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# Dietary Fish and n-3 Fatty Acid Intake and Cardiac Electrocardiographic Parameters in Humans

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**OBJECTIVES** We evaluated the association between dietary fish intake and several cardiac electrocardiographic parameters in humans relevant to arrhythmic risk.

**BACKGROUND** Fish consumption may reduce the incidence of sudden death and atrial fibrillation, possibly related to anti-arrhythmic effects.

**METHODS** In a population-based study of 5,096 men and women, we evaluated cross-sectional associations between usual dietary fish intake and electrocardiographic measures of heart rate, atrioventricular conduction (PR interval), ventricular repolarization (QT interval), and ventricular conduction (QRS interval). Multivariate models were adjusted for age, gender, race, education, smoking, body mass index, diabetes, coronary heart disease, physical activity, and intakes of beef or pork, fried fish, fruits, vegetables, alcohol, and total calories.

**RESULTS** Consumption of tuna or other broiled or baked fish (comparing the highest to the lowest category of intake) was associated with lower heart rate (−3.2 beats/min, 95% confidence interval [CI] = 1.3 to 5.1; p trend <0.001), slower atrioventricular conduction (PR interval +7.2 ms, 95% CI = 1.4 to 12.9; p trend = 0.03), and substantially lower likelihood of prolonged QT (relative risk = 0.50, 95% CI = 0.27 to 0.95; p trend = 0.03). Tuna/other fish intake was not associated with ventricular conduction (p = 0.60). Findings were similar for estimated intake of marine n-3 fatty acids: a 1 g/day higher intake was associated with 2.3 beats/min lower heart rate (95% CI = 0.9 to 3.7), 7.6 ms longer PR interval (95% CI = 3.3 to 11.9), and 46% lower likelihood of prolonged QT (relative risk = 0.54, 95% CI = 0.33 to 0.88).

**CONCLUSIONS** These findings in this large, population-based study suggest that dietary fish intake is associated with cardiac electrophysiology in humans, including heart rate, atrioventricular conduction, and ventricular repolarization, with potential implications for arrhythmic risk. (J Am Coll Cardiol 2006;48:478–84) © 2006 by the American College of Cardiology Foundation

Fatty fish intake is associated with lower risk of cardiac arrhythmias including sudden death (1,2), arrhythmic coronary heart disease (CHD) death (3), and atrial fibrillation (4). However, mechanisms underlying these relationships are not well established. Experimental studies in isolated rat myocytes, exercising dogs, and non-human primates suggest that fish oil has direct cardiac electrophysiologic effects (5,6). In dogs, infusion of fish oil slows the heart rate (HR), slows atrioventricular conduction (the PR interval), and affects ventricular repolarization (the QT interval) (7). Because increased HR and an abnormal QT interval, as defined by surface electrocardiogram, predict arrhythmic events in humans (8–12), these experimental studies provide plausible potential mechanisms that might, in part, explain observed relationships between fish intake and arrhythmic risk in humans. We have previously shown that fish intake is associated with lower HR as determined by physical examination (13), and that fish oil supplementation lowers HR in randomized trials (14) (although doses in the trials were generally higher than achieved by dietary fish intake). The impact of usual dietary fish intake on other cardiac electrocardiographic (ECG) parameters in humans is unclear. We investigated the associations between usual consumption of fish and marine n-3 fatty acids and ECG measures among men and women enrolled in the Cardiovascular Health Study (CHS), a large, population-based cohort study of risk factors for cardiovascular disease in older adults.

## METHODS

**Design and population.** We performed a cross-sectional cohort analysis among participants in the CHS. The design and recruitment experiences have been described (15,16). In 1989 to 1990, 5,201 men and women age ≥65 years were randomly selected and enrolled from Medicare eligibility lists in 4 U.S. communities. 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.

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**Abbreviations and Acronyms**

CHD = coronary heart disease
CHS = Cardiovascular Health Study
CI = confidence interval
DHA = docosahexaenoic acid
ECG = electrocardiographic
EPA = eicosapentaenoic acid
HR = heart rate
QTc = corrected QT interval
QTI = QT index

Each center's institutional review committee approved the study, and all subjects gave informed consent. Participants completed questionnaires on health status, medical history, and cardiovascular risk factors, and underwent standardized physical examination and laboratory evaluation (15–17). After excluding 2 individuals in whom an ECG was not obtained and 103 individuals with incomplete data on fish consumption, 5,096 participants were available for this analysis.

**Dietary assessment.** Usual dietary intake was assessed using a picture-sort version of the National Cancer Institute food frequency questionnaire (18). 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). For each food, participants chose among 5 possible response categories ranging from ≤4/year to 5+/week. Intakes of these fish meals were summed as previously described (13). In a subset of 56 participants, plasma phospholipid levels of eicosapentaenoic acid (EPA) (20:5 n-3) and docosahexaenoic acid (DHA) (22:6 n-3) correlated with intake of tuna fish and other broiled or baked fish ($r = 0.55$, $p < 0.001$), but not fried fish ($r = 0.04$, $p = 0.78$) (3). We focused on the relations between consumption of tuna/other fish and ECG measures, because these fish meals appeared to represent oily fish containing n-3 fatty acids and have been associated with lower risk of arrhythmic events (3,4). Dietary intake of EPA + DHA was calculated from the questionnaire based on estimated content in each seafood serving (3 to 5 oz) (19) and U.S. fisheries commercial landings data (20).

**ECG measures.** A standardized resting 12-lead ECG was obtained on each participant (21). Electrocardiographic characteristics, including HR and time intervals, were defined in a centralized reading center using the NOVACODE classification (22). Ventricular repolarization was evaluated using the QT index (QTI), which more completely corrects for differences in HR compared with other nomograms (23). Prolonged QT was defined as QTI >110 (i.e., QT interval exceeding by >10% the predicted QT interval for a given HR), a traditional definition based on the non-linear relationship between QTI and risk of sudden death (24). For primary QT interval analyses, we excluded individuals with QRS ≥120 ms (bundle branch block; n = 400). We also evaluated a modified QTI in which QTI was replaced with the JT index for individuals with QRS ≥120 ms (25). We also evaluated a corrected QT interval (QTc) using Karjalainen's nomogram (26), excluding individuals with QRS ≥120 ms and also those with HRs outside the nomogram range (≤39 or ≥121 beats/min; n = 23). We evaluated both a shortened QTc (<400 ms) and a prolonged QTc (>440 ms), as both may confer increased risk of sudden death, compared with a normal QTc of 400 to 440 ms (11).

**Statistical analysis.** The associations between fish intake and ECG parameters were evaluated using linear regression for continuous measures and logistic regression for binary measures. Fish intakes were evaluated as indicator categorical variables. Tests for trend were performed evaluating intake categories as ordinal variables. Associations between dietary n-3 fatty acid intake and ECG measures were evaluated by fitting restricted natural cubic splines (27,28) and plotting the fitted smooth curve. This method uses piecewise third-order polynomials at equally spaced quantiles to model the best non-linear fit of a relationship, constrained to be linear beyond the extreme knots and to be everywhere twice continuously differentiable. Potential threshold effects were evaluated by adding a multiplicative interaction term (threshold indicator variable times continuous variable), the significance of which was evaluated using a likelihood-ratio test. Not all ECG measures were obtainable on every participant due to underlying rhythm, structural, or artifactual irregularities. Therefore, for each measure, individuals with missing values (1.3% to 5.9% of participants, depending on the measure) were excluded from that analysis. To minimize potential confounding, covariates were included based on clinical relevance as factors that may influence both 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, CHD, physical activity, and intakes of beef or pork, fruits, vegetables, 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, use of aspirin, beta-blockers, calcium-channel blockers, class 1A or class III antiarrhythmics, tricyclic antidepressants, lipid-lowering medication, and estrogen, and estimated intake of total fat, saturated fat, linolenic acid, carbohydrates, protein, fiber, and wine. Few participants (3.7%) were taking fish oil supplements, and adjustment for fish oil use or exclusion of these participants had little effect on results. Missing covariate values (<4% for dietary covariates; <1% for other covariates) were imputed using 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 pre-specified subgroups for treated hypertension and prevalent CHD using stratified analyses, the signifi-

**Table 1.** Relationships Between Intake of Tuna or Other Broiled or Baked Fish and Other Risk Factors Among 5,096 Older Adults

| Frequency of Intake | <1/Month (n = 545) | 1–3/Month (n = 1,200) | 1–2/Week (n = 2,368) | 3–4/Week (n = 762) | 5+/Week (n = 221) |
|---|---|---|---|---|---|
| Age, yrs | 74 ± 7 | 73 ± 6 | 73 ± 5 | 72 ± 5 | 72 ± 5* |
| Gender, % male | 47 | 47 | 43 | 36 | 32* |
| Education, % ≥ high school | 51 | 67 | 76 | 83 | 77* |
| Body mass index, kg/m$^2$ | 26 ± 5 | 26 ± 5 | 26 ± 4 | 27 ± 5 | 27 ± 5* |
| Diabetes mellitus, % | 24 | 23 | 22 | 22 | 28 |
| Coronary heart disease, % | 19 | 20 | 19 | 19 | 28 |
| Clinical valvular disease, % | 5 | 6 | 6 | 6 | 9 |
| Treated hypertension, %† | 47 | 47 | 44 | 44 | 49 |
| Current smoking, % | 15 | 14 | 10 | 10 | 7* |
| Smoking history, pack-yrs | 20 ± 30 | 20 ± 28 | 18 ± 27 | 17 ± 25 | 16 ± 26* |
| Leisure-time activity, kcal/week | 1,590 ± 2,106 | 1,786 ± 2,126 | 1,874 ± 2,100 | 1,891 ± 2,032 | 1,680 ± 1,840 |
| Aspirin use, % | 19 | 22 | 21 | 22 | 25 |
| Beta-blocker use, % | 13 | 14 | 12 | 14 | 17 |
| Dietary EPA + DHA, mg/day‡ | 19 ± 10 | 83 ± 39 | 262 ± 129 | 474 ± 0 | 1,070 ± 444* |

Values are mean ± SD or %. *p for trend <0.05; †use of antihypertensive medication (diuretics, angiotensin system agents, calcium-channel blockers, or beta-blockers); ‡intake from these fish meals based on estimated content of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in each serving (3 to 5 oz) (20) and U.S. fisheries commercial landings data (21).

cance of which was evaluated using likelihood-ratio testing with multiplicative interaction terms (exposure times covariate). All p values were 2-tailed (alpha = 0.05). Analyses were performed using Stata 8.2 (Stata Corp., College Station, Texas).

## RESULTS

Bivariate (unadjusted) associations between tuna/other fish intake and selected risk factors are shown (Table 1); relationships with other participant characteristics in the CHS have been reported (3,4). Tuna/other fish consumption was associated with slightly younger age, female gender, higher education, less smoking, and higher body mass index. Tuna/other fish intake was also associated with somewhat higher prevalence of CHD and diabetes (possibly because these individuals increased their fish intake after their diagnosis), but these associations were not statistically significant. Estimated dietary intake of EPA + DHA from these fish meals is also shown.

Associations between tuna/other fish intake and ECG parameters are shown in Table 2. After adjustment for demographic variables, clinical risk factors, and lifestyle and dietary characteristics, tuna/other fish consumption was associated with a lower HR ($p < 0.001$) and longer PR interval ($p = 0.02$). Comparing the highest and lowest categories of intake, the HR difference was 3.2 beats/min (95% confidence interval [CI] = 1.3 to 5.1), and the PR interval difference was 7.2 ms (95% CI = 1.4 to 12.9). Tuna/other fish intake was also associated with lower likelihood of prolonged QT (Table 2), with 50% lower likelihood in the highest category of intake, compared with the lowest (relative risk [RR] = 0.50, 95% CI = 0.27 to 0.95; p trend = 0.03) (Fig. 1). Findings were similar for the modified QTI (using JT index for individuals with QRS ≥120 ms): comparing the highest to the lowest category of tuna/other fish intake, the relative risk was 0.51 (95% CI = 0.28 to 0.93; p trend = 0.06). Tuna/other fish intake was not associated with ventricular conduction time or likelihood of ventricular conduction delay (Table 2). Fried fish intake was not associated with any of these ECG measures (not shown).

Because use of medications might be associated with fish intake and also affect cardiac ECG parameters, we repeated the analyses separately adjusting for or excluding users of relevant medications. The association between tuna/other fish intake and HR was strengthened by exclusion of participants taking beta-blockers (n = 656): comparing the highest and lowest categories of intake, the HR difference

**Table 2.** Electrophysiologic Measures According to Intake of Tuna or Other Broiled or Baked Fish

| Frequency of Intake | <1/Month (n = 545)* | 1–3/Month (n = 1,200)* | 1–2/Week (n = 2,368)* | 3–4/Week (n = 762)* | 5+/Week (n = 221)* | p Trend |
|---|---|---|---|---|---|---|
| Heart rate, beats/min | 66.0 ± 0.1 | 65.7 ± 0.1 | 64.8 ± 0.1† | 64.0 ± 0.1‡ | 62.7 ± 0.2‡ | <0.001 |
| Atrioventricular conduction (PR), ms | 164.5 ± 0.3 | 167.5 ± 0.2 | 167.7 ± 0.1 | 168.2 ± 0.2 | 171.6 ± 0.5† | 0.03 |
| Ventricular conduction (QRS), ms | 89.5 ± 0.2 | 89.0 ± 0.1 | 88.8 ± 0.1 | 89.2 ± 0.1 | 89.2 ± 0.3 | 0.60 |
| Ventricular conduction delay, % | 7.6 | 8.6 | 6.6 | 6.8 | 6.2 | 0.15 |
| Prolonged QT (QTI >110), % | 12.6 | 10.1 | 9.8 | 8.9 | 6.8† | 0.03 |

Values are mean ± SE or percent, adjusted for age (years), gender (male/female), race (white/non-white), education (<high school, high school, >high school), smoking (never, former, current), body mass index (kg/m$^2$), diabetes mellitus (yes/no), coronary heart disease (yes/no), leisure-time physical activity (kcal/day), and intakes of beef or pork (servings/day), fruits (servings/day), vegetables (servings/day), fried fish (3 categories), alcohol (drinks/week), and total calories (kcal/day). *Total number; for each outcome, individuals in whom the electrocardiogram measure was not available (between 1.3% to 5.9% of participants) were not included in the analysis; we also excluded individuals with bundle branch block (QRS ≥120 ms; n = 400) in analyses of ventricular conduction (QRS) or prolonged QT; †$p < 0.05$, and ‡$p < 0.01$ compared with intake <1/month.
QTI = QT index.

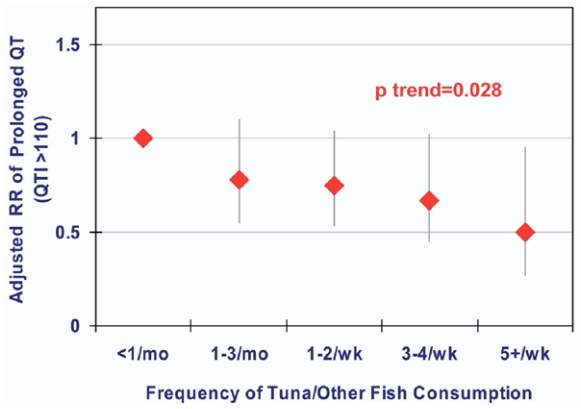


**Figure 1.** The likelihood of prolonged QT (QT index [QTI] >110) according to intake of tuna or other broiled or baked fish, after adjustment for other risk factors (see Table 2 footnote).

was 3.9 beats/min (95% CI = 1.8 to 6.0; p trend <0.001). Additional adjustment for or exclusion of participants taking beta-blockers, calcium-channel blockers, class 1A or class III antiarrhythmics, aspirin, or tricyclic antidepressants did not appreciably alter these findings or results for the other ECG measures (data not shown).

Heart rate was inversely correlated with the PR interval ($r = -0.18$, $p < 0.001$) and QTc interval ($r = -0.22$, $p < 0.001$), the latter correlation indicating that effects of HR are incompletely accounted for by Karjalainen QT interval correction. (In comparison, QTI was minimally correlated with HR: r = 0.02.) Therefore, we evaluated the associations of tuna/other fish intake with the PR and QTc intervals after adjustment for HR to account for HR-related differences in cardiac conduction and repolarization intervals. After adjustment for HR (other covariates per Table 2 footnote), the association between tuna/other fish intake and the PR interval was partly attenuated (~25%): comparing the highest and lowest category of intake, the PR interval difference was 5.5 ms (95% CI = 0.0 to 11.1). In similar analyses, tuna/other fish intake was associated with lower likelihood of prolonged QTc (>440 ms): compared with intake <1/month, the adjusted relative risks across categories of increasing tuna/other fish intake were 0.96, 0.80, 0.79, and 0.71 (p trend = 0.048), or 29% lower likelihood in the highest category of intake, compared with the lowest. Tuna/other fish intake was not associated with likelihood of shortened QTc (<400 ms) (p trend = 0.35).

In pre-specified subgroup analyses, the associations of tuna/other fish intake with the ECG measures did not vary significantly according to presence or absence of treated hypertension or prevalent CHD (p interaction >0.05 for each). For example, after excluding individuals with prevalent CHD at baseline (n = 997), tuna/other fish intake (comparing the highest to the lowest category of intake) was still associated with lower HR (−2.5 beats/min, 95% CI = 0.4 to 4.7), slower atrioventricular conduction (PR interval +5.8 ms, 95% CI = −0.6 to 12.1), and lower likelihood of prolonged QT (RR = 0.50, 95% CI = 0.24 to 1.06). Gender or racial-based differences were also not apparent (p interaction >0.05 for each). In a prior meta-analysis of randomized controlled trials, fish oil supplementation had a greater effect on HR among individuals with higher resting HR than among those with lower resting HR (14). A similar effect was seen in the current study with dietary fish intake (p interaction = 0.01). Among individuals with HR above the median (≥65 beats/min), the HR was 2.7 beats/min lower (95% CI = 0.2 to 5.2) in the highest category of tuna/other fish intake, compared with the lowest. In contrast, among individuals with HR below the median (<65 beats/min), the HR was only 0.4 beats/min lower (95% CI = −1.6 to 0.8) in the highest category of tuna/other fish intake, compared with the lowest. Results were similar if participants taking beta-blockers were excluded (not shown).

The associations between estimated dietary EPA + DHA and HR and prolonged QT were evaluated nonparametrically (Fig. 2). For HR, a possible threshold effect was seen, particularly after exclusion of participants taking beta-blockers, with steeper decline in HR between intakes of 0 and ~300 mg/day, and then more gradual decline at higher intakes (p threshold effect = 0.066). For prolonged QT, a somewhat similar pattern was seen, although with less evidence for departure from a linear relationship (p threshold effects >0.20). Evaluated continuously over the entire range, a 1 g/day higher EPA + DHA intake was associated with 2.3 beats/min lower HR (95% CI = 0.9 to 3.7), 7.6 ms longer PR interval (95% CI = 3.3 to 11.9), and 46% lower likelihood of prolonged QT (RR = 0.54, 95% CI = 0.33 to 0.88) (covariates per Table 2 footnote).

Fish intake may reduce systemic vascular resistance and improve blood pressure (13). To determine whether the associations of fish intake with ECG characteristics could partly be mediated by effects on these or other cardiac parameters, we repeated the analyses further adjusting for systolic blood pressure, diastolic blood pressure, left ventricular mass (29), and left ventricular systolic function (30) (other covariates per Table 2 footnote). Results were not appreciably altered: comparing extreme categories of tuna/other fish intake, HR was 3.3 beats/min lower (95% CI = 1.3 to 5.2), PR interval was 8.5 ms longer (95% CI = 2.8 to 14.3), and likelihood of prolonged QT was 53% lower (RR = 0.47, 95% CI = 0.24 to 0.91).

## DISCUSSION

In this population-based cohort of more than 5,000 men and women, higher intake of tuna or other broiled or baked fish was associated with several ECG parameters, including lower HR, slower atrioventricular conduction (PR interval), and lower likelihood of abnormal ventricular repolarization (prolonged QT). Only 3 small prior studies (n = 42, n = 53, n = 74) have evaluated relations between fish or fish oil intake and these ECG-defined parameters in humans, with

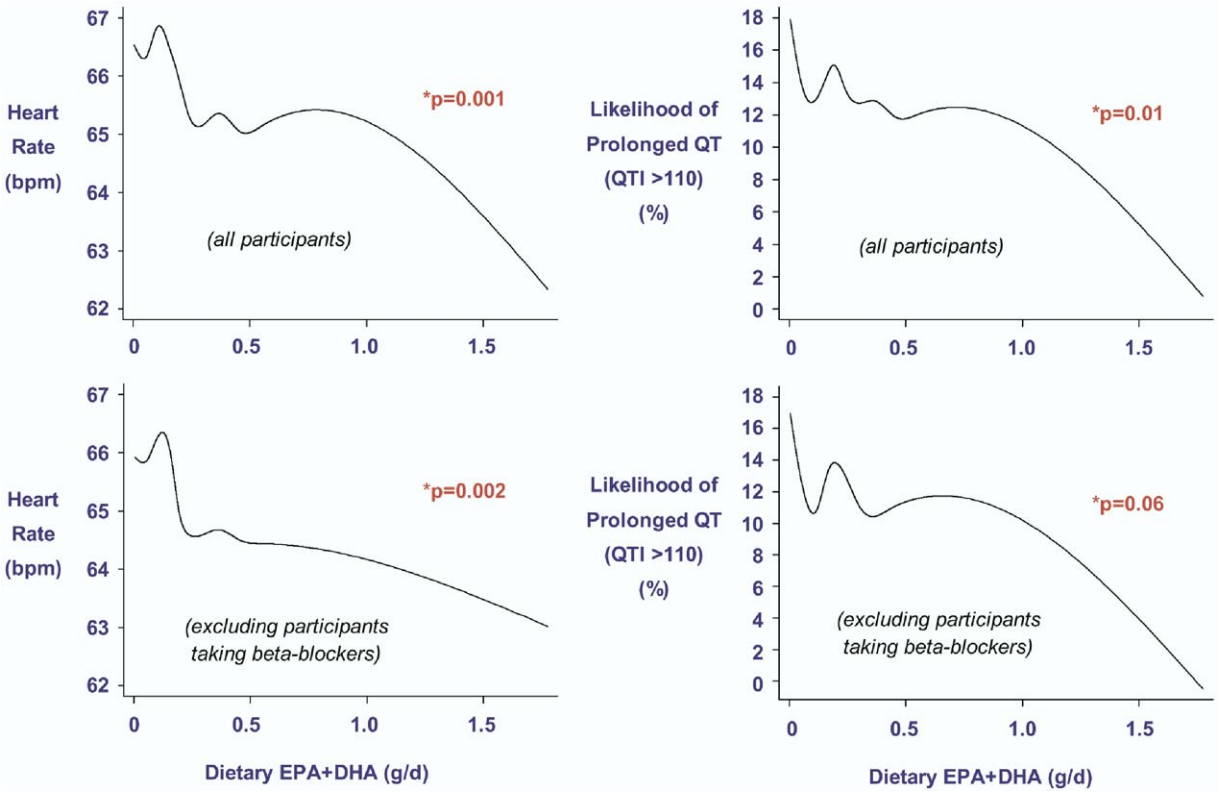


**Figure 2.** The association of dietary eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) with heart rate and prolonged QT, evaluated non-parametrically using restricted cubic splines and adjusted for other risk factors (see Table 2 footnote). For heart rate, a possible threshold effect was present at intake of ~300 mg/day, particularly after exclusion of participants taking beta-blockers (n = 656) (p threshold effect = 0.066), with steeper decline in heart rate with intakes between 0 and ~300 mg/day, and then more gradual decline. A somewhat similar pattern was seen for prolonged QT, although with less evidence for departure from a linear relationship (p threshold effects >0.20). Few subjects with intakes >1.5 g/day (n = 24) limited the certainty of associations at these high levels of intake. *The p value for the continuous association over the entire range. bpm = beats/min; QTI = QT index.

generally null results (31–33). To our knowledge, this is the first study to demonstrate in humans a relationship between usual dietary intake of fish or marine n-3 fatty acids and atrioventricular conduction or ventricular repolarization.

**HR.** The inverse association between tuna/other fish intake and HR is consistent with the HR reduction produced by fish oil supplementation in double-blind, placebo-controlled, randomized trials (14). A dose-response effect was not seen at the fish oil doses utilized in these trials (between ~1 and 15 g/day EPA + DHA) (14). Our present findings suggest that a dose-response effect may exist at lower, dietary doses, with graded reductions in HR as dietary consumption increases, at least up to ~300 mg/day. (Table 2, Fig. 2). The association of tuna/other fish intake with lower HRs was greater among participants with higher HR (−2.7 beats/min with HR ≥65 vs. −0.4 beats/min with HR <65; p interaction = 0.01). These results are remarkably similar to the findings of the randomized fish oil trials, in which HR was reduced to a greater extent in populations with higher baseline HR (−2.5 beats/min with HR ≥69 vs. −0.4 beats/min with HR <69; p interaction = 0.03) (14). These findings suggest that consumption of oily fish or fish oil may affect HR to a greater extent among individuals with higher resting HR, a group that may have increased sinus node automaticity, lower resting vagal tone, greater sympathetic tone, or lower ventricular efficiency.

**Atrioventricular conduction and ventricular repolarization.** The demonstration of relationships, in humans, between fish or marine n-3 fatty acid intake and atrioventricular conduction (i.e., PR interval) and ventricular repolarization (i.e., QT interval) is novel. These findings are consistent with animal-experimental studies showing effects of fish oil intake on the PR and QT intervals (7). The association of tuna/other fish intake with atrioventricular conduction was only partly attenuated by differences in HR, likely reflecting the only modest correlation (r = −0.18) between these 2 parameters. Slowing of atrioventricular conduction could be due to direct effects on atrioventricular nodal cells (e.g., via ion channel effects) or to effects on autonomic tone. Ventricular repolarization is a complex process influenced by ion channel function, intra- and extracellular ion concentrations, electrical coupling, and autonomic tone (34). Repolarization is initially due to $Na^+$ channel inactivation and transient $K^+$ efflux, followed by a balance of depolarizing L-type $Ca^{2+}$ currents and repolarizing $K^+$ currents, and then late $K^+$ efflux through delayed rectifier channels. In experimental studies, marine n-3 fatty acids inhibit the fast voltage-

dependent $Na^+$ current and the L-type $Ca^{2+}$ current (6). These in-vitro effects could, at least in part, explain the lower risk of prolonged repolarization seen with tuna/other fish intake in the present study. Djousse et al. (35) recently reported that intake of alpha-linolenic acid, a plant-derived n-3 fatty acid, was associated with lower risk of prolonged QT. Our findings suggest that dietary intake of oily fish and marine n-3 fatty acids may also lower the risk of QT prolongation.

**Potential clinical implications.** A higher resting HR is associated with increased risk of sudden death (8,9,36–38). This may reflect greater myocardial vulnerability to ischemia or arrhythmia, or lower underlying cardiovascular health as manifested by increased sympathetic tone, decreased vagal tone, or decreased ventricular efficiency. Based on Jouven et al. (9), our finding of a 3.2 beats/min lower HR with higher tuna/other fish consumption would correspond to ~7.5% lower risk of sudden death. The relevance of atrioventricular conduction time to arrhythmic risk has not been established. However, a prolonged QT interval is associated with a higher risk of sudden death (10–12). Among individuals without left ventricular systolic dysfunction, those with a normal QT interval had a 57% lower risk of sudden death, compared with those with a prolonged QT interval (10). Thus, although other mechanisms may also contribute to reductions in clinical risk, the observed differences in HR and ventricular repolarization may, in part, account for the lower incidence of arrhythmic events seen with fish and fish oil intake.

**Proarrhythmia versus antiarrhythmia.** In a randomized trial among patients with implantable defibrillators (n = 200), fish oil supplementation increased the risk of re-entrant ventricular tachycardia in a subset of patients (39). In contrast, in a second similar trial (n = 402), fish oil supplementation decreased the risk of ventricular fibrillation or tachycardia (40). In a large trial of fish oil supplementation among patients with recent myocardial infarction (n = 11,324), fish oil supplementation reduced sudden death by ~55% (41). It is well recognized that drugs that affect ventricular conduction or repolarization can be both anti- and proarrhythmic (42). An effect of fish oil on ventricular repolarization, as suggested by our findings, could lower risk of ventricular fibrillation in most individuals, particularly in the setting of acute ischemia, but also possibly increase risk of re-entrant tachycardia in a small and specific subset of individuals with a slow re-entrant arrhythmic loop around a region of scarred myocardium.

**Study limitations.** Although the diet questionnaire assessed usual dietary intake in the year before the ECG, a cross-sectional analysis cannot establish temporality. Fish consumption among some older individuals may be partially driven by lifestyle changes in response to chronic disease development and physician guidance; consistent with this, individuals with the highest tuna/other fish consumption were slightly more likely to have CHD, diabetes, or valvular disease and to use aspirin and beta-blockers (Table 1). Because these individuals would be more likely to have abnormal cardiac electrophysiology, this would drive the observed beneficial associations toward the null. These associations were observed in older, predominantly white individuals participating in a cohort study and may not be generalizable to other populations. More detailed information on fish species consumed or other preparation methods was not available. While a range of covariates were available in the CHS and were evaluated as potential confounders, residual confounding due to unknown or incompletely measured factors cannot be excluded. On the other hand, the consistency with results of animal-experimental studies and short-term trials of fish oil supplementation in humans make it unlikely that residual confounding entirely accounts for our findings. The assessments of both fish and n-3 fatty acid intake and the ECG parameters were subject to both random error and biologic variability, which would produce bias toward the null and result in underestimation of the magnitude of the associations.

**Conclusions.** Our results suggest that consumption of fish and marine n-3 fatty acids is associated with cardiac electrophysiology in humans, including HR, atrioventricular conduction, and ventricular repolarization. Additional studies are warranted to confirm these findings, and cellular mechanisms and implications for arrhythmic risk deserve further investigation.

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