

Dietary Fish and ω -3 Fatty Acid Consumption and Heart Rate Variability in US Adults

Dariush Mozaffarian, MD, DrPH; Phyllis K. Stein, PhD;
Ronald J. Prineas, MD, PhD; David S. Siscovick, MD, MPH

Background—Fish and ω -3 fatty acid consumption reduce risk of cardiac death, but mechanisms are not well established. Heart rate variability (HRV) predicts cardiac death and reflects specific electrophysiological pathways and influences. We hypothesized that habitual consumption of fish and marine ω -3 fatty acids would be associated with more favorable HRV, elucidating electrophysiological influences and supporting effects on clinical risk.

Methods and Results—In a population-based cohort of older US adults, we evaluated cross-sectional associations of usual dietary fish and ω -3 consumption during the prior year and ECG-derived ($n=4263$) and 24-hour Holter monitor-derived ($n=1152$) HRV. After multivariable adjustment, consumption of tuna or other broiled/baked fish was associated with specific HRV components, including indices suggesting greater vagal predominance and moderated baroreceptor responses (eg, higher root mean square successive differences of normal-to-normal intervals [$P=0.001$]; higher normalized high-frequency power [$P=0.008$]; and lower low-frequency/high-frequency ratio [$P=0.03$]) and less erratic sinoatrial node firing (eg, lower Poincaré ratio [$P=0.02$] and higher short-term fractal scaling exponent [$P=0.005$]) but not measures of circadian fluctuations (eg, 24-hour standard deviation of normal-to-normal intervals). Findings were similar for estimated dietary consumption of marine ω -3 fatty acids. For magnitudes of observed differences in HRV comparing the highest to lowest category of fish intake, differences in relative risk of cardiac death during 10.8 years of follow-up ranged from 1.1% (for difference in standard deviation of normal-to-normal intervals) to 5.9% and 8.4% (for differences in Poincaré ratio and short-term fractal scaling exponent) lower risk.

Conclusions—Habitual tuna/other fish and marine ω -3 consumption are associated with specific HRV components in older adults, particularly indices of vagal activity, baroreceptor responses, and sinoatrial node function. Cellular mechanisms and implications for clinical risk deserve further investigation. (*Circulation*. 2008;117:1130-1137.)

Key Words: electrophysiology ■ epidemiology ■ fatty acids ■ heart rate ■ nutrition

Consumption of fish or fish oil is associated with lower risk of arrhythmic outcomes including sudden death, arrhythmic coronary heart disease (CHD) death, and atrial fibrillation.¹ The mechanisms underlying these relationships are not well established and may include direct or indirect effects on cardiac electrophysiology. Heart rate variability (HRV) is a measure of cardiac electrophysiology that independently predicts sudden death in CHD patients and reflects autonomic regulation related to respiratory, baroreflex, and circadian fluctuations and the underlying cardiac responses to this regulation.² However, higher HRV is not always better: Certain HRV measures can be increased by disorganized sinoatrial variation resulting from unhealthy nonrespiratory (erratic) sinus arrhythmia.³ Effects of fish or fish oil intake on HRV would be of considerable interest both to elucidate

potential mechanisms and to provide additional evidence for clinical benefits. However, such effects are not well established. Experimental trials evaluating fish oil and HRV have been limited by small numbers of subjects (range, $n=10$ to $n=84$), relatively short durations of intake (weeks to months), and in some cases limited periods of HRV measurement (≤ 60 minutes), with highly divergent results.⁴⁻¹³ Additionally, these studies often utilized pharmacological doses of fish oil (3 to 6 g/d), and the relevance of such results to effects of dietary fish intake is unclear. We hypothesized that habitual consumption of fish and dietary long-chain ω -3 fatty acids would be associated with more favorable indices of HRV. We evaluated the associations between usual dietary consumption of fish and ω -3 fatty acids during the prior year, as assessed by a food frequency questionnaire, and measures of HRV, as

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From the Division of Cardiovascular Medicine, Brigham and Women's Hospital and Harvard Medical School, and the Departments of Epidemiology and Nutrition, Harvard School of Public Health, Boston, Mass (D.M.); Heart Rate Variability Laboratory, Cardiovascular Division, Washington University School of Medicine, St Louis, Mo (P.K.S.); Department of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, NC (R.J.P.); and Cardiovascular Health Research Unit, Departments of Medicine and Epidemiology, University of Washington, Seattle (D.S.S.).

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Correspondence to D. Mozaffarian, MD, DrPH, 665 Huntington Ave, Bldg 2-319, Boston, MA 02115. E-mail dmozaffa@hsph.harvard.edu

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Table 1. Measures of HRV and Their Intercorrelations

	Time-Domain Measures					Frequency-Domain Measures				Nonlinear Measures	
	SDNN _{ECG}	rMSSD _{ECG}	SDNN	rMSSD	SDNNIDX	NLF	NHF	VLF	ULF	Poincaré Ratio	DFA1
SDNN _{ECG}	...										
rMSSD _{ECG}	0.92	...									
SDNN	0.23	0.24	...								
rMSSD	0.30	0.37	0.54	...							
SDNNIDX	0.39	0.43	0.69	0.87	...						
NLF	0.10	0.06	-0.01	-0.14	0.03	...					
NHF	0.02	0.08	0.02	0.34	0.09	-0.83	...				
VLF	-0.31	0.34	0.70	0.82	0.94	0.01	0.07	...			
ULF	0.19	0.20	0.98	0.46	0.58	0.00	0.01	0.61	...		
Poincaré ratio	0.19	0.24	-0.08	0.35	0.07	-0.35	0.58	-0.16	-0.11	...	
DFA1	-0.13	-0.18	0.10	-0.25	0.00	0.72	-0.80	-0.22	0.12	-0.92	...

Values are Pearson correlation coefficients ($P < 0.001$ for all correlations > 0.10). SDNN_{ECG} and rMSSD_{ECG} were derived from 12-lead ECG recordings ($n = 4263$). All other measures were derived from 24-hour Holter recordings ($n = 1252$); rMSSD, NLF, and NHF were evaluated among individuals with lower erratic HRV (DFA1 $>$ median; $n = 590$). Each measure was log-transformed before analysis except for NLF, NHF, and DFA1, which were approximately normally distributed. See text for abbreviations.

assessed by both resting surface ECG and 24-hour Holter monitoring, in the Cardiovascular Health Study, a large, population-based, prospective cohort study of determinants of cardiovascular risk in older adults sponsored by the National Heart, Lung, and Blood Institute.

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Methods

Design and Population

The design and recruitment experience have been described.^{14,15} Briefly, 5201 men and women ≥ 65 years of age were randomly selected and enrolled from Medicare eligibility lists in 4 US communities in 1989–1990; an additional 687 black participants recruited and enrolled in 1992 were not included in this analysis because a food frequency questionnaire was not administered to these participants at baseline. The institutional review committee at each center approved the study, and all subjects gave informed consent. Baseline evaluation included standardized physical examination, diagnostic testing, laboratory evaluation, and questionnaires on health status, medical history, and cardiovascular risk factors.^{14–16} After the exclusion of 105 individuals with incomplete data on fish consumption and 631 individuals without ECG or Holter HRV measures, 4465 participants were included in this analysis. Included individuals were slightly younger (mean \pm SD age, 72 ± 5 versus 73 ± 6 years) but were otherwise very similar to the overall cohort. Other measure-specific exclusions are detailed below.

Dietary Assessment

Usual dietary intake was assessed with the use of a picture-sort version of the National Cancer Institute food frequency questionnaire.¹⁷ Participants were asked to indicate how often, on average, they had consumed various specified foods over the prior year, including questions on intake of tuna fish, other fish (broiled or baked), and fried fish or fish sandwiches (fish burgers). Intakes of these fish meals were summed as previously described.¹⁸ In a subset of participants, plasma phospholipid levels of the long-chain ω -3 fatty acids eicosapentaenoic acid (EPA) (20:5) and docosahexaenoic acid (DHA) (22:6) correlated with consumption of tuna fish and other broiled or baked fish ($r = 0.55$, $P < 0.001$) but not fried fish ($r = 0.04$, $P = 0.78$).¹⁹ We therefore focused on the relations between consumption of tuna/other fish and measures of HRV because these fish meals likely represented oily fish containing ω -3 fatty acids, the

consumption of which has been associated with lower risk of clinical arrhythmic events.^{19,20} Dietary intake of EPA + DHA was calculated from the questionnaire on the basis of estimated content in all seafood (including shellfish) servings (3 to 5 oz)²¹ and US fisheries commercial landings data.²² Nutrient intakes were adjusted for total energy with the use of separate regression analyses.²³

ECG Measures

A resting 12-lead ECG was obtained at the baseline clinic visit with the use of standardized techniques.²⁴ On ECGs with $> 50\%$ normal-to-normal (N-N) interbeat intervals (representing time between adjacent R-wave peaks of normal sinus beats) ($n = 4263$), 2 ECG measures of HRV were calculated with the use of a consecutive 10-second recording: the standard deviation of N-N intervals (SDNN_{ECG}) and the root mean square of successive differences of N-N intervals (rMSSD_{ECG}). The calculation of these measures was verified by senior electrocardiographers and a biostatistician in a test data set of 264 ECGs. In a subset of 1361 participants, 2-channel 24-hour Holter monitor recordings were also obtained (Del Mar Medical Systems, Irvine, Calif), and HRV was determined at the Washington University School of Medicine HRV Laboratory (GE Marquette Mars 8000 Holter analyzer, Milwaukee, Wis). Beat onset detection and classification were reviewed and edited by trained technicians and overread in detail (by P.K.S.). Individuals with atrial fibrillation or pacemakers ($n = 36$) or markedly irregular cardiac rhythms ($n = 48$) were excluded. Recordings were acceptable for analysis if they provided at least 18 hours of usable data (≥ 216 of 288 five-minute segments), requiring for time-domain analyses at least 50% of each segment to consist of N-N interbeat intervals ($n = 1252$) and, for frequency-domain and nonlinear analyses, which are more sensitive to missing data, at least 80% of each segment to consist of N-N interbeat intervals ($n = 1177$).

HRV measures included time-domain, frequency-domain, and nonlinear indices² (Table 1). The ECG-derived measures SDNN_{ECG} and rMSSD_{ECG} do not capture circadian-, activity-, or sleep-related influences and thus reflect shorter-term, resting parasympathetic (respiratory) variation. Conversely, 24-hour SDNN reflects longer-term circadian differences in HRV, and 24-hour rMSSD reflects the average of daytime and nighttime parasympathetic respiratory variation. The SDNN index (SDNNIDX) reflects short-term (5-minute cycle) fluctuations in average HRV over the course of 24 hours. Normalized low-frequency power (NLF) is modulated by baroreceptors and reflects both sympathetic and parasympathetic influences; normalized high-frequency power (NHF) reflects parasympathetic (vagal mediated) respiratory variation; and the LF/HF ratio may

Table 2. Cardiovascular Risk Factors According to Consumption of Tuna or Other Broiled or Baked Fish Among 4465 Older Adults

	Frequency of Consumption					
	<1/mo (n=447)	1–3/mo (n=1066)	1–2/wk (n=2094)	3–4/wk (n=668)	≥5/wk (n=190)	
Age, y	74±6	73±5	72±5	71±5	72±5	*
Gender, % male	44	47	42	34	29	*
Education, % ≥high school	51	69	77	84	78	*
Body mass index, kg/m ²	26±5	26±5	26±4	27±5	27±5	...
Diabetes mellitus, %	25	23	22	19	28	...
CHD, %	18	19	18	18	23	...
Clinical valvular disease, %	5	5	6	6	9	...
Current smoking, %	15	14	10	11	7	*
Smoking history, pack-years	20±29	20±28	18±26	17±25	16±26	*
Leisure-time activity, kcal/wk	1586±2078	1847±2135	1914±2124	1917±2027	1698±1828	...
Aspirin use, %	18	22	20	20	22	...
β-Blocker use, %	13	14	12	14	14	...
Dietary EPA+DHA,† mg/d	47±35	122±59	307±150	491±113	927±435	*

Values are mean±SD (continuous variables) or percentage (categorical variables).

**P* for trend <0.05, calculated by entering exposure categories as ordinal variables in tests for trend and using linear (continuous characteristics) or logistic (dichotomous characteristics) regression.

†Estimated energy-adjusted consumption based on content of EPA and DHA in all seafood servings (3–5 oz)²¹ and US fisheries commercial landings data.²²

reflect relative sympathetic-parasympathetic activity. Very-low-frequency power (VLF) may reflect parasympathetic and renin-aldosterone activity, and ultra-low-frequency power (ULF) reflects circadian fluctuations (correlating highly with 24-hour SDNN). The short-term fractal scaling exponent (DFA1) (calculated by detrended fluctuation) and the Poincaré ratio (SD12) (the ratio of the axes of an ellipse fitted to a plot of each N-N beat versus the next) quantify erratic HRV due to abnormal (random) firing of the sinoatrial node, manifested as noncyclical (nonrespiratory) sinus arrhythmia. Thus, HRV is a complex phenomenon resulting from both normal cardiac autonomic control (quantified by time-domain and frequency-domain indices) and abnormal erratic sinus arrhythmia (quantified by nonlinear indices). Because rMSSD, NLF, and NHF are strongly altered by erratic HRV,³ when erratic HRV is present, these measures no longer accurately reflect cardiac autonomic control. This is especially problematic among older adults, in whom erratic sinus arrhythmia is common.³ Thus, in analyses of rMSSD, NLF, and NHF, we excluded individuals with higher erratic HRV (DFA1 < median of 1.078; n=587).

Statistical Analysis

Associations between fish and ω-3 fatty acid intake and HRV measures were evaluated by linear regression. To evaluate differences in baseline characteristics, linear and logistic regression were used for continuous and dichotomous characteristics, respectively. Fish intakes were evaluated as categorical (indicator) variables, with intake categories entered as ordinal variables in tests for trend. To minimize potential confounding, covariates were included on the basis of clinical relevance as factors that may influence exposures and outcomes, previously published associations, or associations with exposures/outcomes in the current data set. The final model was adjusted for age, gender, race, education, smoking, body mass index, diabetes mellitus, prevalent CHD, β-blocker use, physical activity, and intakes of beef or pork, fried fish, alcohol, and total calories. For parsimony in model construction, other covariates that did not materially alter the relations between fish consumption and the outcome measures were excluded from the final model, including enrollment site; annual income; treated hypertension; exercise intensity; frequency and severity of depressive symptoms; use of aspirin, lipid-lowering medication, fish oil, and estrogen; and estimated

intake of total fat, saturated fat, linolenic acid, carbohydrates, protein, fiber, fruits, vegetables, and wine. Missing covariate values (typically <1%) were imputed with the use of age, race, gender, diabetes, and prevalent cardiovascular disease; analyses using the population median or excluding missing data were not appreciably different. Potential effect modification was assessed in prespecified analyses for treated hypertension and prevalent CHD with the use of stratification and likelihood-ratio testing with multiplicative interaction terms (exposure×covariate). Incidence of fatal CHD according to differences in HRV was evaluated by Cox proportional hazards, censoring on other deaths or last day of adjudicated follow-up (June 30, 2003). All probability values were 2 tailed (α=0.05). Analyses were performed with the use of Stata 8.2 (College Station, Tex).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Intercorrelations of the HRV measures are presented in Table 1. The ECG-derived (shorter-term) time-domain measures (SDNN_{ECG} and rMSSD_{ECG}) were highly correlated with each other (*r*=0.92) but not with their 24-hour counterparts (SDNN and rMSSD; *r*≤0.37) or other Holter-derived measures (*r*≤0.43). Among the Holter-derived measures, highly correlated indices included, as expected, SDNN and ULF (*r*=0.98); SDNNIDX and VLF (*r*=0.94); and DFA1 and Poincaré ratio (*r*=−0.92).

Bivariate (unadjusted) associations between tuna/other fish intake and selected risk factors are shown in (Table 2). Tuna/other fish consumption was associated with slightly younger age, female gender, higher education, and less smoking. Those consuming tuna/other fish intake most frequently also had a slightly higher prevalence of CHD and diabetes (perhaps because these individuals increased their fish intake after their diagnosis), but these associations were not statistically significant (and were even smaller if the 2

Table 3. HRV, Assessed from 12-Lead ECG (n=4263), According to Consumption of Tuna or Other Broiled or Baked Fish

	Frequency of Consumption					P for Trend
	<1/mo (n=425)	1–3/mo (n=1022)	1–2/wk (n=1984)	3–4/wk (n=648)	≥5/wk (n=184)	
SDNN _{ECG} , ms	14.0 (1.2)	13.7 (1.1)	14.7 (1.2)	15.4 (1.2)	15.5 (1.5)	0.004
rMSSD _{ECG} , ms	15.7 (1.6)	15.0 (1.5)	16.4 (1.6)	16.9 (1.7)	17.9 (2.1)	0.001

Measures were log-transformed for analysis and then exponentiated. Values are mean (SD), adjusted for age (years), gender (male/female), race (white/nonwhite), education (<high school, high school, >high school), smoking (never, former, current), body mass index (kg/m²), diabetes mellitus (yes/no), CHD (yes/no), β-blocker use (yes/no), leisure-time physical activity (kcal/d), and intakes of beef or pork (servings per day), fried fish (3 categories), alcohol (drinks per week), and total calories (kcal/d).

highest categories of fish intake were combined). Estimated dietary intake of EPA+DHA is also shown.

After adjustment for demographic variables, clinical risk factors, and lifestyle and dietary characteristics, tuna/other fish intake was associated with greater HRV as measured by SDNN_{ECG} (P=0.004) and rMSSD_{ECG} (P=0.001) (both reflecting short-term, parasympathetic HRV) (Table 3). Consistent with this, tuna/other fish intake was also associated with a trend toward higher 24-hour rMSSD (reflecting averaged daytime and nighttime parasympathetic HRV) (P=0.059) (Table 4). Tuna/other fish intake was not significantly associated with 24-hour SDNN (long-term circadian HRV) or SDNNIDX (short-term HRV fluctuations). Among frequency-domain measures, tuna/other fish consumption was associated with lower NLF (P=0.02) and higher NHF (P=0.008) and a lower LF/HF ratio (Figure 1), suggestive of enhanced vagal activity and parasympathetic predominance. Tuna/other fish intake was not associated with ULF (circadian HRV) (P=0.44), consistent with the lack of association with 24-hour SDNN. Greater consumption of tuna/other fish was associated with lower Poincaré ratio (P=0.02) and higher DFA1 (P=0.005), each indicative of less erratic (more normal) sinoatrial firing patterns. Fried fish intake was not associated with any of these HRV measures (data not shown).

Because of their short time frame of measurement, SDNN_{ECG} and rMSSD_{ECG} reflect different aspects of HRV compared with 24-hour SDNN and rMSSD, consistent with their relatively low intercorrelations and divergent correlations with other indices (eg, ULF) (Table 1). We confirmed that the varying relationships of tuna/other fish intake with the ECG versus 24-hour indices were not due to differences in the subjects having these measures by limiting evaluation of the ECG measures to participants who also had the Holter measures (SDNN, n=1153; rMSSD, n=590 excluding highly erratic HRV). Findings were similar to the overall results: When we compared extreme categories of tuna/other fish consumption, the difference in SDNN_{ECG} became 1.7 ms (rather than 1.5 ms; Table 1), and the difference in rMSSD_{ECG} became 3.6 ms (rather than 2.2 ms; Table 1) (P for trend=0.06 and 0.07, respectively).

We investigated the relationships between estimated dietary EPA+DHA consumption and HRV. In multivariable-adjusted analyses, dietary EPA+DHA was associated with higher rMSSD_{ECG} (P=0.03), NHF (P=0.01), and DFA1 (P=0.03) and lower NLF (P=0.003), LF/HF ratio (P=0.049), and Poincaré ratio (P=0.03) (Figure 2). Other relationships were similar in direction and magnitude to those

Table 4. HRV, Assessed by 24-Hour Holter (n=1252), According to Consumption of Tuna or Other Broiled /Baked Fish

	Frequency of Consumption				P for Trend
	<1/mo (n=111)*	1–3/mo (n=280)*	1–2/wk (n=632)*	≥3/wk (n=229)*	
Time-domain indices					
SDNN, ms	118.8 (13.2)	113.7 (11.4)	118.0 (10.8)	118.6 (10.9)	0.69
rMSSD, † ms	19.1 (1.8)	18.4 (1.9)	18.6 (1.8)	19.4 (2.1)	0.06
SDNNIDX, ms	40.6 (4.8)	40.9 (4.5)	41.8 (4.4)	43.0 (4.6)	0.07
Frequency-domain indices					
NLF, † %	70.6 (1.4)	69.8 (1.5)	69.6 (1.5)	68.4 (1.3)	0.02
NHF, † %	17.3 (1.2)	17.9 (1.1)	17.8 (1.1)	19.4 (1.1)	0.008
VLF, ms ²	946 (253)	936 (243)	1000 (248)	1058 (269)	0.02
ULF, 1000 ms ²	12.2 (2.8)	10.9 (2.2)	12.1 (2.2)	12.3 (2.3)	0.44
Nonlinear indices					
Poincaré ratio (SD12)	0.26 (0.03)	0.26 (0.03)	0.25 (0.02)	0.24 (0.02)	0.02
DFA1	1.02 (0.07)	1.03 (0.07)	1.06 (0.06)	1.07 (0.06)	0.005

Values are mean (SD), adjusted for other risk factors as in Table 3 footnote. Measures (except NLF, NHF, and DFA1) were log-transformed for analysis and then exponentiated.

*Participants with intake ≥5/wk (n=55) were combined with 3–4/wk. Numbers are shown for time-domain measures (n=1252); slightly fewer individuals (n=1177) had frequency-domain and nonlinear measures.

†rMSSD, NLF, and NHF were evaluated among individuals with lower erratic HRV (DFA1>median; n=590).

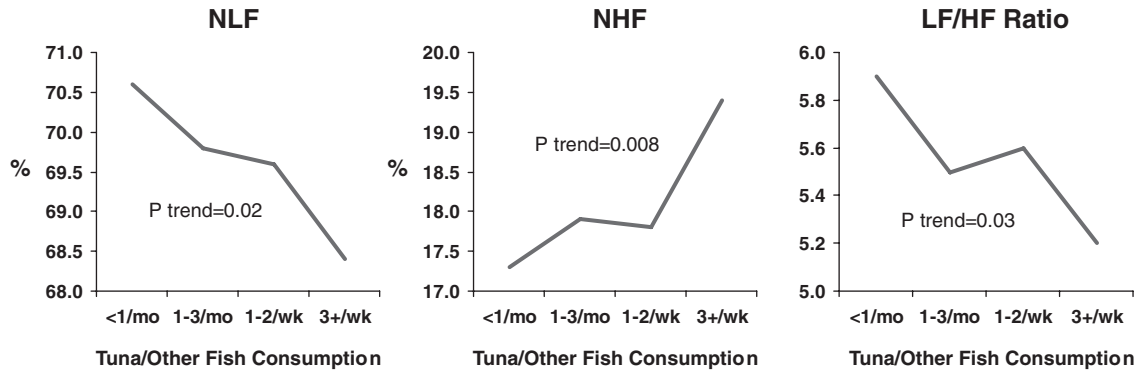


Figure 1. Frequency-domain measures of HRV according to usual consumption of tuna or other broiled or baked fish. Values are multi-variable adjusted as in Table 3 footnote.

seen for tuna/other fish intake but were not statistically significant (data not shown).

Exclusion of individuals taking β -blockers (13%) had little effect on the results. For example, tuna/other fish intake continued to be associated with higher $SDNN_{ECG}$ ($P=0.03$), $rMSSD_{ECG}$ ($P=0.006$), $RMSSD$ ($P=0.06$), NHF ($P=0.008$), and $DFA1$ ($P=0.003$); lower NLF ($P=0.01$) and Poincaré ratio ($P=0.01$); and a trend toward higher VLF ($P=0.08$). Few participants were taking fish oil supplements (3.8%), and

exclusion of these participants or adjustment for fish oil use had little effect on results (data not shown).

Fish oil lowers resting heart rate in randomized clinical trials,²⁵ and dietary fish consumption is also associated with lower resting heart rate.¹⁸ We therefore evaluated the extent to which the relationships between tuna/other fish intake and HRV might be mediated by differences in resting heart rate. After adjustment for resting heart rate, the magnitudes of the differences in HRV seen with tuna/other fish consumption

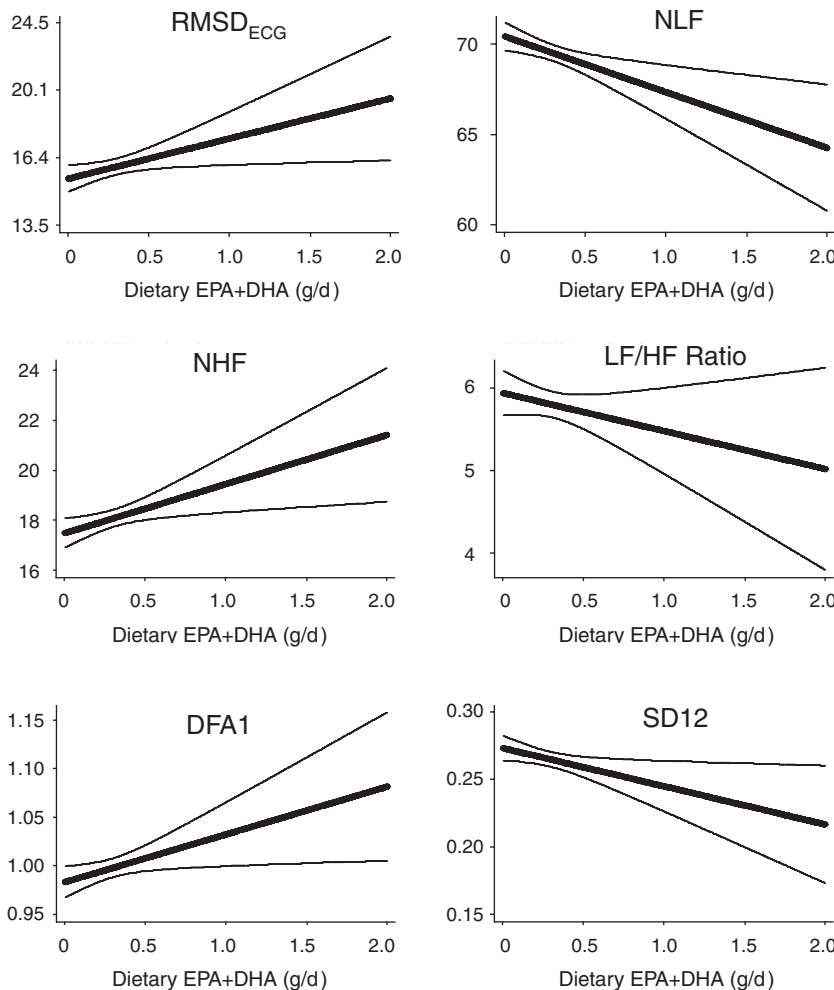


Figure 2. Measures of HRV according to dietary EPA+DHA consumption. Dark lines represent multivariable-adjusted linear regression (covariates as in Table 3 footnote); light lines represent 95% confidence intervals.

were only slightly attenuated. For example, when extreme categories of intake are compared, the difference in $SDNN_{ECG}$ became 1.4 ms (rather than 1.5 ms; Table 1); the difference in $rMSSD_{ECG}$ became 2.0 ms (rather than 2.2 ms; Table 1); the difference in NLF became 2.1% (rather than 2.2%; Table 4); and the difference in NHF became 1.9% (rather than 2.1%; Table 4).

Finally, to elucidate the potential clinical relevance of the observed differences in HRV, we investigated the relationship between the HRV indices significantly associated with fish intake and incidence of fatal CHD in this population. During 48 277 person-years of follow-up (mean follow-up, 10.8 years), 542 CHD deaths occurred. We evaluated associations between the HRV parameters and risk of CHD death, adjusting for age, gender, race, education, smoking, diabetes, prevalent CHD, treated hypertension, and body mass index. For the magnitudes of the observed differences in HRV comparing the highest to lowest category of fish intake, the following significant differences in relative risk (hazard) of CHD death were found: increased $SDNN_{ECG}$: 1.1% lower risk ($P=0.06$); increased $SDNN_{IDX}$: 3.5% lower risk ($P=0.02$); increased VLF: 4.8% lower risk ($P=0.003$); decreased Poincaré ratio: 5.9% lower risk ($P=0.003$); and increased DFA1: 8.4% lower risk ($P<0.001$).

Discussion

In this population-based cohort of older adults, greater consumption of tuna or other broiled or baked fish was associated with more optimal values of several HRV indices after adjustment for other clinical risk factors, lifestyle characteristics, and dietary habits. Similar findings were seen for estimated consumption of long-chain ω -3 fatty acids, suggesting that these findings may relate to the ω -3 fatty acids in these fish meals. To our knowledge, this is the first large, population-based study to demonstrate that usual dietary consumption of fish and ω -3 fatty acids is independently associated with HRV.

Fish consumption was not related to all HRV parameters equally. Positive associations were seen with measures that reflect vagally mediated respiratory variation ($SDNN_{ECG}$, $rMSSD_{ECG}$, $rMSSD$, NHF) and neurohormonal modulation (VLF), and inverse associations were seen with measures that reflect combined sympathetic and parasympathetic influences on baroreceptor function (NLF) and abnormal (erratic) heart rate patterns (DFA1, Poincaré ratio). No significant associations were seen with measures of circadian variation (24-hour $SDNN$, ULF). These findings suggest that fish consumption may have relatively specific effects on parameters influencing HRV: for example, augmenting vagal tone, modulating adrenergic-mediated baroreceptor activity, and improving sinoatrial node function as reflected by reductions in erratic sinus firing.

These putative effects are supported by and elucidate other clinical, epidemiological, and experimental evidence. For example, enhancement of vagal control by tuna/other fish consumption is consistent with and provides a plausible explanation for decreases in resting heart rate produced by fish oil consumption in randomized controlled trials.²⁵ Both greater vagal influence and moderated adrenergic influences

could in part produce the lower systemic vascular resistance seen with fish or ω -3 fatty acid consumption in observational analyses¹⁸ and experimental studies.²⁶ Vascular endothelial cell function is improved by ω -3 fatty acid intake,^{27–30} and enhanced vascular responsiveness could modulate baroreceptor-mediated cardiac responses. ω -3 fatty acids may also directly affect cardiac electrophysiology by reducing myocyte excitability and cytosolic calcium fluctuations via inhibition of Na^+ and L-type Ca^{2+} channels.^{31,32} The higher DFA1 and lower Poincaré ratio seen with tuna/other fish intake are each indicative of diminished erratic (random) sinus firing, supporting such stabilizing effects. This latter finding is particularly novel and interesting and has direct implications for how ω -3 fatty acids may reduce arrhythmic risk in humans.

These differences in HRV may also elucidate potential clinical effects of fish or fish oil consumption. For example, tuna/other fish intake was associated with higher VLF, and diminished VLF is strongly associated with mortality, particularly arrhythmic death, after myocardial infarction.³³ The associations of indices of vagal activity (eg, $rMSSD_{ECG}$, NHF) and relative parasympathetic versus sympathetic influence (eg, NLF, LF/HF ratio) with clinical outcomes have been mixed,² perhaps partly because of confounding of these measures by erratic HRV; thus, the clinical implications of the associations between tuna/other fish intake and these measures require further investigation. The absence of certain associations is also illuminating. For example, tuna/other fish intake was not associated with other indices of HRV that predict cardiovascular outcomes (eg, 24-hour $SDNN$, ULF), suggesting that fish intake does not affect the pathways (such as circadian rhythms) reflected by these HRV measures. Our findings support the need for further investigation of effects of ω -3 fatty acids on specific electrophysiological pathways, particularly vagal activity and erratic firing of the sinoatrial node.

Experimental trials evaluating fish oil and HRV have shown divergent results,^{4–13} possibly due to small size (range, $n=10$ to $n=84$), shorter durations of intake (weeks to months), limited periods of HRV assessment (often ≤ 60 minutes), or variable pharmacological doses of fish oil (3 to 6 g/d). Few prior studies have examined the relationship of fish or dietary ω -3 fatty acid consumption with HRV. In a prior small study,³⁴ granulocyte membrane levels of DHA were associated with time-domain indices ($SDNN$, $rMSSD$) in a subset of subjects ($n=43$) with type 1 diabetes, but only crude (unadjusted) results were presented. In a group of patients referred for angiography ($n=291$),³⁵ tissue EPA and DHA levels correlated with time-domain indices ($SDNN$, $rMSSD$, $SDNN_{IDX}$) in multiple regression analyses. Associations of dietary (nonpharmacological) consumption of fish or ω -3 fatty acids with frequency-domain or nonlinear HRV measures have not been reported previously.

Although the demonstration of independent relationships between habitual dietary consumption of fish and specific indices of HRV is by itself important to elucidate effects on particular electrophysiological pathways and clarify potential mechanisms of effects (eg, the preponderance of effects on parasympathetic-influenced indices of HRV, rather than cir-

cadian rhythms, suggests the importance of vagally mediated effects), the potential correspondence of such mechanistic effects to clinical risk is also relevant. Our findings suggest that some of these differences in individual HRV parameters may correspond to between 1% and 8% lower CHD risk, which could in sum correspond to a meaningful proportion of the $\approx 35\%$ lower risk of CHD death¹ seen with fish consumption.

Our analysis had several strengths. Information on dietary habits, HRV measures, and other risks were collected prospectively by standardized methods. We evaluated both fish and estimated ω -3 fatty acid consumption, as well as time-domain, frequency-domain, and nonlinear HRV indices. Participants were randomly selected and enrolled from Medicare eligibility lists in several US communities, providing a population-based sample of older adults. Large numbers of subjects with HRV measures increased the power to determine associations. A wide range of covariates was available to adjust for potential confounding factors.

Potential limitations were also present. Although the dietary questionnaire assessed usual dietary habits in the year before the HRV measures, a cross-sectional analysis cannot establish temporality. These associations were observed in older, predominantly white individuals and may not be generalizable to other populations. More detailed information on fish species consumed or other preparation methods was not available. Although a range of covariates were available and evaluated as potential confounders, residual confounding due to unknown or incompletely measured factors cannot be excluded. The assessments of both fish and ω -3 fatty acid intake and the HRV parameters were subject to both random error and biological variability, which would produce bias toward the null and result in underestimation of the magnitude of the associations.

Our results suggest that dietary consumption of tuna or other broiled or baked fish and marine ω -3 fatty acids may affect specific components of HRV in older adults. Cellular mechanisms and implications for clinical risk deserve further investigation.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Consumption of fish and ω -3 fatty acid reduces risk of cardiac death, but mechanisms are not well established. Heart rate variability (HRV) predicts cardiac death and reflects specific electrophysiological pathways and influences. To elucidate electrophysiological influences and support effects on clinical risk, we evaluated the associations between habitual consumption of fish and marine ω -3 fatty acids and HRV, assessed by both 12-lead ECG (n=4263) and 24-hour Holter monitoring (n=1152), in a population-based cohort of older US adults. After multivariable adjustment, consumption of tuna or other broiled/baked fish was associated with specific HRV components, including indices suggestive of greater vagal predominance and moderated baroreceptor responses (eg, higher root mean square successive differences of normal-to-normal intervals, higher normalized high-frequency power, and lower low-frequency/high-frequency ratio) and less erratic sinoatrial node firing (eg, lower Poincaré ratio and higher short-term fractal scaling exponent). Findings were similar for estimated dietary consumption of marine ω -3 fatty acids. For the magnitudes of the observed differences in HRV comparing the highest with the lowest category of fish intake, the differences in relative risk of coronary heart disease death during 10.8 years of follow-up ranged from 1.1% lower risk for the difference in standard deviation of normal-to-normal intervals to 5.9% and 8.4% lower risk for the differences in the Poincaré ratio and short-term fractal scaling exponent, respectively. Thus, habitual consumption of tuna/other fish and marine ω -3 fatty acid are associated with specific and clinically relevant differences in HRV in older adults, including indices of more favorable vagal activity, baroreceptor responses, and sinoatrial node function. Cellular mechanisms and implications for clinical risk deserve further investigation.