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Predicting Risk for Incident Heart Failure With Omega-3 Fatty Acids

From MESA

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ABSTRACT

OBJECTIVES The aim of this study was to determine if plasma eicosapentaenoic acid (EPA) abundance (%EPA) is associated with reduced hazard for primary heart failure (HF) events in the MESA (Multi-Ethnic Study of Atherosclerosis) trial.

BACKGROUND Clinical trials suggest that omega-3 polyunsaturated fatty acids (ω3 PUFAs) prevent sudden death in coronary heart disease and HF, but this is controversial. In mice, the authors demonstrated that the ω3 PUFA EPA prevents contractile dysfunction and fibrosis in an HF model, but whether this extends to humans is unclear.

METHODS In the MESA cohort, the authors tested if plasma phospholipid EPA predicts primary HF incidence, including HF with reduced ejection fraction (EF) (EF <45%) and HF with preserved EF (EF ≥45%) using Cox proportional hazards modeling.

RESULTS A total of 6,562 participants 45 to 84 years of age had EPA measured at baseline (1,794 black, 794 Chinese, 1,442 Hispanic, and 2,532 white; 52% women). Over a median follow-up period of 13.0 years, 292 HF events occurred: 128 HF with reduced EF, 110 HF with preserved EF, and 54 with unknown EF status. %EPA in HF-free participants was 0.76% (0.75% to 0.77%) but was lower in participants with HF at 0.69% (0.64% to 0.74%) ($p = 0.005$). Log %EPA was associated with lower HF incidence (hazard ratio: 0.73 [95% confidence interval: 0.60 to 0.91] per log-unit difference in %EPA; $p = 0.001$). Adjusting for age, sex, race, body mass index, smoking, diabetes mellitus, blood pressure, lipids and lipid-lowering drugs, albuminuria, and the lead fatty acid for each cluster did not change this relationship. Sensitivity analyses showed no dependence on HF type.

CONCLUSIONS Higher plasma EPA was significantly associated with reduced risk for HF, with both reduced and preserved EF. (Multi-Ethnic Study of Atherosclerosis [MESA]; NCT00005487) (J Am Coll Cardiol HF 2019;■:■-■) © 2019 by the American College of Cardiology Foundation.

Heart failure (HF) is a leading cause of hospitalization in the United States (1). Its incidence increases with age and is higher in men than women (2,3). Currently, 26 million patients globally have HF, with >1 million annual hospitalizations in the United States and Europe, accounting for 1% to 2% of total health expenditures (4,5).

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ABBREVIATIONS AND ACRONYMS

AA = arachidonic acid

CHD = coronary heart disease

CI = confidence interval

DHA = docosahexaenoic acid

DPA = docosapentaenoic acid

EPA = eicosapentaenoic acid

FA = fatty acid

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

HR = hazard ratio

MI = myocardial infarction

ω3 PUFA = omega-3 polyunsaturated fatty acid

Clinically, HF manifests in 2 modes defined by ventricular function: HF with reduced ejection fraction (HFrEF) (ejection fraction ≤45%) and HF with preserved ejection fraction (HFpEF) (ejection fraction >45%) (6). Half of all current diagnoses are HFpEF (7), and the incidence rate of HFpEF has surpassed that of HFrEF (8). Survival for HFpEF is marginally higher than for HFrEF but is only 35% at 5 years (6,9). Generally, patients with HFpEF are older, female, and more likely to have hypertension, renal disease, atrial fibrillation, and/or pulmonary disease (10). Unfortunately, standard pharmacological therapies for HFrEF show no efficacy in HFpEF (6).

In humans, the omega-3 polyunsaturated fatty acids (ω3 PUFAs) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are important regulators of cardiovascular health (11-13). Several clinical trials have demonstrated that ω3 PUFAs confer a survival benefit in coronary heart disease (CHD) by preventing sudden death (14-18), and clinical trials have indicated ω3 PUFAs might improve outcomes in patients with HF (19-23). Despite these potential benefits, the use of ω3 PUFAs in patients with CHD and HF remains controversial. A recent meta-analysis involving more than 77,000 participants reported no evidence supporting supplemental ω3 PUFAs in patients with CHD (24) but did not evaluate either HF as an endpoint or studies using doses sufficient to achieve protective concentrations in animals (25) or humans (26,27).

We have shown that dietary ω3 PUFAs at supraphysiological levels preserve left ventricular function and prevent interstitial fibrosis in a mouse model of pressure overload-induced HF (28). Follow-up with a diet designed to achieve ω3 PUFA levels closer to those achieved in patients treated with high-dose prescription omega-3 acid ethyl esters showed that only EPA was protective (13,25).

MESA (Multi-Ethnic Study of Atherosclerosis) is a longitudinal cohort study African American, Hispanic, Asian, and white adults in the United States. Because of its population characteristics, baseline plasma phospholipid fatty acid (FA) measurements, and HF outcomes, we used this cohort to determine whether higher levels of EPA predict reduced risk for HF. Our goal was to test the following hypotheses: 1) in humans, plasma %EPA is inversely associated with all HF incidence; 2) high plasma %EPA is inversely associated with incidence of HFpEF; and 3) the inverse association of high plasma %EPA with HF incidence is unique among ω3 PUFAs.

METHODS

STUDY PARTICIPANTS. MESA is a prospective, population-based study designed to investigate the prevalence, risk factors, and progression of subclinical cardiovascular disease in a multiethnic cohort in the United States (29,30). Its design, population, and methods have been described (29). Between July 2000 and July 2002, 6,814 participants 45 to 84 years of age were recruited from 6 U.S. communities. MESA was approved by the Institutional Review Boards of all participating study sites. All participants gave informed consent.

PLASMA FA MEASUREMENTS. Fasting blood was drawn, and serum and ethylenediaminetetraacetic acid anticoagulant tubes were collected and processed at the first (baseline) study visit using a standardized protocol as previously described (31).

HF EVENTS. Participants completed study visits approximately every other year after the baseline examination (32,33). HF events were adjudicated by physicians on the basis of medical records (34). We used ejection fraction reported in the hospital record to define HFrEF (<45%) versus HFpEF (≥45%).

STATISTICAL ANALYSES. Descriptive statistics were used to compare the baseline characteristics of participants (**Table 1**). All covariates were measured at the baseline visit. Only the first HF event was accounted for in our analyses, and each person's data were included only once. Four ejection fraction status groups exist in the MESA dataset: 1) subjects free of HF during the study; 2) those with HFrEF; 3) those with HFpEF; and 4) those with HF but unmeasured ejection fraction. For continuous variable comparisons, the 2-sample Student's t test was used. For categorical variables, the chi-square test was used (Online Table 1). Statistical significance was defined as $\alpha < 0.05$.

Some values of heptadecanoic acid were nonphysiological (>1.0%) and likely resulted from methylation artifacts. FA levels were log-transformed to improve normality and clustered to identify groups of FAs with high collinearity. For adjusters, the FA with the largest within-cluster correlation was identified as the "lead" FA and used as an adjuster (Online Table 2). This approach maximized independence and interpretability. %EPA was the lead member of a cluster of 3 PUFAs that also included DHA and ω3 docosapentaenoic acid (DPA).

Participants who did not develop HF were censored at the last attended follow-up examination. Cox proportional hazard modeling was used to estimate hazard ratios (HRs) associated with continuous

TABLE 1 Descriptive Statistics for Demographic Variables By Heart Failure Status

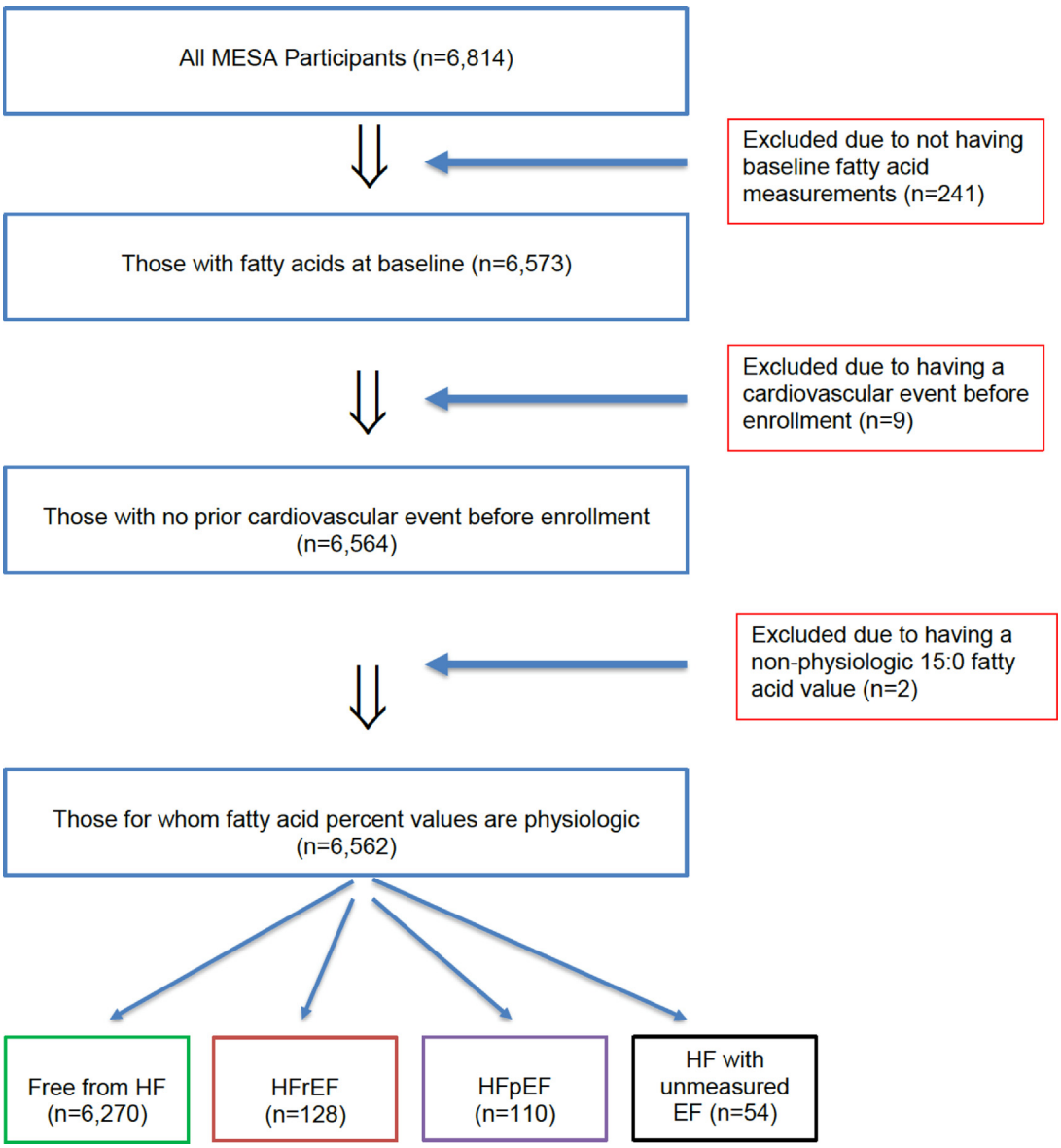
			HF Subtypes Defined by Ejection Fraction Status		
	No HF* (n = 6,270)	**All HF** (n = 292)	**HFrEF** (n = 128)	**HFpEF** (n = 110)	**HF_{unk}** (n = 54)
Age (yrs)	62 ± 10	69 ± 9†	67 ± 9†	69 ± 8†	70 ± 9†
BMI (kg/m^2)	28.3 ± 5.4	29.8 ± 5.9†	29.4 ± 5.4†	29.6 ± 5.6†	31.0 ± 7.4†
LDL cholesterol (mg/dl)	117 ± 31	114 ± 33	114 ± 34	112 ± 31	114 ± 33
Non-HDL cholesterol (mg/dl)	143 ± 35.88	141 ± 36	142 ± 37	139 ± 35	142 ± 34
HDL cholesterol (mg/dl)	51.1 ± 14.9	48.6 ± 13.9†	47.6 ± 12.8†	49.9 ± 14.1	48.6 ± 15.8
Triglycerides (mg/dl)	131 ± 88	142 ± 113	136 ± 78	146 ± 154	145 ± 84
eGFR (ml/min/1.73 m^2)	78.4 ± 16.1	71.9 ± 18.5†	71.4 ± 18.2†	72.6 ± 18.4†	71.7 ± 19.3†
Male	46.6	58.9†	69.5†	49.1	53.7
Site					
WFU	15.4	24.0	20.3	30.9	18.5
COL	16.0	17.5	17.2	16.4	20.4
JHU	15.7	12.0	13.3	8.2	16.7
UMN	15.7	18.5	21.9	18.2	11.1
NWU	17.5	12.7	14.8	10.9	11.1
UCLA	19.7	15.4	12.5	15.5	22.2
Race/ethnicity					
White	38.5	39.7	37.5	46.4	31.5
Chinese American	12.3	7.2	3.1	10.9	9.3
Black	27.1	31.9	39.8	22.7	31.5
Hispanic	22.0	21.2	19.5	20.0	27.8
Hypertension	43.5	70.6†	68.0†	72.7†	72.2†
ACE inhibitor	12.2	29.2†	25.8†	32.1†	31.5†
Alpha-blocker	3.8	6.2	7.8†	4.6	5.6
Beta-blocker	9.4	13.1	12.5	13.8	13
Loop diuretic	1.7	6.9†	7.0†	4.6†	11.1†
Any lipid-lowering medication	16	18.6	21.9	15.6	16.7
Statin	14.7	17.8	20.3	14.6	18.5
Urine					
Albuminuria normal	91.2	72.7†	72.4†	72.5†	73.6†
Microalbuminuria	7.6	20.4	22.1	19.3	18.9
Macroalbuminuria	1.2	6.9	5.5	8.3	7.6
Smoking status					
Never	90.4	90.2	83.6†	90	88.9
Former	7.3	7.4	11.7	5.5	9.3
Current	1.8	1.9	3.9	4.6	1.9
Diabetes					
Normal	74.5	57.9†	60.9†	54.6†	57.4†
Impaired fasting glycemia	13.9	13.4	14.8	14.6	7.4
Untreated diabetes	2.5	5.1	4.7	4.6	7.4
Treated diabetes	9.1	23.6	19.5	26.4	27.8
EPA (mass), %	0.76 (0.75–0.77)	0.69 (0.64–0.74)†	0.68 (0.61–0.76)†	0.69 (0.61–0.76)	0.71 (0.60–0.84)
DHA (mass), %	3.75 (3.71–3.78)	3.50 (3.35–3.66)†	3.45 (3.21–3.70)†	3.44 (3.21–3.69)†	3.76 (3.39–4.17)
EPA + DHA (mass), %	4.58 (4.54–4.63)	4.25 (4.06–4.45)†	4.18 (3.89–4.5)†	4.19 (3.9–4.5)†	4.54 (4.08–5.05)

Values are mean ± SD, %, or median (interquartile range). *Free from heart failure. †Statistically significant ($p < 0.05$) difference between the category and those in the no HF group.

ACE = angiotensin-converting enzyme; BMI = body mass index; COL = Columbia; DHA = docosahexaenoic acid; eGFR = estimated glomerular filtration rate; EPA = eicosapentaenoic acid; HDL = high-density lipoprotein; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HF_{unk} = heart failure with ejection fraction unmeasured; JHU = Johns Hopkins University; LDL = low-density lipoprotein; NWU = Northwestern University; UCLA = University of California, Los Angeles; UMN = University of Minnesota; WFU = Wake Forest University.

plasma phospholipid %EPA on a log scale. We developed hazard models in blocks by including %EPA first as a univariate predictor; second after adjustment for age, sex, race, and study center; third after adjusting for other lead FAs; and fourth after full adjustment for all factors considered, including body mass index, blood pressure (systolic), pulse pressure, heart rate, fasting glucose, non-high-density lipoprotein cholesterol, fasting triglycerides, diabetes mellitus status, use of hypertension medication, use of oral

FIGURE 1 Derivation of the Data Analysis Cohort After Applying Exclusion Criteria



EF = ejection fraction; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; MESA = Multi-Ethnic Study of Atherosclerosis.

hypoglycemic medication, smoking status, and albuminuria status. In the final 2 blocks, we used backward stepwise elimination, using the likelihood ratio method. Assumptions for proportional hazard were confirmed using time-dependent covariates approach. Consideration was given to the pattern of missing values when deciding which adjusters would be used in the models. We conducted subgroup analyses on outcomes by evaluating when only participants with HFpEF or only those with HFrEF were included. Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina), SPSS version 24 (IBM, Armonk, New York), and JMP version 13.2.1 (SAS Institute).

RESULTS

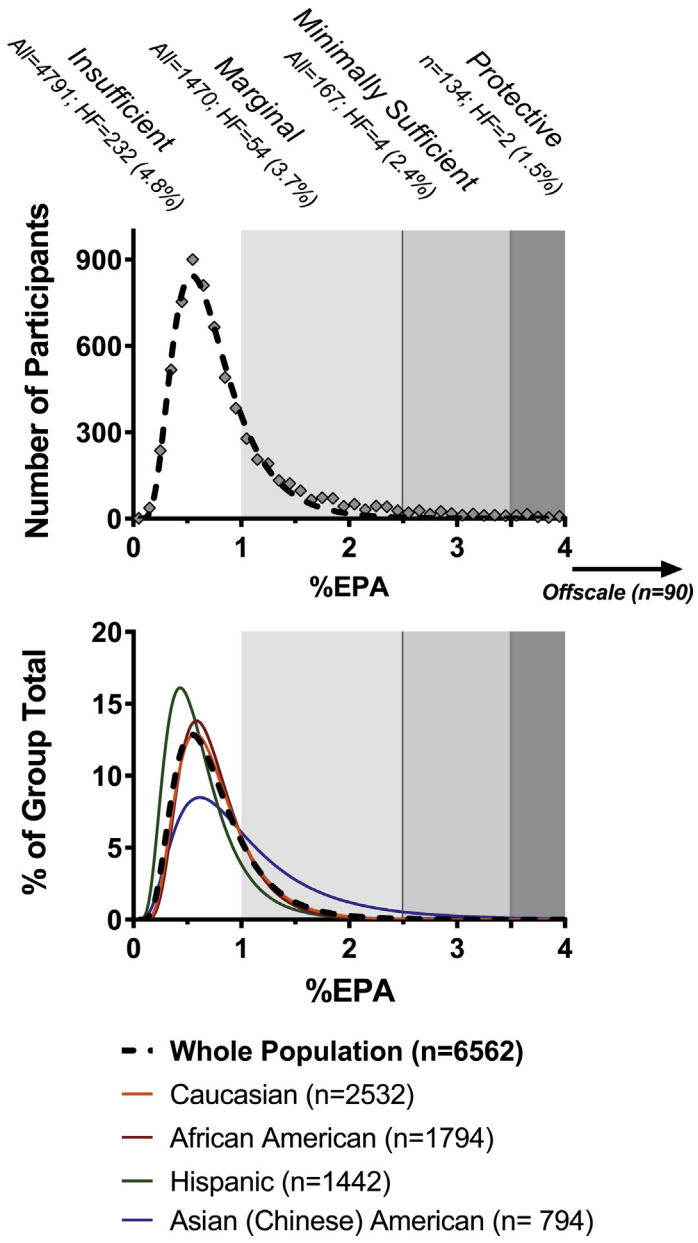
PARTICIPANT BASELINE DEMOGRAPHICS. The inclusion and exclusion of study participants for our analysis are outlined in Figure 1. Of the 6,814 total

MESA participants, 6,562 (96%) were included. During a median follow-up period of 4,774 days (13.0 years), 292 participants had positive HF evaluations, including 128 with HFrEF, 110 with HFpEF, and 54 with unknown ejection fraction status. Baseline descriptive characteristics for each group are reported in **Table 1**. Details of post hoc tests are in Online Table 1, and details for differences among ethnic groups are in Online Table 2. HF-free participants had higher baseline plasma phospholipid %EPA, %DHA, and %EPA plus %DHA. Age, body mass index, diabetes mellitus, glomerular filtration rate, hypertension, use of a loop diuretic agent, urine microalbuminuria, and use of an angiotensin-converting enzyme inhibitor were significantly different ($p < 0.05$) between participants with and those without HF.

PARTICIPANT PLASMA PHOSPHOLIPID EPA LEVELS. We first evaluated the distribution of %EPA (**Figure 2A**, Online Table 3). Median %EPA was 0.70% for all MESA participants. Participant %EPA status was defined as insufficient (<1.0%), marginal (≥1.0% and ≤2.5%), or sufficient (>2.5%) to prevent HF on the basis of prior definition of EPA levels that prevent HF in animal models (13); 73.1% of participants had insufficient plasma EPA, 2.4% had marginal levels, and 4.5% had sufficient levels (**Figure 2A**). Hispanic participants had the lowest %EPA levels, with only 1.4% having sufficient EPA (**Figure 2B**), followed by black (4.4%), white (4.9%), and finally Chinese (9.8%) participants. Variance among Chinese participants was greater than it was among the other 3 races, which were each nearly identical. We evaluated the distribution of other PUFAs (Online Figure 1). Plasma %EPA was highly skewed, proportion ω3 DPA and %DHA were moderately skewed, and proportion arachidonic acid (AA) was least skewed; all fit better to a lognormal distribution than a normal distribution (Online Table 3).

FA CLUSTERING. Twenty-five FAs were measured in all participants. Strong collinearities existed among %FA, making it difficult to distinguish between direct and replacement effects on FA levels. Plasma %EPA and %DHA were strongly correlated because they co-occur in food products; both typically replace other PUFAs such as AA, hence increased %EPA can also report the replacement of AA. Eight FA clusters were identified (Online Table 4), explaining 63% of the total variability. The marine ω3 PUFAs clustered together with EPA as the most representative. The remaining PUFAs clustered together with AA as the lead PUFA. Lead FAs in each cluster were used as adjusters in developing hazard models, which allowed us to preserve interpretability and avoid collinearity.

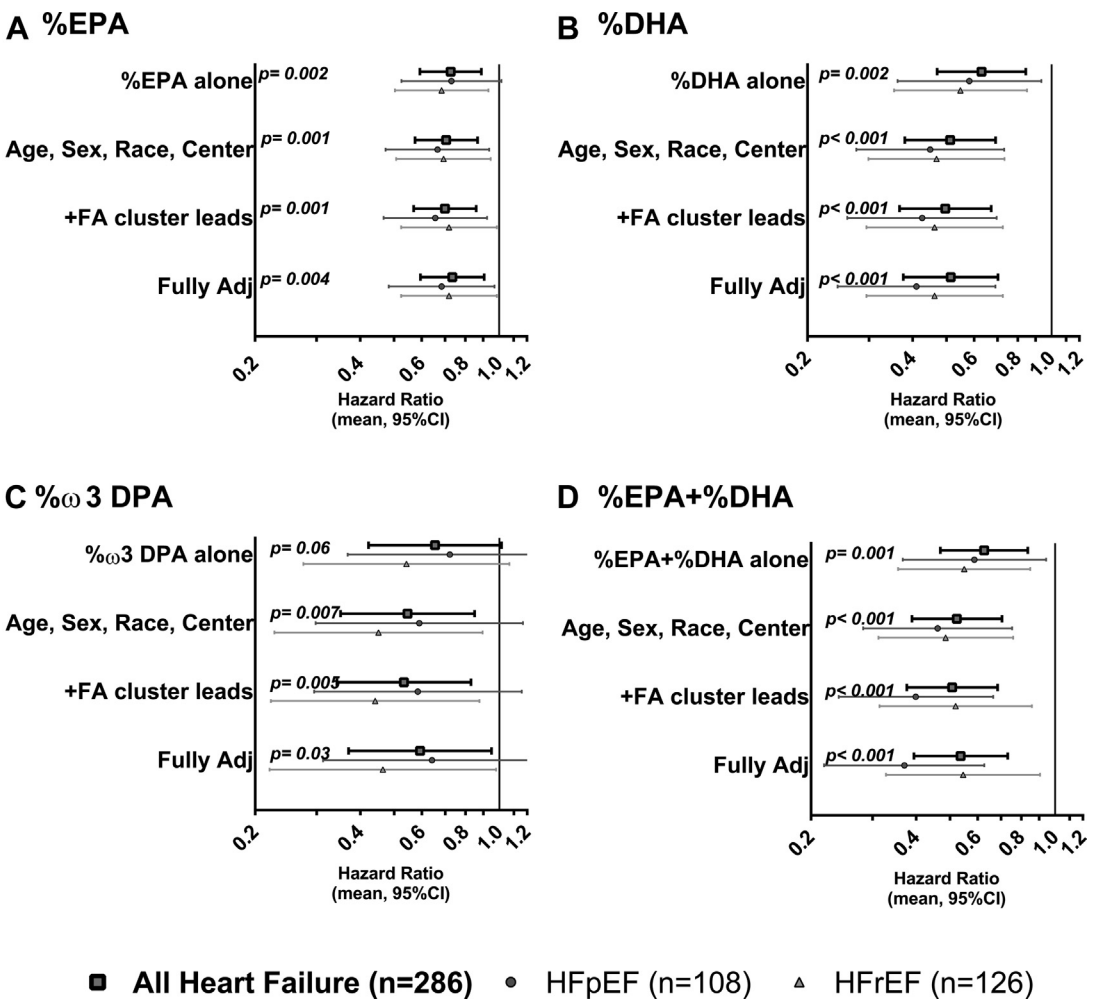
FIGURE 2 Distribution of Percentage Eicosapentaenoic Acid Among MESA Participants and Their Grouping by Eicosapentaenoic Acid Sufficiency on the Basis of Eclov et al. (25)



(Top) Total population. **(Bottom)** By race/ethnicity. See Online Figure 1 for distributions of other omega-3 polyunsaturated fatty acids. EPA = eicosapentaenoic acid; HF = heart failure.

PROPORTIONAL HAZARD MODELS FOR EPA AND OTHER ω3 PUFAs. We tested for associations of EPA with HF risk using a 4-step approach: 1) testing a

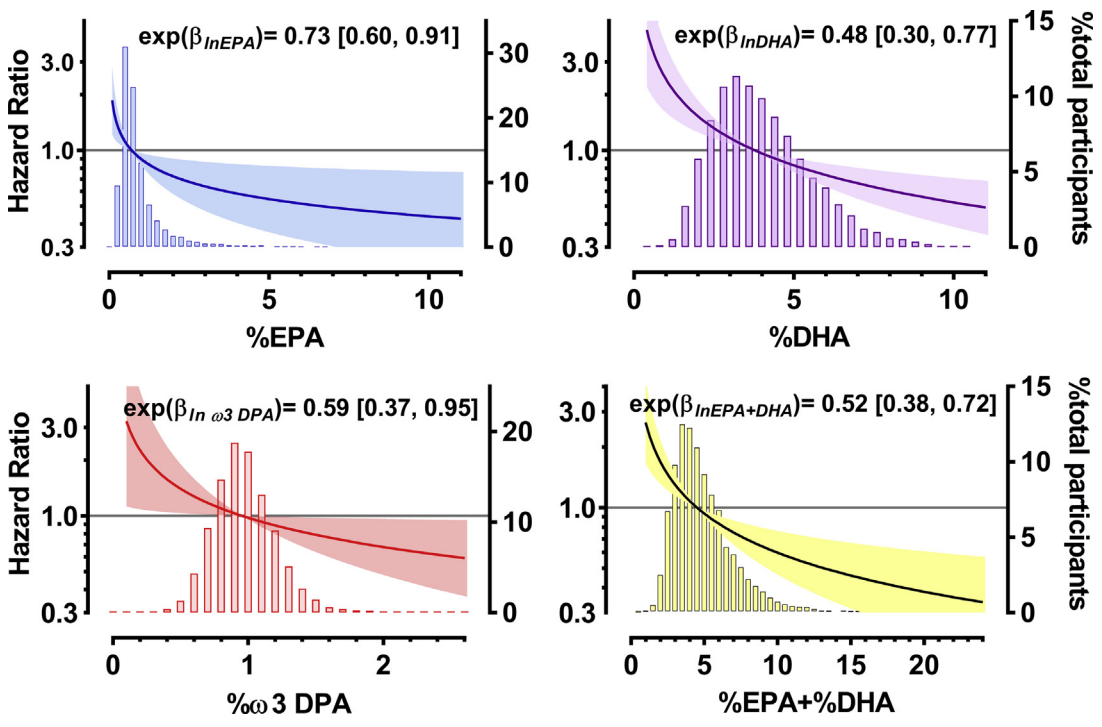
FIGURE 3 Hazard Ratios for Percentage Eicosapentaenoic Acid and Other Marine Omega-3 Polyunsaturated Fatty Acids by Adjustment and Sensitivity



The hazard ratio (mean; 95% confidence interval [CI]) for models of proportion eicosapentaenoic acid (EPA) **(A)**, proportion docosahexaenoic acid (DHA) **(B)**, proportion ω3 docosapentaenoic acid (DPA) **(C)**, and %EPA plus %DHA **(D)** with successive blocks of adjustments are shown in bold compared with sensitivity analyses including participants with heart failure with preserved ejection fraction (HFpEF) **(circle)** and those with heart failure with reduced ejection fraction (HFrEF) **(triangle)**. %EPA and age, sex, race, and study center (ASRC) were entered into all models. For fatty acid (FA) cluster leads, see Online Table 3. Lead FAs were selected backward using the likelihood ratio method. in the fully adjusted model, %EPA, ASRC, and behenic acid were entered into the model, and remaining adjusters subjected using the same method. See "Results" section for adjusters. Online Table 5 lists hazard ratios (95% CIs). Missing values in some adjustors reduced the number of events.

univariate association; 2) adjusting for age, sex, race, and study center; 3) adjusting for other lead FAs; and 4) adjusting for other known risk factors. This approach allowed us to evaluate the independence and robustness of associations. At each step we performed sensitivity analyses in which we included only participants with HFrEF or HFpEF in order to evaluate the associations by HF type. In step 1, high plasma phospholipid %EPA at visit 1 was associated with reduced HF risk, regardless of HF type. **Figure 3A** shows the HR (95% confidence interval [CI]) from proportional hazard models for log %EPA with each successive adjustment block. Sensitivity analyses demonstrated that the association was not dependent on HF type. For step 2, we adjusted for age, sex, race, and study center. %EPA remained significantly associated with risk, without any change in the strength of association, indicating

FIGURE 4 **Marine Omega-3 Polyunsaturated Fatty Acids Predict Hazards For All Heart Failure**



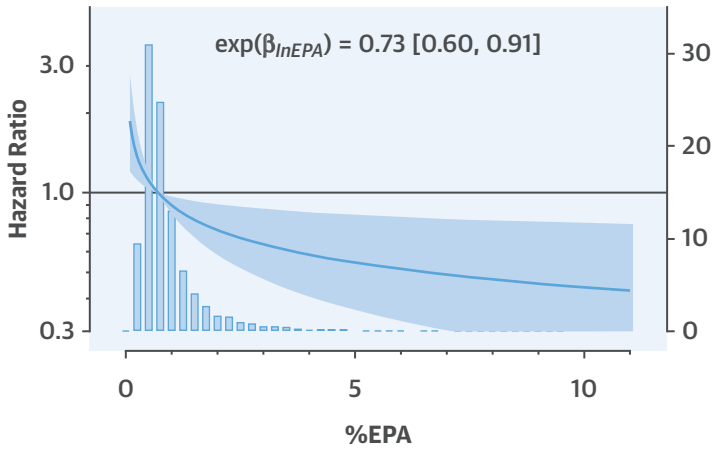
The relationships between eicosapentaenoic acid (EPA) **(blue)**, docosahexaenoic acid (DHA) **(purple)**, ω3 docosapentaenoic acid (DPA) **(red)**, and the %EPA plus DHA **(yellow)** are plotted in relationship to the relative risk (left y-axis) for heart failure, referencing median values. The polyunsaturated fatty acid distribution across the participant population is plotted (right y-axis) for comparison. Note axis scales.

that age, sex, race, and study center did not mediate the association. Each successive model included these adjusters. In step 3, FA cluster leads were entered, and backward stepwise selection eliminated those unrelated to risk. Only proportion behenic acid was selected, but it did not change the association of %EPA. In step 4, all other HF-related adjusters were entered into the model and subjected to backward selection: body mass index, heart rate, fasting glucose, use of hypertensive medication, smoking status, pulse pressure, and urinary albuminuria status were selected; systolic blood pressure, non-high-density lipoprotein cholesterol, log triglycerides, and diabetes mellitus status were not selected. The final adjusted HR was a 0.73-fold reduction (95% CI: 0.60 to 0.91; $p = 0.004$) in risk per unit increase in log %EPA, which was not dependent on HF type. In summary, %EPA was inversely related to HF risk, the relationship was robust and independent to adjustment, and this association was present among all participants, including those with HFrEF and those with HFpEF (see Online Table 5).

To evaluate associations with other ω3 PUFAs, we used the same 4-step approach as for %EPA, with sensitivity analyses. As univariate predictors, %DHA and %EPA plus %DHA were both associated with reduced risk for HF; proportion ω3 DPA was not. The HRs (95% CIs) and sensitivity analyses for each are shown in **Figures 3B to 3D** (see also Online Table 5). After step 2, proportion ω3 DPA became significant. Adjustment in step 3 again showed that only the cluster represented by proportion behenic acid was significantly associated, but again, the ω3-PUFA HRs were unchanged and independent. Final adjustment not did not substantially alter the HRs, indicating that other proportion ω3 PUFAs are also significant and independent predictors of HF risk. The final adjusted HR for %DHA was 0.51 (95% CI: 0.38 to 0.70; $p < 0.0001$); for proportion ω3 DPA, it was 0.59 (95% CI: 0.37 to 0.95; $p = 0.03$); and for %EPA plus %DHA, it was 0.54 (95% CI: 0.39 to 0.73). Across all ω3 PUFAs,

CENTRAL ILLUSTRATION **Eicosapentaenoic Acid Predict Hazard for All Heart Failure**

Higher EPA Levels are Associated with Reduced HF Incidence, But Most Participants have Levels Associated with High Risk



Block, R.C. et al. J Am Coll Cardiol HF. 2019;■(■):■-■.

Eicosapentaenoic acid (EPA) as a percent of total plasma phospholipid fatty acids is plotted in relationship to relative risk for heart failure (HF) (left y-axis), referencing media %EPA. The distribution of polyunsaturated fatty acids across the participant population is plotted (right y-axis) for comparison.

sensitivity analyses showed no substantial differences when only participants with HFrEF or only those with HFpEF were included. Because HRs derived from log-transformed predictors are difficult to interpret, **Figure 4** plots hazards for all HF relative to median across the entire observed PUFA ranges.

DISCUSSION

Here we show in the MESA study that high plasma phospholipid EPA is associated with reduced risk for all HF, including both HFrEF and HFpEF **Central Illustration**, confirming our primary hypothesis. In addition, we found that high plasma DHA, ω3 DPA, and EPA plus DHA are similarly associated, indicating that unlike mice, humans may benefit from marine ω3 PUFAs generally. The findings were true in univariate analysis; after adjusting for age, sex, race, and study center; after accounting for replacement effects of other FAs; and after further selective adjustment for covariate factors known to predict HF. Finally, the protective associations remained evident after sensitivity analyses in which only HFpEF or only HFrEF participants were included.

Previous clinical trials have demonstrated that combined EPA and DHA administration improve HF outcomes. The CHS (Cardiovascular Health Study), a prospective cohort study from 1992 to 2006, also found an association between plasma phospholipid % EPA and a reduction in incident HF, 50% lower in the highest versus the lowest quartile (18). In our analysis, we estimated a more modest contrast, likely reflective of other care-related improvements since the CHS report.

In GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Heart Failure), low-dose ω3 PUFAs (0.84 g/day) reduced hazards for total mortality (HR: 0.91; 95% CI: 0.83 to 0.99) and HF hospitalization when added to standard therapy (19). Red blood cell EPA plus DHA was measured in a subset of participants, and an increase from 4.8% to 6.7% was found (35), indicating that the participants did not achieve the proposed cardioprotective level of 8.0% (36,37). The final erythrocyte EPA was 1.2%, corresponding to 0.9% plasma phospholipid EPA (38), indicating that the dose did not achieve sufficient levels. In another smaller HF trial in patients with left ventricular insufficiency, combined EPA and DHA (1.7 g/day) improved systolic

and diastolic dysfunction (20). We estimate that the dose would increase red blood cell %EPA plus %DHA from the Italian average of 4.7% (39) to 6.7% in 3 months, again still not reaching optimal levels. Furthermore, in OMEGA-REMODEL (Effect of High Dose Fish Oil Supplementation After Recent Heart Attack Using Magnetic Resonance Imaging), high-dose ω3 PUFA therapy (3.4 g/day) for 6 months post-myocardial infarction (MI) reduced infarct size, improved ventricular systolic function, and reduced noninfarct myocardial fibrosis (26). Treatment increased %EPA plus %DHA from 5.5 ± 1.8% to approximately 10%. A number of smaller studies also showed that ω3 PUFA therapy improves systolic and diastolic function (21,22). In each study, the beneficial effects of ω3 PUFAs were observed in patients with HFrEF. Therefore, evidence from 1 major HF trial (GISSI-HF), several smaller trials, and 1 trial examining post-MI remodeling all suggest that ω3 PUFAs prevent HF even when optimal tissue enrichment is not achieved.

We found that high plasma EPA is associated with reduced risk for HFpEF, a condition for which there are currently no U.S. Food and Drug Administration-approved therapies that reduce mortality or hospitalizations. Our prior studies in mice indicated a concentration-dependent effect for EPA to prevent pathological remodeling, preserving diastolic function and preventing interstitial fibrosis, in a pressure-overload model of HF that resembles HFpEF remodeling (13,25,28). We did not find strong evidence for the EPA cardioprotective threshold that exists in animals, but only 301 participants had %EPA levels with minimal sufficiency or greater (>2.5%), with only 6 HF events among them. To our knowledge this is the first clinical study to suggest a specific benefit for EPA or ω3 PUFAs in HFpEF.

Recently, the VITAL (Vitamin D and Omega-3 Trial) study reported that low-dose ω3 PUFAs failed to prevent composite cardiovascular death, nonfatal MI, and stroke over 5-year follow-up; a secondary outcome suggested a reduced risk for MI (40). VITAL was preceded by a meta-analysis suggesting that low-dose ω3 PUFAs do not prevent CHD (24). Neither study directly reported HF outcomes. These results stand in contrast to results from REDUCE-IT (Reduction of Cardiovascular Events With Icosapent Ethyl-Intervention Trial), which demonstrated that high-dose icosapent ethyl (an EPA precursor) at 4 g/day produced a 25% reduction in the risk for composite cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, and unstable angina (27). These results are supported by the results of OMEGA-REMODEL, which indicate that high-dose ω3 PUFAs (4 g/day) prevent post-MI remodeling (26). Consistently, subjects achieving the highest red blood cell %EPA plus %DHA levels were associated with the greatest treatment benefits (26). These newer trials examining the effects of high-dose ω3-PUFA intake suggest a concentration-dependent cardioprotective effect as previously suggested (13). REDUCE-IT reported no difference in HF incidence (4.1% with placebo vs. 4.3% with EPA) (27), but the HF incidence was modest and could not exclude a large range of effects (+17% to −23% risk). MESA had a broader age range, a longer follow-up period, and broader diversity. Furthermore, REDUCE-IT included only subjects with hypertriglyceridemia on statin therapy, with known cardiovascular disease or equivalents (27).

The overall HF rate observed in MESA was similar to those seen in other observational cohorts. HF occurred in 4.4% of PREVEND (Prevention of Renal and Vascular End-Stage Disease) participants during a median of 11.5 years (41), similar to 4.5% incidence in 13 years for MESA. The Physicians' Health Study I (1982 to 2008) reported a lifetime HF risk of 13.8% over a much longer 22.4 years (42).

CLINICAL IMPLICATIONS. We propose 3 clinical implications of our findings. First, on the basis of prior work in animals and related findings in humans, it is reasonable to expect this finding to translate to ω3 PUFA intervention. In the interventional setting, each unit change in log %DHA would yield a greater risk reduction than each unit change in log %EPA, but this does not take into account that in the typical interventional setting, each gram per day of EPA proportionally increases %EPA more than each gram per day of DHA increases %DHA. Each gram per day of DHA increases the absolute erythrocyte %DHA more than EPA raises %EPA. However, when considered on the proportional or log scale, each gram per day of EPA is more effective than each gram per day of DHA (43). The latter expectation conforms better to our analysis, but more studies are required to determine which, if any, ω3 PUFA is superior. Second, patients with HF, regardless of ejection fraction status, would benefit from safe, effective therapies, with no adverse interactions with current medications, and ω3 PUFAs appear to meet these criteria (44). Third, the

differences among ethnicities in ω3 PUFAs could explain a component of HF health disparities (45).

STUDY STRENGTHS. Strengths of this study include a large sample size, ethnic diversity, long duration of follow-up, modern medical therapy. and accounting for the competing effects of other FAs. No published studies exist in which a clinical trial of ω3 PUFAs in primary prevention of HF incidence has occurred (46), making this observation relevant.

STUDY LIMITATIONS. Limitations include a population with few patients having HFpEF and few participants with protective levels of EPA, by our animal models. In addition, only baseline data were available, and we could not account for changes in ω3 PUFAs and other risk factors. We consider this study to strongly determine that a benefit of EPA exists but insufficient to determine whether a threshold for %EPA exists near 3%. In our discussion, we used red blood cell and plasma phospholipid abundance somewhat interchangeably. The analytic answers are valid, but the enrichment of red blood cells is 0.71-fold lower for EPA and 1.13-fold higher for DHA (38).

CONCLUSIONS

We show here that plasma phospholipid %EPA is inversely associated with all HF incidence, both HFpEF and HFrEF. In contrast to findings in animals, the inverse association was also found for other ω3 PUFAs and was strongest for combined %EPA plus % DHA.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: This study is the first to determine the ability of plasma phospholipid %EPA to predict HF outcomes in white, African American, Asian, and Hispanic populations. Given that plasma %EPA can be increased by the ingestion of seafood or fish oil capsules while being safe and relatively inexpensive, this preventive measure is limited in the response it produces but is quite feasible.

TRANSLATIONAL OUTLOOK 1: The study provides evidence for measuring plasma phospholipid ω3 PUFAs as an approach to estimating HF risk in adults.

TRANSLATIONAL OUTLOOK 2: A follow-up study should be considered that includes participants with higher levels of %EPA. Such a study would be better powered to detect a threshold for protective effect at high (%EPA >4.0%) levels.

TRANSLATIONAL OUTLOOK 3: An interventional study should be considered that includes a dose of EPA or EPA derivative capable of increasing %EPA from 0.70% to >4.0%.

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APPENDIX **For supplemental tables and a figure, please see the online version of this paper.**