether omega-3 supplementation is protective against ischemic stroke in a US population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CAD	Coronary artery disease
MVP	The Million Veteran Program
HR	hazard ratio
CI	confidence interval
EHR	electronic health record
VHA	Veterans Health Administration
ICD	Internal Classification of Disease
VA	Veterans Affairs
BMI	body mass index
EPA	eicosapentaenoic acid
DHA	docosahexaenoic acid

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Table 1:

Baseline characteristics of 197,761 US Veterans according to omega-3 fatty acid supplement use

	Omega-3 supplement use	
	Yes (n=42,316)	**No (n=155,445)**
Age, years	65.9 (10.9)	65.4 (11.8)
Sex, male %	91.6	91.8
Race, white %	85.6	82.3
Education, ≥ high school diploma/GED %	82.5	74.7
BMI, kg/m^2	29.4 (5.3)	29.3 (5.6)
Exercise %		
<1 time/week	52.3	45.1
1 time/week	11.7	13.3
2–4 times/week	23.2	28.0
≥5 times/week	12.7	13.6
Smoking status %		
Never	29.4	27.0
Former	58.5	54.2
Current	12.2	18.8
Alcohol intake %		
Never	7.6	8.0
Former	38.2	41.7
Current	54.2	50.4
Frequency of fish Intake %		
<1/month	12.2	17.5
1–3/month	29.4	33.9
1/week	33.6	31.0
2–4/week	21.2	15.1
≥5/week	3.5	2.6

Data are Mean (Standard Deviation) or Percent. BMI = Body Mass Index, GED = General Education Degree

Table 2:

Hazard ratios (95% CI) for non-fatal coronary artery disease by omega-3 fatty acid supplement use (yes/no)

	Cases/person-years	Hazard ratio (95% CI)		
		Crude	Model 1	Model 2
Total study population				
Omega-3 supplement use				
No	4,923/313,732	1.0 (ref)	1.0 (ref)	1.0 (ref)
Yes	1,342/89,257	0.96 (0.90, 1.02)	0.93 (0.88, 0.99)	0.99 (0.93, 1.06)
Men				
Omega-3 supplement use				
No	4,742/282,606	1.0 (ref)	1.0 (ref)	1.0 (ref)
Yes	1,285/79,880	0.96 (0.90, 1.02)	0.93 (0.88, 0.99)	0.99 (0.93, 1.06)
Women				
Omega-3 supplement use				
No	181/31,126	1.0 (ref)	1.0 (ref)	1.0 (ref)
Yes	57/9,378	1.05 (0.76, 1.41)	0.93 (0.69, 1.25)	1.03 (0.76, 1.40)

Model 1: adjusted for age, sex, and race; Model 2: Model 1 + BMI, education, smoking status, alcohol intake, exercise.

Table 3:

Hazard ratios (95% CI) for non-fatal ischemic stroke by omega-3 fatty acid supplement use (yes/no)

	Cases/person-years	Hazard ratio (95% CI)		
		Crude	Model 1	Model 2
Total study population				
Omega-3 supplement use				
No	3,261/451,567	1.0 (ref)	1.0 (ref)	1.0 (ref)
Yes	781/131,808	0.82 (0.76, 0.89)	0.80 (0.75, 0.87)	0.88 (0.81, 0.95)
Men				
Omega-3 supplement use				
No	3,114/413,622	1.0 (ref)	1.0 (ref)	1.0 (ref)
Yes	743/120,477	0.82 (0.76, 0.89)	0.80 (0.74, 0.87)	0.88 (0.81, 0.95)
Women				
Omega-3 supplement use				
No	147/37,945	1.0 (ref)	1.0 (ref)	1.0 (ref)
Yes	38/11,331	0.87 (0.61, 1.24)	0.79 (0.55, 1.13)	0.88 (0.61, 1.27)

Model 1: adjusted for age, sex, and race; Model 2: Model 1 + BMI, education, smoking status, alcohol intake, exercise.