ORIGINAL ARTICLE

Predictors of Omega-3 Index in Patients With Acute Myocardial Infarction

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OBJECTIVE: **To identify the patient and dietary characteristics associated with low omega-3 levels in patients with acute myocardial infarction (AMI) and determine whether these characteristics are useful to identify patients who may benefit from omega-3 testing and treatment.**

PATIENTS AND METHODS: **Dietary habits of 1487 patients in the 24-center Translational Research Investigating Underlying disparities in acute Myocardial infarction Patients' Health status (TRIUMPH) registry between April 11, 2005, and September 28, 2007, were assessed by asking about the frequency of fast food and nonfried fish consumption. All patients had erythrocyte omega-3 index measured at the time of hospital admission for AMI. We used multivariable linear regression to identify independent correlates of the omega-3 index and modified Poisson regression to predict risk of a low omega-3 index (<4%).**

RESULTS: **The proportion of patients with a low omega-3 index increased with more frequent fast food intake (18.9% for <1 time monthly, 28.6% for 1-3 times monthly, 28.8% for 1-2 times weekly, and 37.6% for ≥3 times weekly; *P*<.001). In contrast, a low omega-3 index was less common among patients with more frequent fish intake (35.1% for <1 time monthly, 24.9% for 1-3 times monthly, 16.1% for 1-2 times weekly, and 21.1% for ≥3 times weekly; *P*<.001). Fish intake, older age, race other than white, and omega-3 supplementation were independently associated with a higher omega-3 index, whereas frequent fast food intake, smoking, and diabetes mellitus were associated with a lower omega-3 index.**

CONCLUSION: **Potentially modifiable factors, such as patient-reported fast food intake, fish intake, and smoking, are independently associated with the omega-3 index in patients with AMI. These characteristics may be useful to identify patients who would benefit most from omega-3 supplementation and lifestyle modification.**

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AMI = acute myocardial infarction; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; RBC = red blood cell; TRIUMPH = Translational Research Investigating Underlying disparities in acute Myocardial infarction Patients' Health status

A low red blood cell (RBC) omega-3 index (the sum of eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) is associated with greater long-term mortality in patients with coronary artery disease.[1,2] Because omega-3 supplementation reduces mortality in patients with cardiovascular disease,[3-5] it is possible that augmenting omega-3 levels in those with the lowest omega-3 indices would yield the greatest treatment benefit. Accordingly, routine assessment of patients' omega-3 index could identify the highest-risk patients who are ideal targets for dietary modification and aggressive omega-3 supplementation. Despite these potential benefits and the availability of well-tolerated, affordable omega-3 supplements, routine testing of omega-3 fatty acid levels has been limited in acute myocardial infarction (AMI) populations because of its cost and limited availability at the point of care. Therefore, simple and inexpensive screening mechanisms are needed to identify patients who are likely to have a low omega-3 index and who may experience greater benefit from omega-3 index testing and treatment than those with a higher omega-3 index.

Studies in asymptomatic patients, many of whom had no coronary artery disease, identified several patient characteristics associated with omega-3 levels. Specifically, omega-3 supplements, age, body mass index, diabetes, and smoking were independently associated with the omega-3 index.[6,7] To our knowledge, the patient characteristics and dietary behaviors associated with the omega-3 index have not been described in patients with incident AMI, a particularly high-risk population. Moreover, although poor dietary habits, such as frequent consumption of fast food, may influence omega-3 levels, no studies have examined the association between fast food intake and the omega-3 index. Therefore, we studied patients enrolled in a contemporary registry of AMI treatment and outcomes, the Translational Research Investigating Underlying disparities in acute Myocardial infarction Patients' Health status (TRIUMPH) study, to describe the association between patient characteristics and omega-3 levels at the time of AMI. Our goal was to identify the independent predictors

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of omega-3 levels so that patients likely to have low levels of omega-3 could be recognized and considered for further testing and treatment.

PATIENTS AND METHODS

The TRIUMPH registry is a prospective study of patients with AMI from 24 US centers that enrolled 4340 patients from April 11, 2005, through December 31, 2008. Patients were 18 years or older, had elevated cardiac biomarkers (elevated levels of troponin or creatine kinase MB within 24 hours of admission), had supporting evidence of AMI (electrocardiographic ST-segment changes or prolonged ischemic signs or symptoms), and presented to the enrolling institution or were transferred to that facility within 24 hours of their initial presentation. Trained data collectors performed medical record abstractions to document each patient's medical history, processes of inpatient care, laboratory results, and treatments. Patients also underwent a standardized interview to document more detailed demographic, socioeconomic, and clinical data. All patients signed an informed consent form approved by the participating institution.

The omega-3 index was assessed in a subset of the initial enrollees in TRIUMPH (n=1523) who were enrolled before September 28, 2007. We excluded individuals who did not respond to the baseline fast food or fish dietary assessments (n=11 and n=19, respectively) and patients who died during the index admission (n=6), yielding an analytic cohort of 1487 patients.

Assessment of RBC Omega-3 Fatty Acids

Blood samples were obtained from patients for assessment of the omega-3 index at the time of enrollment into the TRIUMPH study. The omega-3 index quantifies the percentage of EPA and DHA in RBC membranes and reflects a time-averaged value of omega-3 fatty acid levels over the lifespan of a RBC (120 days). The RBCs were obtained from EDTA blood samples after the plasma and buffy coat were removed. The samples were stored at −70ºC until thawed for analysis. Briefly, RBC aliquots were heated at 100ºC for 10 minutes with methanol containing 14% boron trifluoride. The fatty acid methyl esters generated were extracted with hexane and water and were analyzed with a GC2010 gas chromatograph (Shimadzu Corporation, Columbia, MD) equipped with a 30-m capillary column (Omegawax 250; Supelco, Bellefonte, PA). Fatty acids were identified through comparison with a standard fatty acid methyl ester mixture (GLC-727; Nuchek Prep, Elysian, MN). The coefficient of variation for the omega-3 index is less than 5%. Values are expressed as EPA plus DHA as a percentage of total RBC fatty acids. Congruent with prior work, patients were classified as having a low (high-risk) omega-3 index if their omega-3 index was less than 4%.[8,9]

Dietary Assessments

Baseline patient interviews assessed fish intake with the question, "How often do you eat tuna or other nonfried fish (eg, baked, broiled, poached, grilled)?" Similarly, fast food intake was assessed with the question, "How often do you eat at fast food restaurants?" Responses to both items were recorded as less than 1 time monthly, 1 to 3 times monthly, 1 to 2 times weekly, 3 to 4 times weekly, and 5 or more times weekly. We collapsed the 2 categories representing the greatest consumption of each food item into a single group because both represent high dietary intake and relatively few patients reported eating either fast food (n=109 [7.3%]) or nonfried fish 5 or more times weekly (n=13 [0.9%]).

Statistical Analyses

For descriptive purposes, we presented categorical data as frequencies and compared differences between groups using the χ^2 or Fisher exact test, as appropriate. Continuous variables were reported as the mean ± SD, and differences were compared using *t* tests. We then studied the association of dietary variables and patient characteristics that we identified a priori, based on clinical experience, with the omega-3 index, which was modeled as a continuous variable using multivariable linear regression. Independent variables included known and potential correlates of omega-3 index, including the enrolling hospital, age, sex, race, body mass index, diabetes, smoking, chronic heart failure, socioeconomic status, and patient-reported nonfried fish intake and fast food intake. This linear regression approach enabled us to directly assess the independent association of each covariate with values on the omega-3 index and provided a clinically meaningful illustration of the strength of association across the entire range of potential omega-3 indices.

Because the clinical decision to pursue further testing or treatment rests on identifying patients with a low omega-3 index, we also categorized omega-3 levels as less than 4% or 4% or greater. Because the outcome of interest was prevalent, the odds ratios generated by logistic regression models can overestimate the true relative risk between the exposures of interest and the omega-3 index. Accordingly, we then used modified Poisson regression to identify patients with a low omega-3 index.[10] This method yields accurate relative risks even in the setting of prevalent outcomes and appropriately adjusts confidence intervals using robust error variance when using a Poisson distribution to model binomial data. We initially included the same co-

TABLE 1. **Patient Characteristics of the Overall Cohort and Comparing Patients With Low to Those With Intermediate to Favorable Omega-3 Index**

Characteristic	Overall (n=1487)	Omega-3 index <4% Yes (n=395)	Omega-3 index <4% No (n=1092)	*P* value
Age (y), mean ± SD	59.1±12.3	54.4±10.9	60.8±12.4	<.001
Male	1005 (67.6)	279 (70.6)	726 (66.5)	.13
Race				<.001
White	1100/1485 (74.1)	328 (83.0)	772/1090 (70.8)	
Black/African American	284/1485 (19.1)	38 (9.6)	246/1090 (22.6)	
Other	101/1485 (6.8)	29 (7.3)	72/1090 (6.6)	
College education	781/1483 (52.7)	178/394 (45.2)	603 (55.2)	<.001
Work full or part-time	751/1478 (50.8)	238/392 (60.7)	513/1086 (47.2)	<.001
Financial situation				.008
Some money left	651/1472 (44.2)	159/392 (40.6)	492/1080 (45.6)	
Just enough to make ends meet	524/1472 (35.6)	133/392 (33.9)	391/1080 (36.2)	
Not enough to make ends meet	297/1472 (20.2)	100/392 (25.5)	197/1080 (18.2)	
Omega-3 index, mean ± SD	5.0±1.6	3.3±0.5	5.7±1.4	<.001
Omega-3 supplement	243/1476 (16.5)	24/393 (6.1)	219/1083 (20.2)	<.001
Body mass index, mean ± SD	29.6±6.5	29.4±6.5	29.7±6.4	.46
Diabetes mellitus	444 (29.9)	119 (30.1)	325 (29.8)	.89
Hypertension	948 (63.8)	235 (59.5)	713 (65.3)	.04
Dyslipidemia	764 (51.4)	186 (47.1)	578 (52.9)	.05
Chronic kidney disease	98 (6.6)	16 (4.1)	82 (7.5)	.02
Current smoking	592/1482 (40.0)	226 (57.2)	366/1087 (33.7)	<.001
Chronic heart failure	120 (8.1)	20 (5.1)	100 (9.2)	.01
Peripheral arterial disease	81 (5.4)	13 (3.3)	68 (6.2)	.03
Prior stroke	65 (4.4)	9 (2.3)	56 (5.1)	.02
History of prior myocardial infarction	279 (18.8)	70 (17.7)	209 (19.1)	.54
History of prior coronary artery bypass grafting	172 (11.6)	30 (7.6)	142 (13.0)	.004
ST-elevation myocardial infarction	677 (45.5)	203 (51.4)	474 (43.4)	.04

Data are presented as number (percentage) of patients unless otherwise indicated. Continuous variables compared using independent *t* tests. Categorical variables compared using the χ^2 or Fisher exact test, as appropriate.

variates that were included in the initial linear regression model into this model. To simplify the application of the model to clinical practice, we removed variables that were not significant correlates of low omega-3 from this model to arrive at a final, more parsimonious model. Discrimination was determined using the C statistic, and its calibration was tested with the Hosmer-Lemeshow test.[11] All analyses were conducted with SAS statistical software, version 9.2 (SAS Institute, Cary, NC).

RESULTS

Baseline Characteristics and Association of Patient-Reported Diet to the Omega-3 Index

A low omega-3 index was common, occurring in more than 1 in 4 patients with AMI (395 patients [26.6%]). Characteristics of the overall cohort and baseline comparisons of patients with low (<4%) vs intermediate to high (≥4%) omega-3 levels are listed in Table 1. Patients with a low omega-3 index were younger, more frequently white, less likely to have a college education, more likely to report current smoking, and less likely to take omega-3 supplements. Patients with a low omega-3 index were also less likely to have hypertension, dyslipidemia, chronic heart failure, peripheral arterial disease, and prior stroke. Patients with a low omega-3 index less frequently reported nonfried fish consumption and more frequently reported eating fast food (Figure 1).

Figure 2 presents the relative independence of the association between fast food and nonfried fish intake with low omega-3 levels. In general, the more frequently patients reported fast food intake and the less often patients consumed nonfried fish, the more likely they were to have low omega-3 indexes. Notably, among patients who reported heavy fast food intake, even those who reported high fish consumption had low omega-3 index values.

Independent Predictors of the Omega-3 Index

The independent correlates of the omega-3 index in the linear regression model are presented in Figure 3. Demographic characteristics associated with higher omega-3 index included age and race other than white. In contrast, diabetes and current smoking were associated with lower omega-3 indices. There was a graded association between consumption of nonfried fish and omega-3 index. Compared with patients who ate fish infrequently (less than once monthly),

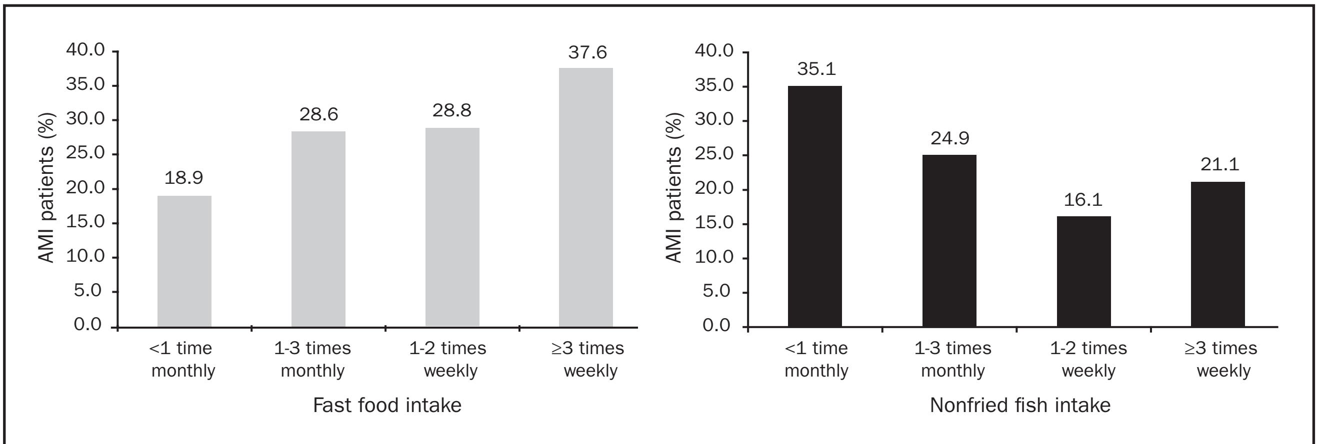

FIGURE 1. Proportion of patients with acute myocardial infarction (AMI) with an omega-3 index less than 4% within each category of fast food (left) and nonfried fish (right) consumption.

more frequent fish consumption was associated with progressively higher omega-3 indices. In contrast, compared with patients who ate fast food the least (less than once monthly), patients who ate fast food more frequently had a lower omega-3 index. Finally, use of omega-3 supplements was associated with a higher omega-3 index. With respect to identifying patients likely to have a low omega-3 index, the modified Poisson regression model, including the 7 significant, independent correlates of low omega-3 index, demonstrated acceptable calibration (Hosmer-Lemeshow *P*=.35) and good discrimination between patients with and without low omega-3 index (C statistic of 0.76; Table 2). Although the dose-response association between fast food and fish intake and the omega-3 index was less apparent in this model than in the linear regression model, consumption of fish was consistently associated with a lower risk of

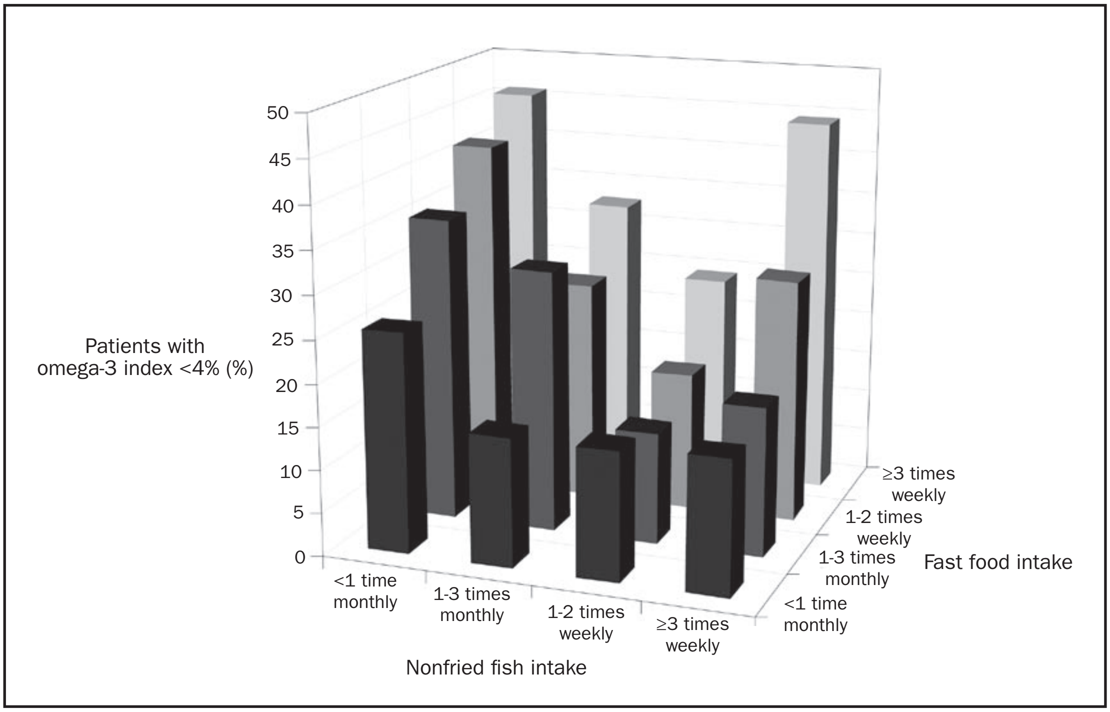

FIGURE 2. Proportion of patients with a low omega-3 index are presented within each combination of patient-reported fast food and nonfried fish intake.

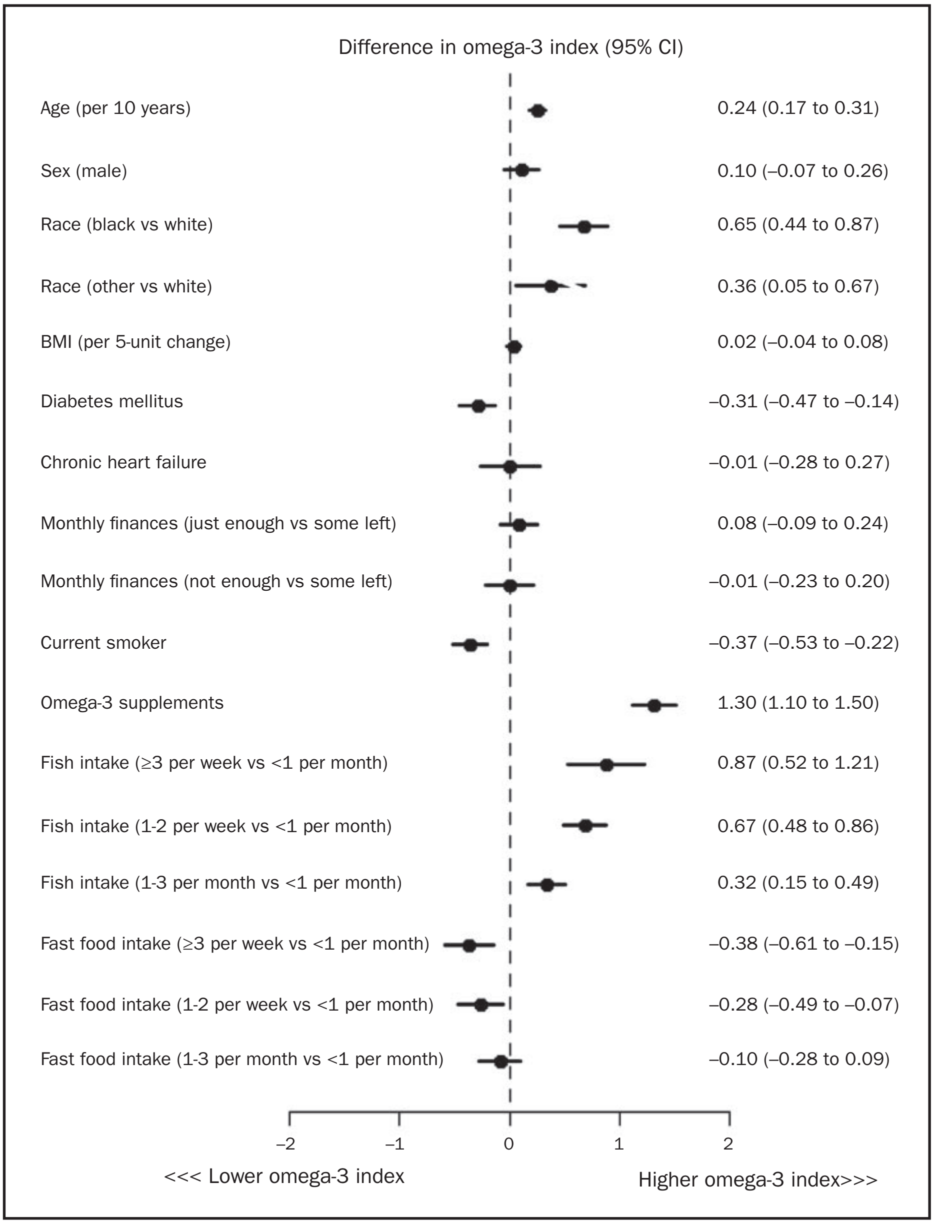

FIGURE 3. Forest plot of the multivariable adjusted association between patient and dietary characteristics and the omega-3 index. Values represent percentage points on the omega-3 index ± 95% confidence interval (CI). BMI = body mass index.

having a low omega-3 index, whereas consumption of fast food was independently associated with a higher risk of a low omega-3 index.

DISCUSSION

Although low levels of omega-3 fatty acids are a prognostically important and potentially modifiable risk factor for adverse cardiovascular events, to our knowledge the prevalence and predictors of low omega-3 levels have never been described in patients with AMI. In this multicenter population of AMI patients, we found that a low omega-3 index was common, occurring in more than 1 in 4 patients. Moreover, we found that readily assessable patient characteristics, including self-reported diet, were strongly associated with the omega-3 index, potentially enabling clinical identification of a cohort of AMI patients at high risk of low omega-3 levels for whom further testing and

TABLE 2. **Risk Model for Low Omega-3 Index**

	Relative risk (95% CI)	*P* value
Age	0.78 (0.72-0.84) per 10-y increase	<.001
Current smoking	1.63 (1.38-1.92)	<.001
Omega-3 supplement	0.38 (0.26-0.56)	<.001
Race		<.001
Black vs white	0.37 (0.27-0.51)	
Other vs white	0.81 (0.59-1.11)	
Nonfried fish intake		<.001
≥3 times weekly vs <1 time monthly	0.71 (0.46-1.09)	
1-2 times weekly vs <1 time monthly	0.53 (0.41-0.69)	
1-3 times monthly vs <1 time monthly	0.74 (0.62-0.88)	
History of diabetes	1.22 (1.03-1.45)	.02
Fast food intake		.04
≥3 times weekly vs <1 time monthly	1.40 (1.11-1.76)	
1-2 times weekly vs <1 time monthly	1.21 (0.94-1.55)	
1-3 times monthly vs <1 time monthly	1.26 (1.02-1.57)	

P values were generated based on F tests from the full modified Poisson regression model. CI = confidence interval.

treatment may be most beneficial. Importantly, several of these factors are potentially modifiable, including dietary patterns, smoking, and omega-3 supplementation, and could be targets for further counseling at discharge and in follow-up. These findings, particularly the association of a lower omega-3 index with greater fast food and lower fish intake, even after adjusting for omega-3 supplements, reinforce the importance of counseling patients to pursue a healthy, low-fat diet, as recommended in current guidelines, and to consider adding omega-3 supplements. The fact that our prediction model discriminated patients with and without a low omega-3 index strongly supports the validity of using these characteristics to identify patients who may benefit most from omega-3 testing and treatment.

Joint scientific statements from the American Heart Association and American College of Cardiology have strongly supported diets high in omega-3 fatty acids, advising fish consumption at least twice weekly and omega-3 supplements for patients with coronary artery disease.[12] A more recent study, however, found no benefit from low-dose omega-3 supplements in patients with a history of AMI.[13] The benefit of omega-3 fatty acids in that trial may have been attenuated by a number of factors, including the remote nature of many patients' myocardial infarction (median time from index myocardial infarction to enrollment was 3.7 years), the low dose of the study drug (376 mg of EPA and DHA), or the relatively high background intake of omega-3 fatty acids (130 mg/d compared with 32 mg/d in the United States).[14] Similarly, a randomized trial conducted by Rauch et al[15] failed to detect a difference in sudden cardiac death, all-cause mortality, or major adverse cardiovascular events between post-AMI patients randomized to 1 g of omega-3 fatty acids daily for 1 year compared with placebo. However, as the authors note, event rates were considerably lower than expected, perhaps reflecting temporal improvements in AMI care, including a greater provision of revascularization compared with prior studies, such as the GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca) Prevenzione study. These results should be interpreted in consideration of the fact that this study may have been underpowered to detect a smaller difference in the primary end point of sudden cardiac death in contemporary practice. Moreover, fish consumption increased substantially from baseline to completion of the study among patients randomized to both arms of the study, which could have reduced the effect of the intervention. Further studies are needed to understand whether selectively targeting omega-3 fatty acid supplements to patients with lower baseline omega-3 levels would yield greater clinical benefit. Our findings suggest that screening patients on the basis of routinely available clinical and dietary characteristics can identify those with low RBC omega-3 indices.

The current study supports and extends the prior literature on predictors of omega-3 levels. Long-term omega-3 intake is indicated by the EPA and DHA content in RBC membranes. Because RBCs have a lifespan of 120 days, the omega-3 index is a means of assessing long-term omega-3 intake. In this regard, the index is similar to hemoglobin A_{1c} as a time-averaged marker of blood glucose levels.[8] Previous studies have shown that demographic characteristics are associated with the omega-3 index. Consistent with reports by Sands et al[6] and Block et al,[7] older patients in our study had higher omega-3 indices, suggesting a possible survivor bias or differing lifestyle and diet behavior. This may reflect that older patients, who more frequently have prior diagnoses of coronary artery disease and often have a greater burden of coronary disease risk factors than younger AMI patients, have more frequently received diet and lifestyle counseling and have changed their behavior accordingly. The finding of an independent, dose-response association between fish intake and omega-3 index, as well as a strong association between fish oil supplementation and omega-3 index, is also consistent with prior literature from non-AMI populations.[6,7] We also found that omega-3 levels were associated with race. African American patients and patients of races other than white had significantly higher omega-3 levels than white patients. The reason for this racial difference is unclear and is particularly interesting given its persistence after controlling for socioeconomic status and for fish and fast food intake. Overall, our findings extend the omega-3 literature by testing these associations in high-risk AMI patients and identifying several potentially modifiable factors. Further studies are needed to better understand why older patients and patients of races other than white have higher omega-3 indices.

A new finding of our current research is that poor lifestyle choices, such as frequent fast food consumption, are inversely associated with the omega-3 index. This suggests that interventions to improve omega-3 levels should focus on patients' overall dietary and smoking behaviors. Moreover, *both* dietary supplements and consumption of fish rich in omega-3 fatty acids appear to be important in increasing omega-3 levels because both are independently associated with higher omega-3 levels, whereas unhealthy foods, such as fast food, also appear to be important. Future studies are needed to evaluate the extent to which omega-3 levels might be improved with comprehensive counseling that goes beyond simply advising use of omega-3 supplements and to determine whether such improvements are associated with better outcomes.

Several potential limitations should be considered when interpreting these data. Our assessments of fast food and nonfried fish intake were obtained by self-report, which could have resulted in misclassification of the exposure. In addition, the dietary assessment questions did not specifically define fast food or nonfried fish. Moreover, the emerging trend of offering healthier dietary options at fast food restaurants was not taken into account. However, misclassification introduced by these factors should have biased our findings toward the null, and the important associations we detected may be underestimates of the actual effect of these factors. Furthermore, although more detailed dietary assessments could have provided a more precise estimate of the association of dietary patterns with omega-3 levels, the simplicity of our questions supports use for screening in routine clinical practice. In addition, hospitals enrolling patients in the TRIUMPH registry were predominantly located in urban centers and did not include hospitals from the West Coast or rural areas. Accordingly, regional differences in food consumption patterns may limit the generalizability of these data to other regions of the United States. Finally, we were unable to validate our risk prediction model in a separate cohort, so further studies are needed to validate the performance of this model in a different AMI cohort. However, the primary purpose of building this model was not to create a validated bedside risk prediction model but to illustrate the potential of these variables to identify patients with a low omega-3 index in the TRIUMPH cohort.

CONCLUSION

Potentially modifiable factors, such as smoking, fast food intake, use of omega-3 supplements, and nonfried fish consumption, are independently associated with the omega-3 index in patients with AMI. Our findings suggest that a thorough patient history can identify patients who may benefit from intensive lifestyle modification and omega-3 supplementation. Further studies are needed to understand whether targeting these interventions to patients at high risk of low omega-3 levels results in greater clinical benefit after AMI than treating those less likely to have low omega-3 levels.

REFERENCES

1. Harris WS, Poston WC, Haddock CK. Tissue n-3 and n-6 fatty acids and risk for coronary heart disease events. *Atherosclerosis*. 2007;193(1):1-10.

2. Pottala JV, Garg S, Cohen BE, Whooley MA, Harris WS. Blood eicosapentaenoic and docosahexaenoic acids predict all-cause mortality in patients with stable coronary heart disease: the Heart and Soul study. *Circ Cardiovasc Qual Outcomes.* 2010;3(4):406-412.

3. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet*. 1999;354(9177):447-455.

4. Wang C, Harris WS, Chung M, et al. n-3 Fatty acids from fish or fish-oil supplements, but not alpha-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. *Am J Clin Nutr*. 2006;84(1):5-17.

5. Tavazzi L, Maggioni AP, Marchioli R, et al. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;372(9645):1223-1230.

6. Sands SA, Reid KJ, Windsor SL, Harris WS. The impact of age, body mass index, and fish intake on the EPA and DHA content of human erythrocytes. *Lipids*. 2005;40(4):343-347.

7. Block RC, Harris WS, Pottala JV. Determinants of blood cell omega-3 fatty acid content. *Open Biomark J.* 2008;1:11-16.

8. Harris WS, Von Schacky C. The Omega-3 Index: a new risk factor for death from coronary heart disease? *Prev Med*. 2004;39(1):212-220.

9. Block RC, Harris WS, Reid KJ, Sands SA, Spertus JA. EPA and DHA in blood cell membranes from acute coronary syndrome patients and controls. *Atherosclerosis*. 2008;197(2):821-828.

10. Zou G. A modified Poisson regression approach to prospective studies with binary data. *Am J Epidemiol*. 2004;159(7):702-706.

11. Hosmer DW, Lemeshow S. *Applied Logistic Regression*. New York, NY: John Wiley and Sons, Inc; 2000.

12. Kris-Etherton PM, Harris WS, Appel LJ. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation*. 2002;106(21): 2747-2757.

13. Kromhout D, Giltay EJ, Geleijnse JM. n-3 fatty acids and cardiovascular events after myocardial infarction. *N Engl J Med*. 2010;363(21):2015-2026.

14. Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes for Energy, Carbohydrates, Fiber, Fat, Protein and Amino Acids (Macronutrients).* Washington, DC: National Academies Press; 2005.

15. Rauch B, Schiele R, Schneider S, et al. OMEGA, a randomized, placebo-controlled trial to test the effect of highly purified omega-3 fatty acids on top of modern guideline-adjusted therapy after myocardial infarction. *Circulation*. 2010;122(21):2152-2159.