JAMA Internal Medicine | Original Investigation

Associations of Fish Consumption With Risk of Cardiovascular Disease and Mortality Among Individuals With or Without Vascular Disease From 58 Countries

Deepa Mohan, PhD; Andrew Mente, PhD; Mahshid Dehghan, PhD; Sumathy Rangarajan, MSc; Martin O'Donnell, MD, PhD; Weihong Hu, MSc; Gilles Dagenais, MD; Andreas Wielgosz, MD, PhD; Scott Lear, PhD; Li Wei, PhD; Rafael Diaz, MD; Alvaro Avezum, MD, PhD; Patricio Lopez-Jaramillo, MD, PhD; Fernando Lanas, MD, PhD; Sumathi Swaminathan, PhD; Manmeet Kaur, PhD; K. Vijayakumar, MD; Viswanathan Mohan, MD, DSc; Rajeev Gupta, PhD; Andrzej Szuba, MD, PhD; Romaina Iqbal, PhD; Rita Yusuf, PhD; Noushin Mohammadifard, PhD; Rasha Khatib, PhD; Khalid Yusoff, MBBS; Sadi Gulec, MD; Annika Rosengren, MD, PhD; Afzalhussein Yusufali, MD; Edelweiss Wentzel-Viljoen, PhD; Jephat Chifamba, DPhil; Antonio Dans, MD, MSc; Khalid F. Alhabib, MBBS; Karen Yeates, MD; Koon Teo, MBBCh, PhD; Hertzel C. Gerstein, MD, MSc; Salim Yusuf, MBBS, DPhil; for the PURE, ONTARGET, TRANSCEND, and ORIGIN investigators

IMPORTANCE Cohort studies report inconsistent associations between fish consumption, a major source of long-chain ω-3 fatty acids, and risk of cardiovascular disease (CVD) and mortality. Whether the associations vary between those with and those without vascular disease is unknown.

OBJECTIVE To examine whether the associations of fish consumption with risk of CVD or of mortality differ between individuals with and individuals without vascular disease.

DESIGN, SETTING, AND PARTICIPANTS This pooled analysis of individual participant data involved 191 558 individuals from 4 cohort studies—147 645 individuals (139 827 without CVD and 7818 with CVD) from 21 countries in the Prospective Urban Rural Epidemiology (PURE) study and 43 413 patients with vascular disease in 3 prospective studies from 40 countries. Adjusted hazard ratios (HRs) were calculated by multilevel Cox regression separately within each study and then pooled using random-effects meta-analysis. This analysis was conducted from January to June 2020.

EXPOSURES Fish consumption was recorded using validated food frequency questionnaires. In 1 of the cohorts with vascular disease, a separate qualitative food frequency questionnaire was used to assess intake of individual types of fish.

MAIN OUTCOMES AND MEASURES Mortality and major CVD events (including myocardial infarction, stroke, congestive heart failure, or sudden death).

RESULTS Overall, 191 558 participants with a mean (SD) age of 54.1 (8.0) years (91 666 [47.9%] male) were included in the present analysis. During 9.1 years of follow-up in PURE, compared with little or no fish intake (≤50 g/mo), an intake of 350 g/wk or more was not associated with risk of major CVD (HR, 0.95; 95% CI, 0.86-1.04) or total mortality (HR, 0.96; 0.88-1.05). By contrast, in the 3 cohorts of patients with vascular disease, the HR for risk of major CVD (HR, 0.84; 95% CI, 0.73-0.96) and total mortality (HR, 0.82; 95% CI, 0.74-0.91) was lowest with intakes of at least 175 g/wk (or approximately 2 servings/wk) compared with 50 g/mo or lower, with no further apparent decrease in HR with consumption of 350 g/wk or higher. Fish with higher amounts of ω-3 fatty acids were strongly associated with a lower risk of CVD (HR, 0.94; 95% CI, 0.92-0.97 per 5-g increment of intake), whereas other fish were neutral (collected in 1 cohort of patients with vascular disease). The association between fish intake and each outcome varied by CVD status, with a lower risk found among patients with vascular disease but not in general populations (for major CVD, I^2 = 82.6 [P = .02]; for death, I^2 = 90.8 [P = .001]).

CONCLUSIONS AND RELEVANCE Findings of this pooled analysis of 4 cohort studies indicated that a minimal fish intake of 175 g (approximately 2 servings) weekly is associated with lower risk of major CVD and mortality among patients with prior CVD but not in general populations. The consumption of fish (especially oily fish) should be evaluated in randomized trials of clinical outcomes among people with vascular disease.

JAMA Intern Med. 2021;181(5):631-649. doi:10.1001/jamainternmed.2021.0036
Published online March 8, 2021. Corrected on May 3, 2021.

Invited Commentary
page 649

Multimedia

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The PURE, ONTARGET, TRANSCEND, and ORIGIN investigators are listed at the end of the article.

Corresponding Author: Andrew Mente, PhD, Population Health Research Institute, Hamilton Health Sciences and McMaster University, Second Floor, Room C2-105, 237 Barton St East, Hamilton, ON L8L 2X2, Canada (andrew.mente@phri.ca).

Dietary guidelines recommend at least 2 servings of fish per week for the prevention of cardiovascular disease (CVD).[1,2] Fish is a major source of the long-chain ω-3 fatty acids docosahexaenoic acid and eicosapentaenoic acid, which have been suggested to have beneficial effects on cardiovascular health.[3-5] In interventional studies, fish and ω-3 consumption have been shown to improve some cardiovascular risk markers, including triglycerides and blood pressure, especially in people with triglycerides of 500 mg/dL or greater (to convert to millimoles per liter, multiply by 0.0113).[6,7] Two recent meta-analyses of randomized trials in high-risk individuals showed that ω-3 supplementation (typically approximately 1 g/d) was not associated with risk of cardiovascular events, coronary heart deaths, coronary heart disease events, stroke, heart irregularities, or all-cause mortality.[8,9] By contrast, another recent meta-analysis[10] that included 3 new trials[11-13] showed that ω-3 supplementation was associated with significant benefit against risk of CVD outcomes (summary relative risk of 0.92; 95% CI, 0.86-0.98),[10] even after excluding a recent trial of patients with elevated triglyceride levels that used a much higher dose of fish oil (4 g daily).[13] Observational cohorts of participants without diagnosed vascular disease have found modest protective associations of moderate fish consumption (approximately ≥2 servings/wk) with fatal coronary heart disease (ie, summary relative risks in multiple meta-analyses ranging from 2% to 15% lower risk) and, usually less strongly, with total CVD.[14] To date, most cohort studies evaluating fish consumption and CVD events have been conducted in Europe, North America, Japan, and China, with little information from other world regions, where varying amounts and types of fish are consumed. Furthermore, whether the associations of fish consumption with CVD events vary between those with and those without vascular disease is unclear.

Because increasing fish intake may improve blood lipid levels, especially among high-risk individuals,[6,7] we hypothesized that there would be differences in the association between fish intake and major CVD outcomes and mortality among individuals with vascular disease compared with those without vascular disease. In the present pooled analysis, we studied 191 558 people (51 731 with vascular disease and 139 827 generally healthy individuals) from 58 countries who had been included as participants in 4 large prospective studies.

Key Points

Question Is there a difference in the association of fish consumption with risk of cardiovascular disease (CVD) or of mortality between individuals with and individuals without vascular disease?

Findings In this analysis of 4 international cohort studies of 191 558 people from 58 countries on 6 continents, a lower risk of major CVD and total mortality was associated with higher fish intake of at least 175 g (2 servings) weekly among high-risk individuals or patients with vascular disease, but not in general populations without vascular disease; a similar pattern of results was observed for sudden cardiac death. Oily fish but not other types of fish were associated with greater benefits.

Meaning Study findings suggest that fish intake of at least 175 g (2 servings) weekly is associated with lower risk of major CVD and mortality among patients with prior CVD, but not in the general population.

Methods

Study Design and Participants

Details of the studies' designs and population characteristics have been published before and are described in the eAppendix in the Supplement.

In brief, the Prospective Urban Rural Epidemiology (PURE) study[15-19] is an ongoing large-scale epidemiologic cohort study that has enrolled 166 762 individuals, 35 to 70 years of age, in 21 low-, middle-, and high-income countries on 5 continents. For the present analysis, we included 147 645 participants (including 7818 [5.3%] with a history of CVD) with complete information on their diet (eFigure 1 in the Supplement). We included all outcome events known until July 31, 2019.

The Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial (ONTARGET) is a randomized clinical trial of antihypertension medication (ramipril, telmisartan, and their combination) for 25 620 patients aged 55 years or older with vascular disease or diabetes.[20] The Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease (TRANSCEND) was a randomized clinical trial of telmisartan vs placebo for 5926 participants.[21] For the present analysis, we included 31 491 participants from ONTARGET and TRANSCEND with dietary assessments in 40 countries on 6 continents.

The Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial was a randomized clinical trial of insulin glargine therapy or standard care and ω-3 fatty acid or placebo supplementation (2 × 2 factorial design) that included 12 537 people (mean [SD] age, 63.5 [7.8] years) with cardiovascular risk factors plus impaired fasting glucose or diabetes.[22,23] For the present analysis, we included 12 422 participants from ORIGIN with dietary assessments in 40 countries on 5 continents. We collected information on the type of fish consumed in ORIGIN but not in other studies. All studies were coordinated by the Population Health Research Institute, Hamilton Health Sciences and McMaster University, Hamilton, Ontario, Canada.

Procedures

The information about the study variables was collected with similar approaches and data collection forms in each of the studies. Information about demographic factors, lifestyle, health history, and medication use was recorded. Physical assessments included weight, height, waist and hip circumferences, and blood pressure.

In PURE, participants' habitual food intake was recorded using country-specific validated food frequency questionnaires (FFQs; eAppendix in the Supplement).[24,25] In ONTARGET and TRANSCEND, dietary information was obtained using a 19-item qualitative FFQ.[20,21] In ORIGIN, a 25-item qualitative FFQ was used to obtain information on

individual foods or food groups, except for fish.[22,23] A separate 28-item qualitative FFQ was used to assess fish intake (24 types of fish and 4 types of shellfish) (eAppendix in the Supplement).

Standardized case report forms were used to capture clinical data and to record major CVD events and death during follow-up in each study. Major cardiovascular events and deaths during follow-up were recorded and adjudicated centrally in each country using standard definitions. Events were classified according to the definitions used in each study, but these definitions were broadly similar.

Statistical Analysis

Median fish intake was calculated overall and according to geographic region and country, with adjustment for age and sex. For all 3 cohorts, participants were grouped according to fish consumption into lower than 50 g/mo, 50 g/mo to lower than 175 g/wk, 175 to lower than 350 g/wk, and 350 g/wk or higher (ie, equivalent to fixed increments of about 25 g/d); the lowest intake group was used as the reference. Analysis of covariance was performed to calculate mean blood lipid levels and blood pressure levels among fish intake groups, adjusting for covariates.

We used a 2-stage individual participant data meta-analysis.[26] First, we assessed the associations between fish intake and events in each cohort separately. For the PURE cohort, estimates were obtained overall and separately for 2 subcohorts of people with or without CVD (the other 3 cohort studies were composed entirely of patients with vascular disease). Second, the cohort-specific hazard ratios (HRs) and 95% CIs were pooled (separately by cohort of people with or without CVD) in a random-effects meta-analysis.[27] The proportionality assumption was tested using the global goodness-of-fit test with Schoenfeld residuals in each cohort. No evidence of a violation was found. Tests of heterogeneity were conducted using the I^2 statistic.

In the PURE study, Cox frailty models with random effects (to account for clustering within study centers) were used to assess the association between fish intake and the outcomes.[28] In a minimally adjusted model, we adjusted for age, sex, and study center (as a random effect). The primary model adjusted for age, sex, study center (as a random effect), body mass index, educational level, wealth index, smoking status, urban or rural location, physical activity, history of diabetes, use of statin or antihypertension medication, and fruit, vegetables, red meat, poultry, dairy, and total energy intake, as in articles previously published by members of our group.[24,25,29] To test for linear trends, we used the median fish intake value in each of the categories of fish intake and included the variable as a quantitative risk factor. In ONTARGET and TRANSCEND, because the entry criteria and study conduct were similar for the 2 trials, we pooled the data from both studies in our analysis. As in the PURE analyses, in ONTARGET/TRANSCEND and in ORIGIN, we used Cox frailty models with similar adjustment models, but additionally adjusted for treatment allocation.

In sensitivity analyses for each study, estimates were assessed in the primary models after removing potential associated factors (body mass index, waist to hip ratio, diabetes, and hypertension). In addition, we assessed whether the association of fish intake varied by geographic region using tests of interaction. All statistical analyses were conducted using SAS, version 9.4 (SAS Institute Inc). A 2-sided $P < .05$ was considered statistically significant. The present analysis was conducted from January to June 2020.

Results

Participant characteristics from each study are provided in **Table 1**.[15,19] Overall, 191 558 participants with a mean (SD) age of 54.1 (8.0) years (91 666 [47.9%] males) were included in the present analysis. The median duration of follow-up was 7.5 years (interquartile range [IQR], 4.9-9.4 years), with follow-up completed for 96% of the participants. The median follow-up in PURE was 9.1 years (IQR, 6.8-10.4 years), 4.5 years (IQR, 4.4-5.0 years) in ONTARGET and TRANSCEND, and 6.2 years (IQR, 5.8-6.7 years) in ORIGIN.

Overall, there were 8949 deaths (6.4%) among individuals without prior CVD and 6763 (13.1%) among individuals with prior CVD. There were 6825 (4.9%) major CVD events among individuals without prior CVD and 8565 (16.6%) among individuals with prior CVD.

Median fish intake ranged from 4.2 g/wk in South Asia to 468.3 g/wk in Southeast Asia (eFigure 2 in the Supplement). By country, fish intake was lowest in Argentina (0.7 g/wk) and India (1.4 g/wk) and highest in Malaysia (452.2 g/wk), Philippines (522.9 g/wk), and United Arab Emirates (1350 g/wk).

Associations of Fish Intake With CVD and Mortality

In PURE, no significant association between fish intake and any health outcome was found, after adjustment for known confounders. Compared with little or no fish intake (≤50 g/mo; reference category), an intake of 350 g/wk or more (approximately 4 servings) was not significantly associated with risk of major CVD (HR, 0.95; 95% CI, 0.86-1.04), CVD mortality (HR, 0.94; 95% CI, 0.80-1.10), non-CVD mortality (HR, 1.00; 95% CI, 0.90-1.12), or total mortality (HR, 0.96; 95% CI, 0.88-1.05) (**Table 2**; **Figure 1**). The association between fish intake and outcome events did not differ significantly by history of CVD status within PURE (Figure 1; eFigure 5 in the Supplement).

By contrast, in 2 cohorts of patients with vascular diseases (ONTARGET and TRANSCEND study, 40 countries, and 6 continents), a higher fish intake of at least 175 g/wk (approximately 2 servings/wk) was associated with lower risk of major CVD (HR, 0.89; 95% CI, 0.80-1.00), CVD mortality (HR, 0.87; 95% CI, 0.74-1.02), non-CVD mortality (HR, 0.83; 95% CI, 0.68-1.01), and total mortality (HR, 0.86; 95% CI, 0.76-0.98) compared with 50 g/mo or lower, with no further apparent decrease in HR with consumption of 350 g/wk or higher (Table 2; eFigure 4 in the Supplement).

In the ORIGIN study of patients with vascular dieases (40 countries, 5 continents), a higher fish intake of at least 175 g/wk (approximately 2 servings/wk) was associated with lower risk of major CVD (HR, 0.77; 95% CI, 0.66-0.89), CVD mortality

Table 1. Baseline Characteristics of Participants by Category of Fish Intake and by Study

Characteristic	Category of fish intake			
	<50 g/mo	50 g/mo to <175 g/wk	175 to <350 g/wk	≥350 g/wk
PURE trial (n = 147 541)				
No. of participants	37 514	61 950	21 661	25 225
Intake, median (IQR), g/wk	0.07 (0 to 7.0)	67.9 (32.9 to 109.9)	231.0 (197.4 to 273.7)	593.6 (450.1 to 1050)
Age, mean (SD), y	50.2 (10.3)	50.5 (9.9)	51 (9.9)	51.3 (9.9)
Male, No. (%)	15 020 (40.0)	26 449 (42.7)	9525 (44.0)	10 472 (41.5)
Location, No. (%)				
Urban	18 226 (48.6)	31 516 (50.9)	14 346 (66.2)	13 804 (54.7)
Rural	19 288 (51.4)	30 434 (49.1)	7315 (33.8)	11 421 (45.3)
Geographical region, No. (%)				
South Asia	13 460 (35.9)	10 000 (16.1)	1769 (8.2)	5017 (19.9)
China	10 610 (28.3)	22 884 (36.9)	6564 (30.3)	5378 (21.3)
Southeast Asia	238 (0.6)	1246 (2)	2500 (11.5)	7378 (29.2)
Africa	1462 (3.9)	2700 (4.4)	840 (3.9)	735 (2.9)
North America or Europe	1468 (3.9)	10 391 (16.8)	4947 (22.8)	2870 (11.4)
Middle East	2596 (6.9)	4338 (7)	1607 (7.4)	1702 (6.7)
South America	7680 (20.5)	10 391 (16.8)	3434 (15.9)	2145 (8.5)
Educational level, No. (%)				
None, primary, or unknown	20 962 (56.1)	26 492 (42.9)	6663 (30.8)	8368 (33.2)
Secondary, high, or higher secondary	11 496 (30.8)	23 407 (37.9)	8988 (41.6)	11 357 (45.1)
Trade, college, or university	4912 (13.1)	11 890 (19.2)	5979 (27.6)	5461 (21.7)
Wealth index, median (IQR)[a]	-0.26 (-1.14 to 0.42)	0.14 (-0.70 to 0.82)	0.48 (-0.15 to 1.07)	0.21 (-0.60 to 0.91)
BMI, mean (SD)	25.2 (5.4)	25.9 (5.2)	26.5 (5.1)	26 (5)
Waist to hip ratio, mean (SD)	0.873 (0.09)	0.872 (0.084)	0.877 (0.084)	0.876 (0.083)
Blood pressure, mean (SD), mm Hg				
Systolic	130.2 (22.6)	131.3 (22.6)	131.5 (21.8)	132.7 (21.8)
Diastolic	81.7 (13.7)	82.2 (17.3)	81.9 (14)	81.6 (13.5)
Smoking, No. (%)				
Former	3247 (8.7)	7786 (12.7)	3402 (15.8)	2883 (11.5)
Current	7605 (20.5)	13 952 (22.7)	4252 (19.8)	4306 (17.2)
Never	26 309 (70.8)	39 711 (64.6)	13 813 (64.3)	17 847 (71.3)
Alcohol, No. (%)				
Former	1625 (4.4)	2974 (4.9)	947 (4.5)	908 (3.6)
Current	6553 (17.7)	17 378 (28.4)	7577 (36.3)	5875 (23.6)
Never	28 808 (77.9)	40 853 (66.7)	12 356 (59.2)	18 163 (72.8)
Physical activity, No. (%)				
Low	7122 (20.9)	9329 (16)	3617 (17.5)	4760 (20.4)
Moderate	12 514 (36.8)	22 439 (38.4)	8061 (39)	8656 (37.1)
High	14 380 (42.3)	26 693 (45.7)	9010 (43.6)	9886 (42.4)
History of diabetes, No. (%)	2775 (7.4)	4392 (7.1)	1875 (8.7)	2854 (11.3)
History of hypertension, No. (%)	7430 (19.8)	12 860 (20.8)	4631 (21.4)	5865 (23.3)
Energy, mean (SD)				
Intake, kcal	1970 (778)	2026 (733)	2197 (784)	2624 (887)
From carbohydrate %	63.6 (12.3)	62.7 (11.5)	58.3 (10.5)	55.8 (9.2)
From protein %	14 (3.6)	15 (3.2)	16.4 (3.1)	17 (3.8)
From total fat %	22.4 (10.2)	22.3 (9.3)	25.4 (8.4)	27.3 (7.5)
Alternative Healthy Index score, mean (SD)	33.0 (7.7)	34.5 (7.8)	35.3 (8.2)	36.6 (9.0)
Dairy, mean (SD), servings/d	1.1 (1.4)	1.5 (2.0)	1.8 (2.3)	1.4 (1.9)
Fruits, mean (SD), servings/d	1.3 (1.8)	1.7 (2.1)	2 (2.2)	2.2 (2.8)
Vegetables, mean (SD), servings/d	2 (2.1)	2.7 (2.8)	3.5 (3.9)	3.3 (3.8)
Meats, mean (SD), servings/d	1.9 (2.8)	2.6 (3.5)	3.6 (5.7)	4.2 (5.8)
Red and processed meat, mean (SD), servings/d	0.6 (0.9)	0.8 (0.9)	1 (1.0)	0.8 (0.9)
White meat, mean (SD), servings/d	0.2 (0.3)	0.3 (0.3)	0.6 (0.4)	1.6 (1.3)
Breads and cereals, mean (SD), servings/d	5.7 (3.2)	5 (2.8)	5.2 (3.2)	6.2 (3.8)

(continued)

Table 1. Baseline Characteristics of Participants by Category of Fish Intake and by Study (continued)

Characteristic	Category of fish intake			
	<50 g/mo	50 g/mo to <175 g/wk	175 to <350 g/wk	≥350 g/wk
ONTARGET and TRANSCEND (n = 31 491)				
No. of participants	2801	16 377	7335	4978
Intake, median (IQR), g/wk	2.8 (0 to 9.2)	119.7 (55.3 to 119.7)	240.1 (200.2 to 249.9)	450.1 (359.8 to 720.3)
Age, mean (SD), y	66.7 (7.5)	66.5 (7.2)	66.6 (7.3)	66.3 (7.0)
Male, No. (%)	1779 (63.5)	11 667 (71.2)	5216 (71.1)	3464 (69.6)
Geographic region, No. (%)				
North America and Europe	1547 (55.2)	11 267 (68.8)	4895 (66.7)	2701 (54.3)
South America or Mexico	855 (30.5)	1365 (8.3)	645 (8.8)	443 (8.9)
Middle East	24 (0.9)	230 (1.4)	97 (1.3)	240 (4.8)
China, Hong Kong, Taiwan, or South Korea	183 (6.5)	1516 (9.3)	536 (7.3)	748 (15)
Southeast Asia	19 (0.7)	350 (2.1)	378 (5.2)	496 (10)
Africa	48 (1.7)	468 (2.9)	224 (3.1)	91 (1.8)
Australia or New Zealand	125 (4.5)	1181 (7.2)	560 (7.6)	259 (5.2)
Educational level, No. (%)				
None primary or unknown	805 (28.7)	5063 (30.9)	2185 (29.8)	1241 (24.9)
Secondary, high, or higher secondary	1239 (44.2)	5306 (32.4)	2274 (31)	1826 (36.7)
Trade, college, or university	757 (27)	6007 (36.7)	2876 (39.2)	1910 (38.4)
BMI, mean (SD)	28.1 (4.6)	28.2 (4.5)	28.1 (4.5)	27.6 (4.6)
Waist to hip ratio, mean (SD)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)
Blood pressure, mean (SD), mm Hg				
Systolic	140.8 (17.2)	141.7 (17.2)	141.8 (17.2)	142 (17.7)
Diastolic	82 (10.3)	82.1 (10.4)	82 (10.2)	81.8 (10.5)
Smoking, No. (%)				
Former	1378 (49.2)	8333 (50.9)	3681 (50.2)	2422 (48.7)
Current	381 (13.6)	2106 (12.9)	808 (11.0)	504 (10.1)
Never	1039 (37.1)	5921 (36.2)	2839 (38.7)	2047 (41.2)
Physical activity, No. (%)				
Low	1256 (44.8)	5817 (35.5)	2332 (31.8)	1512 (30.4)
Moderate	573 (20.5)	3828 (23.4)	1732 (23.6)	1054 (21.2)
High	972 (34.7)	6730 (41.1)	3271 (44.6)	2412 (48.5)
History of diabetes, No. (%)	1028 (36.7)	6103 (37.3)	2675 (36.5)	1902 (38.2)
History of hypertension, No. (%)	2091 (74.7)	11 542 (70.5)	5076 (69.2)	3392 (68.1)
Alternative Healthy Index score, mean (SD)	21.8 (7.3)	24.1 (7.1)	26.5 (7.6)	29.0 (7.9)
Fruits, mean (SD), servings/d	1.1 (1.4)	1.2 (1.3)	1.5 (1.3)	1.6 (2)
Leafy green vegetables, mean (SD), servings/d	0.7 (0.9)	0.8 (1.1)	0.9 (1.0)	1 (1.1)
Dairy, mean (SD), servings/d	0.9 (1.1)	1 (1.1)	1 (1.2)	1 (1.2)
Meat or poultry, mean (SD), servings/d	0.8 (1.1)	0.8 (0.9)	0.8 (0.8)	0.8 (1)

(continued)

(HR, 0.66; 95% CI, 0.54-0.80), and total mortality (HR, 0.77; 95% CI, 0.66-0.90) compared with 50 g/mo or lower, with no further apparent decrease in HR with consumption of 350 g/wk or higher (Table 2; eFigure 4 in the Supplement).

Collectively, in the 3 cohorts of patients with vascular disease, a minimal fish intake of 175 g/wk (approximately 2 servings/wk) was associated with lower major CVD (HR, 0.84; 95% CI, 0.73-0.96) and total mortality (HR, 0.82; 95% CI, 0.74-0.91) compared with 50 g/mo or lower, with no additional benefit with consumption of 350 g/wk or more.

Similar results were found when waist to hip ratio replaced body mass index in the multivariable models and also when waist to hip ratio, body mass index, hypertension, and diabetes were dropped from the models (eTable 2 in the Supplement). Lastly, when participants with an event in the first 2 years were excluded, the findings were unchanged (eTable 2 in the Supplement).

In the ORIGIN study, types of fish with higher amounts of ω-3 fats were strongly associated with a lower risk of major CVD events (HR, 0.94; 95% CI, 0.92-0.97 per 5-g increment of intake), whereas other types of fish were neutral (**Figure 2**).[30] Similar protective associations of high ω-3 fish were found for sudden cardiac death (HR, 0.91; 95% CI, 0.86-0.96 per 5-g increment of intake; $P < .001$), whereas other types of fish were found to be neutral (HR, 0.98; 95% CI, 0.88-1.09; $P = .69$).

Heterogeneity of Associations in Those With or Without Vascular Disease

The association of fish intake with major CVD and CVD death varied significantly by history of CVD status (for major CVD,

Table 1. Baseline Characteristics of Participants by Category of Fish Intake and by Study (continued)

Characteristic	Category of fish intake			
	<50 g/mo	50 g/mo to <175 g/wk	175 to <350 g/wk	≥350 g/wk
ORIGIN trial (n = 12 422)				
No. of participants	3572	5049	1995	1806
Intake, median (IQR), g/wk	2.2 (0 to 8.8)	64.5 (28.0 to 119.7)	248.5 (211.4 to 319.2)	567.7 (445.2 to 874.3)
Age, mean (SD), y	63.6 (7.9)	63.5 (7.8)	63.7 (7.7)	63.5 (7.8)
Male, No. (%)	2136 (59.8)	3249 (64.4)	1372 (68.7)	1317 (72.9)
Geographic region, No. (%)				
North America and Europe	921 (25.8)	2800 (55.5)	1416 (70.9)	1328 (73.5)
South America or Mexico	1944 (54.4)	1414 (28.0)	301 (15.1)	174 (9.6)
Middle East	53 (1.5)	90 (1.8)	57 (2.9)	52 (2.9)
South Asia	289 (8.1)	80 (1.6)	8 (0.4)	10 (0.6)
China, Hong Kong, Taiwan, or South Korea	174 (4.9)	219 (4.3)	82 (4.1)	109 (6.0)
Southeast Asia	60 (1.7)	40 (0.8)	11 (0.6)	22 (1.2)
Africa	118 (3.3)	347 (6.9)	78 (3.9)	52 (2.9)
Australia or New Zealand	14 (0.4)	59 (1.2)	43 (2.2)	60 (3.3)
BMI, mean (SD)	29.6 (5.4)	29.9 (5.2)	29.9 (5.2)	29.8 (5.0)
Blood pressure, mean (SD), mm Hg				
Systolic	147.6 (22.7)	145.9 (21.7)	144.6 (20.7)	143.4 (20.8)
Diastolic	84.8 (12.4)	84.4 (12.0)	83.3 (11.6)	83.0 (11.9)
Smoking, No. (%)				
Former	1471 (41.2)	2324 (46.0)	1015 (50.9)	927 (51.3)
Current smoker	408 (11.4)	635 (12.6)	253 (12.7)	243 (13.5)
Never	1694 (47.4)	2090 (41.4)	728 (36.5)	636 (35.2)
Low physical activity, No. (%)	1127 (31.5)	1050 (20.8)	275 (13.8)	260 (14.4)
History of diabetes, No. (%)	3261 (91.3)	4423 (87.6)	1706 (85.5)	1596 (88.3)
History of hypertension, No. (%)	2856 (79.9)	4054 (80.3)	1561 (78.2)	1400 (77.5)
Fruits, mean (SD), servings/d	86.5 (76.6)	95.2 (78.9)	103.6 (81.8)	118.3 (91.9)
Vegetables, mean (SD), servings/d	133.5 (103.6)	129.9 (99.7)	146.1 (114.0)	176.4 (142.8)
Dairy, mean (SD), servings/d	94.4 (108.3)	112.8 (111.5)	109.8 (103.8)	122.9 (112.2)
Meat or poultry, mean (SD), servings/d	77.8 (70.8)	73.1 (63.7)	73.5 (60.5)	106.3 (129.1)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range; ONTARGET, Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial; ORIGIN, Outcome Reduction With Initial Glargine Intervention; PURE, Prospective Urban Rural Epidemiology; TRANSCEND, Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease.

[a] Wealth index is based on information collected on household possessions, such as electricity, car, computer, television, and telephone.[15,19]

I^2 = 82.6 [P = .02]; for death, I^2 = 90.8 [P = .001]; for composite of death or CVD, I^2 = 87.6 [P = .004]) (Figure 1; eFigure 4 in the Supplement).

Among high-risk individuals or patients with existing vascular disease, a minimal fish intake of 175 g/week (approximately 2 servings/week) was associated with lower risk of major CVD (compared with ≤50 g/month; HR, 0.84; 95% CI, 0.77-0.92; P = .008), total mortality (HR, 0.83; 95% CI, 0.76-0.91; P < .001), and the composite of death or major CVD (HR, 0.86; 95% CI, 0.80-0.92; P = .002), after adjustment for known confounders (Figure 1; eFigure 4 in the Supplement), with no further apparent decrease in HR with consumption of 350 g/week or higher. No significant heterogeneity in the associations with the composite outcome was found across regions.

By contrast, in general populations without vascular disease, a higher fish intake was not significantly associated with major CVD (comparing ≥350 g/wk vs ≤50 g/mo; HR, 0.97; 95% CI, 0.88-1.08; P = .24), total mortality (HR, 0.97; 95% CI, 0.88-1.06; P = .48), or the composite of death or major CVD (HR, 0.97; 95% CI, 0.90-1.04; P = .18) (Figure 1; eFigure 4 in the Supplement).

Similarly, among high-risk individuals or patients with existing vascular disease, a higher fish intake was associated with lower risk of sudden cardiac death (comparing ≥350 g/wk with ≤50 g/mo; HR, 0.79; 95% CI, 0.63-0.99; P = .04). By contrast, in general populations without vascular disease, a higher fish intake was not significantly associated with these events (HR, 1.10; 95% CI, 0.64-1.89; P = .91).

Associations by Geographic Region

In PURE, higher fish intake appeared to be associated with a lower risk of composite events in China and Africa but appeared to be neutral in other regions. For patients with vascular disease, similar associations were found across regions.

Associations of Fish Intake With Cardiovascular Risk Markers

Higher fish intake was associated with lower triglyceride levels both among people with or without vascular disease

Table 2. Association Between Fish Intake and Clinical Events in Each Study[a]

Event	Category of fish intake, HR (95% CI)				*P* value for trend
	<50 g/mo	50 g/mo to <175 g/wk	175 to <350 g/wk	≥350 g/wk	
PURE trial (n = 147 541)					
Intake, median (IQR), g/wk	0.1 (0.0-7.0)	67.9 (32.9-109.9)	231.0 (197.4-273.7)	593.6 (450.1-1050.0)	
Composite of death or major CVD					
No. of participants	37 428	62 391	22 502	25 324	
No. (%) of events (n = 15 019)	4338 (11.6)	6331 (10.2)	1799 (8.0)	2551 (10.1)	
Age and sex adjusted	1 [Reference]	0.98 (0.94-1.02)	0.87 (0.81-0.92)	0.90 (0.84-0.96)	<.001
Multivariable	1 [Reference]	1.00 (0.95-1.04)	0.93 (0.88-1.00)	0.96 (0.89-1.03)	.08
No history of CVD	1 [Reference]	1.00 (0.95-1.05)	0.94 (0.88-1.01)	0.97 (0.90-1.04)	.18
History of CVD	1 [Reference]	0.96 (0.84-1.09)	0.89 (0.74-1.06)	0.90 (0.74-1.09)	.17
Total mortality					
No. of participants	37 428	62 391	22 502	25 324	
No. (%) of deaths (n = 10 076)	3131 (8.4)	4069 (6.5)	1140 (5.1)	1736 (6.9)	
Age and sex adjusted	1 [Reference]	1.00 (0.95-1.05)	0.89 (0.83-0.96)	0.91 (0.84-0.99)	.005
Multivariable	1 [Reference]	1.02 (0.96-1.08)	0.98 (0.90-1.07)	0.96 (0.88-1.05)	.35
No history of CVD	1 [Reference]	1.02 (0.96-1.08)	0.98 (0.90-1.07)	0.97 (0.88-1.06)	.48
History of CVD	1 [Reference]	0.94 (0.79-1.11)	0.92 (0.73-1.16)	0.91 (0.71-1.16)	.36
Major CVD events					
No. of participants	37 428	62 391	22 502	25 324	
No. (%) of events (n = 8201)	2215 (5.9)	3524 (5.6)	1001 (4.4)	1461 (5.8)	
Age and sex adjusted	1 [Reference]	0.98 (0.92-1.04)	0.85 (0.78-0.92)	0.90 (0.83-0.99)	.001
Multivariable	1 [Reference]	1.00 (0.94-1.07)	0.89 (0.82-0.97)	0.95 (0.86-1.04)	.06
No history of CVD	1 [Reference]	1.00 (0.94-1.08)	0.91 (0.83-1.00)	0.97 (0.88-1.08)	.24
History of CVD	1 [Reference]	0.97 (0.83-1.13)	0.83 (0.67-1.03)	0.86 (0.69-1.08)	.08
Myocardial infarction					
No. of participants	37 428	62 391	22 502	25 324	
No. (%) of events (n = 3806)	1146 (3.1)	1486 (2.4)	456 (2.0)	718 (2.8)	
Age and sex adjusted	1 [Reference]	0.97 (0.89-1.06)	0.90 (0.80-1.02)	0.88 (0.77-1.00)	.03
Multivariable	1 [Reference]	1.01 (0.92-1.11)	0.97 (0.85-1.10)	0.90 (0.78-1.04)	.15
No history of CVD	1 [Reference]	1.01 (0.91-1.12)	0.97 (0.84-1.12)	0.96 (0.82-1.11)	.46
History of CVD	1 [Reference]	0.95 (0.76-1.18)	0.96 (0.71-1.29)	0.71 (0.51-0.99)	.07
Stroke					
No. of participants	37 428	62 391	22 502	25 324	
No. (%) of events (n = 3925)	986 (2.6)	1827 (2.9)	478 (2.1)	634 (2.5)	
Age and sex adjusted	1 [Reference]	0.95 (0.87-1.04)	0.80 (0.71-0.90)	0.91 (0.80-1.03)	.01
Multivariable	1 [Reference]	0.97 (0.88-1.06)	0.81 (0.72-0.92)	0.95 (0.83-1.08)	.09
No history of CVD	1 [Reference]	0.96 (0.87-1.06)	0.84 (0.73-0.96)	0.97 (0.84-1.11)	.22
History of CVD	1 [Reference]	1.00 (0.80-1.25)	0.75 (0.55-1.03)	0.91 (0.66-1.27)	.22
Sudden cardiac death					
No. of participants	37 428	62 391	22 502	25 324	
No. (%) of events (n = 371)	109 (0.3)	189 (0.3)	30 (0.1)	43 (0.2)	
Age and sex adjusted	1 [Reference]	0.84 (0.64-1.09)	0.91 (0.57-1.46)	1.03 (0.64-1.65)	.79
Multivariable	1 [Reference]	0.78 (0.58-1.05)	0.83 (0.49-1.40)	0.99 (0.59-1.68)	.69
No history of CVD	1 [Reference]	0.78 (0.56-1.08)	0.75 (0.41-1.36)	1.10 (0.64-1.89)	.91
History of CVD	1 [Reference]	0.31 (0.11-0.87)	0.80 (0.18-3.68)	0.67 (0.02-19.2)	.50
CVD death					
No. of participants	37 428	62 391	22 502	25 324	
No. (%) of events (n = 3102)	993 (2.6)	1206 (1.9)	317 (1.4)	586 (2.3)	
Age and sex adjusted	1 [Reference]	1.02 (0.93-1.12)	0.87 (0.76-1.01)	0.90 (0.78-1.04)	.07
Multivariable	1 [Reference]	1.06 (0.96-1.18)	0.94 (0.81-1.10)	0.94 (0.80-1.10)	.33
No history of CVD	1 [Reference]	1.07 (0.96-1.20)	0.97 (0.82-1.15)	0.99 (0.84-1.20)	.84
History of CVD	1 [Reference]	0.95 (0.75-1.19)	0.81 (0.57-1.13)	0.72 (0.51-1.03)	.047

(continued)

Table 2. Association Between Fish Intake and Clinical Events in Each Study[a] (continued)

Event	Category of fish intake, HR (95% CI)				*P* value for trend
	<50 g/mo	50 g/mo to <175 g/wk	175 to <350 g/wk	≥350 g/wk	
Non-CVD death					
No. of participants	37 428	62 391	22 502	25 324	
No. (%) of events (n = 5904)	1820 (4.9)	2414 (3.9)	707 (3.1)	963 (3.8)	
Age and sex adjusted	1 [Reference]	0.98 (0.92-1.05)	0.91 (0.82-1.00)	0.94 (0.85-1.04)	.11
Multivariable	1 [Reference]	1.00 (0.93-1.07)	1.00 (0.90-1.11)	1.00 (0.90-1.12)	.99
No history of CVD	1 [Reference]	1.00 (0.92-1.07)	0.98 (0.88-1.10)	0.99 (0.88-1.10)	.76
History of CVD	1 [Reference]	0.96 (0.74-1.23)	1.05 (0.75-1.49)	1.09 (0.75-1.58)	.17
ONTARGET and TRANSCEND (n = 31 491)[b,c]					
Intake, median (IQR), g/d	2.8 (0 to 9.2)	119.7 (55.3-119.7)	240.1 (200.2-249.9)	450.1 (359.8-720.3)	
Composite of death or major CVD					
No. of participants	2801	16 377	7252	5061	
No. (%) of events	642 (22.9)	3434 (21.0)	1395 (19.2)	979 (19.3)	
Age and sex adjusted	1 [Reference]	0.94 (0.86-1.03)	0.85 (0.77-0.93)	0.84 (0.75-0.93)	<.001
Multivariable	1 [Reference]	0.96 (0.88-1.05)	0.88 (0.80-0.97)	0.88 (0.79-0.98)	.002
Total mortality					
No. of participants	2801	16 377	7252	5061	
No. (%) of events	404 (14.42)	2005 (12.24)	825 (11.38)	537 (10.61)	
Age and sex adjusted	1 [Reference]	0.90 (0.80-1.00)	0.82 (0.72-0.92)	0.75 (0.66-0.86)	<.001
Multivariable	1 [Reference]	0.92 (0.82-1.02)	0.86 (0.76-0.98)	0.81 (0.70-0.92)	<.001
Major CVD events					
No. of participants	2801	16 377	7252	5061	
No. (%) of events	504 (18.0)	2752 (16.8)	1116 (15.4)	810 (16.0)	
Age and sex adjusted	1 [Reference]	0.96 (0.87-1.06)	0.86 (0.77-0.96)	0.87 (0.78-0.98)	.001
Multivariable	1 [Reference]	0.97 (0.88-1.08)	0.89 (0.80-1.00)	0.91 (0.81-1.03)	.02
Myocardial infarction					
No. of participants	2801	16 377	7252	5061	
No. (%) of events	151 (5.4)	791 (4.8)	360 (5.0)	250 (4.9)	
Age and sex adjusted	1 [Reference]	0.86 (0.72-1.02)	0.85 (0.70-1.03)	0.84 (0.68-1.04)	.22
Multivariable	1 [Reference]	0.86 (0.72-1.03)	0.86 (0.71-1.05)	0.86 (0.69-1.06)	.34
Stroke					
No. of participants	2801	16 377	7252	5061	
No. (%) of events	118 (4.2)	740 (4.5)	285 (3.9)	252 (5.0)	
Age and sex adjusted	1 [Reference]	1.07 (0.87-1.30)	0.93 (0.75-1.16)	1.15 (0.91-1.44)	.64
Multivariable	1 [Reference]	1.11 (0.91-1.36)	0.99 (0.80-1.24)	1.25 (1.00-1.58)	.20
Sudden cardiac death					
No. of participants	2801	16 377	7252	5061	
No. (%) of events	43 (1.5)	221 (1.4)	101 (1.4)	66 (1.3)	
Age and sex adjusted	1 [Reference]	1.04 (0.74-1.47)	1.03 (0.71-1.48)	0.93 (0.62-1.39)	.30
Multivariable	1 [Reference]	1.04 (0.74-1.46)	1.05 (0.72-1.52)	0.94 (0.63-1.42)	.72
CVD death					
No. of participants	2801	16 377	7252	5061	
No. (%) of events	243 (8.7)	1199 (7.3)	497 (6.8)	326 (6.4)	
Age and sex adjusted	1 [Reference]	0.91 (0.79-1.04)	0.83 (0.71-0.98)	0.76 (0.64-0.91)	<.001
Multivariable	1 [Reference]	0.92 (0.80-1.06)	0.87 (0.74-1.02)	0.80 (0.67-0.96)	.01
Non-CVD death					
No. of participants	2801	16 377	7252	5061	
No. (%) of events	161 (5.8)	806 (4.9)	328 (4.5)	211 (4.2)	
Age and sex adjusted	1 [Reference]	0.87 (0.73-1.03)	0.78 (0.64-0.94)	0.73 (0.59-0.90)	.001
Multivariable	1 [Reference]	0.89 (0.75-1.06)	0.83 (0.68-1.01)	0.79 (0.64-0.98)	.02

(continued)

Table 2. Association Between Fish Intake and Clinical Events in Each Study[a] (continued)

Event	Category of fish intake, HR (95% CI)				*P* value for trend
	<50 g/mo	50 g/mo to <175 g/wk	175 to <350 g/wk	≥350 g/wk	
ORIGIN trial (n = 12 422)[b,c]					
Intake, median (IQR), g/d	2.2 (0 to 8.8)	64.5 (28.0-119.7)	248.5 (211.4-319.2)	567.7 (445.2-874.3)	
Composite of death or major CVD					
No. of participants	3572	5049	1995	1806	
No. (%) of events	866 (24.2)	1022 (20.2)	395 (19.8)	391 (21.6)	
Age and sex adjusted	1 [Reference]	0.76 (0.70-0.84)	0.70 (0.62-0.79)	0.77 (0.69-0.87)	<.001
Multivariable	1 [Reference]	0.81 (0.74-0.89)	0.81 (0.72-0.92)	0.88 (0.77-0.99)	.02
Total mortality					
No. of participants	3572	5049	1995	1806	
No. (%) of events	650 (18.2)	707 (14.0)	259 (13.0)	261 (14.4)	
Age and sex adjusted	1 [Reference]	0.73 (0.66-0.81)	0.65 (0.57-0.75)	0.73 (0.63-0.85)	<.001
Multivariable	1 [Reference]	0.79 (0.71-0.88)	0.77 (0.66-0.90)	0.86 (0.74-1.00)	.01
Major CVD events					
No. of participants	3572	5049	1995	1806	
No. (%) of events	656 (18.4)	781 (15.5)	286 (14.3)	297 (16.4)	
Age and sex adjusted	1 [Reference]	0.80 (0.72-0.89)	0.72 (0.62-0.82)	0.82 (0.72-0.95)	<.001
Multivariable	1 [Reference]	0.81 (0.73-0.90)	0.77 (0.66-0.89)	0.87 (0.76-1.01)	.02
Myocardial infarction					
No. of participants	3572	5049	1995	1806	
No. (%) of events	155 (4.34)	224 (4.44)	101 (5.06)	111 (6.15)	
Age and sex adjusted	1 [Reference]	0.96 (0.79-1.18)	1.06 (0.82-1.36)	1.28 (1.00-1.63)	.04
Multivariable	1 [Reference]	0.90 (0.73-1.11)	0.97 (0.74-1.25)	1.16 (0.90-1.49)	.21
Stroke					
No. of participants	3572	5049	1995	1806	
No. (%) of events	173 (4.8)	211 (4.2)	75 (3.8)	74 (4.1)	
Age and sex adjusted	1 [Reference]	0.83 (0.67-1.01)	0.72 (0.55-0.95)	0.79 (0.60-1.04)	.03
Multivariable	1 [Reference]	0.83 (0.68-1.02)	0.75 (0.57-1.00)	0.82 (0.62-1.09)	.09
Sudden cardiac death					
No. of participants	3572	5049	1995	1806	
No. (%) of events	202 (5.6)	170 (3.4)	63 (3.2)	72 (4.0)	
Age and sex adjusted	1 [Reference]	0.56 (0.46-0.69)	0.51 (0.38-0.68)	0.64 (0.49-0.84)	<.001
Multivariable	1 [Reference]	0.61 (0.49-0.75)	0.60 (0.45-0.81)	0.73 (0.55-0.98)	.006
CVD death					
No. of participants	3572	5049	1995	1806	
No. (%) of events	416 (11.6)	433 (8.6)	138 (6.9)	148 (8.2)	
Age and sex adjusted	1 [Reference]	0.70 (0.61-0.80)	0.55 (0.45-0.66)	0.65 (0.54-0.79)	<.001
Multivariable	1 [Reference]	0.76 (0.66-0.87)	0.66 (0.54-0.80)	0.78 (0.64-0.94)	<.001
Non-CVD death					
No. of participants	3572	5049	1995	1806	
No. (%) of events	234 (6.6)	274 (5.4)	121 (6.1)	113 (6.3)	
Age and sex adjusted	1 [Reference]	0.78 (0.66-0.93)	0.84 (0.68-1.05)	0.88 (0.70-1.10)	.23
Multivariable	1 [Reference]	0.84 (0.70-1.01)	0.97 (0.77-1.22)	1.00 (0.79-1.26)	.86

Abbreviations: CVD, cardiovascular disease; IQR, interquartile range; ONTARGET, Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial; ORIGIN, Outcome Reduction With Initial Glargine Intervention; PURE, Prospective Urban Rural Epidemiology; TRANSCEND, Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease.

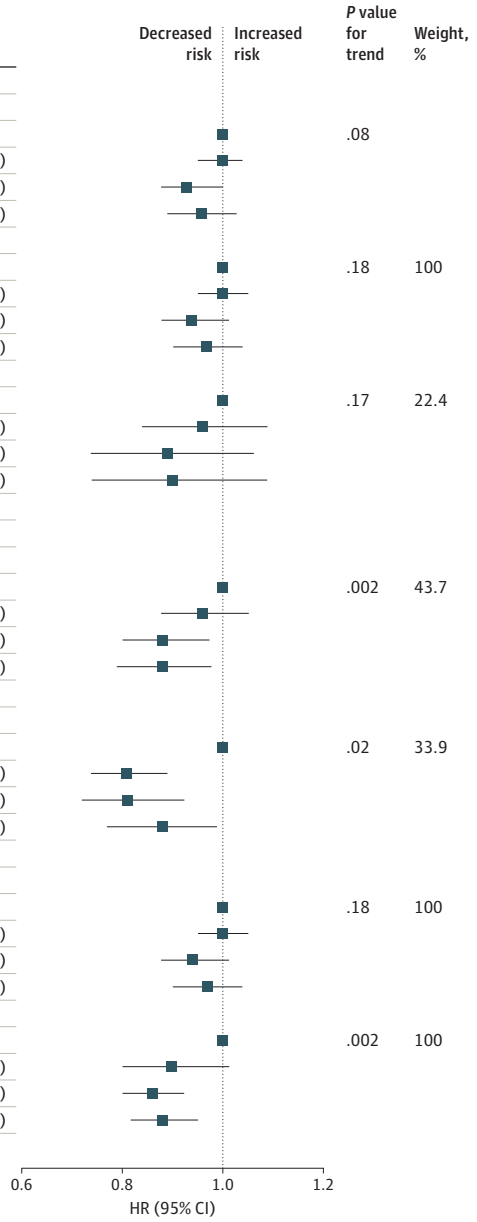
[a] Adjusted for age, sex and study center (latter as random effect). Multivariable model is adjusted for age, sex, study center (random effect), body mass index, educational level (primary or less; secondary; trade, college, or university), smoking status (never, former, or current), alcohol intake, physical activity (low, <600; moderate, 600-3000; high, >3000 metabolic equivalent of task per minute per week), urban or rural location, history of diabetes, cancer, use of statin or antihypertension medications, and intake of fruit, vegetables, red meat, poultry, dairy, and total energy.

[b] In ONTARGET and TRANSCEND combined and in the ORIGIN trial, physical activity categories were: mainly sedentary (reference standard); 1 to 4 times per week; and more than 4 times per week.

[c] ONTARGET and TRANSCEND combined and the ORIGIN trial also adjusted for treatment allocation.

Figure 1. Fish Intake vs Risk of Composite of Death or Major Cardiovascular Disease (CVD) by Study and by Prior Cardiovascular Disease

Study/ CVD status	No. of events	HR (95% CI)	*P* value for trend	Weight, %
PURE				
Overall fish intake				
<50 g/mo	37 428	1 [Reference]	.08	
50 g/mo to <175 g/wk	62 391	1.00 (0.95-1.04)		
175 to <350 g/wk	22 502	0.93 (0.88-1.00)		
350 g/wk[a]	25 324	0.96 (0.89-1.03)		
No prior CVD fish intake				
<50 g/mo	35 414	1 [Reference]	.18	100
50 g/mo to <175 g/wk	58 905	1.00 (0.95-1.05)		
175 to <350 g/wk	21 333	0.94 (0.88-1.01)		
350 g/wk[a]	24 175	0.97 (0.90-1.04)		
Prior CVD fish intake				
<50 g/mo	2014	1 [Reference]	.17	22.4
50 g/mo to <175 g/wk	3486	0.96 (0.84-1.09)		
175 to <350 g/wk	1169	0.89 (0.74-1.06)		
350 g/wk[a]	1149	0.90 (0.74-1.09)		
Subtotal I^2 = 0% (*P* = .48)				
ONTARGET/TRANSCEND				
Prior CVD fish intake				
<50 g/mo	2801	1 [Reference]	.002	43.7
50 g/mo to <175 g/wk	16 377	0.96 (0.88-1.05)		
175 to <350 g/wk	7252	0.88 (0.80-0.97)		
350 g/wk[a]	5061	0.88 (0.79-0.98)		
ORIGIN				
Prior or high-risk CVD fish intake				
<50 g/mo	3572	1 [Reference]	.02	33.9
50 g/mo to <175 g/wk	5049	0.81 (0.74-0.89)		
175 to <350 g/wk	1995	0.81 (0.72-0.92)		
350 g/wk[a]	1806	0.88 (0.77-0.99)		
Overall				
No prior CVD fish intake				
<50 g/mo	35 414	1 [Reference]	.18	100
50 g/mo to <175 g/wk	58 905	1.00 (0.95-1.05)		
175 to <350 g/wk	21 333	0.94 (0.88-1.04)		
350 g/wk[a]	24 175	0.97 (0.90-1.04)		
Prior or high-risk CVD fish intake				
<50 g/mo	8387	1 [Reference]	.002	100
50 g/mo to <175 g/wk	24 912	0.90 (0.80-1.01)		
175 to <350 g/wk	10 416	0.86 (0.80-0.92)		
350 g/wk[a]	8016	0.88 (0.82-0.95)		
Subtotal I^2 = 87.6% (*P* = .004)				



[a] Adjusted for age, sex, study center (random effect), body mass index, educational level, smoking status, physical activity, alcohol intake, urban vs rural location, history of diabetes, cardiovascular disease, cancer, use of statin or antihypertension medication, and intake of fruit, vegetables, red meat, poultry, dairy, and total energy.

(**Figure 3**; eTable 1 in the Supplement). However, no beneficial associations were found with other risk markers, and there were higher levels of low-density lipoprotein cholesterol (LDL-C) (Figure 3; eFigure 3 in the Supplement).

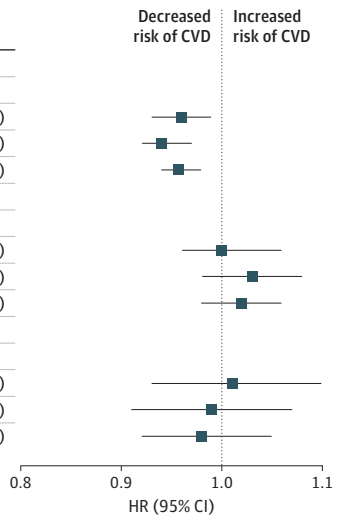
Discussion

In this analysis of 4 international prospective cohort studies with 15 390 major CVD events and 15 712 deaths, among 191 558 people from 58 countries in 6 continents, we noted significant heterogeneity in the association between fish intake and major CVD events by history of CVD status. Lower risk of major CVD, total mortality, and their composite was found with higher fish intake of at least 175 g/wk (approximately 2 servings) among high-risk individuals or patients with vascular disease, but not in general populations without vascular disease. A similar pattern of results was found for sudden cardiac death, with significant protective associations observed among patients with vascular disease, but neutral in general populations without vascular disease. Furthermore, the data available from 1 study on types of fish suggested that oily fish but not other types of fish were associated with greater benefits.

Dietary guidelines generally encourage consumption of a variety of fish, preferably oily types (eg, salmon, sardines, tuna,

Figure 2. Associations Between Types of Fish (per 5-g Increment) and Clinical Events in the Outcome Reduction With Initial Glargine Intervention (ORIGIN) Trial (n = 12 422)

Study	No. of CVD events, %	HR (95% CI)	P value
High or moderate ω-3 fish			
Event			
Total mortality	1877	0.96 (0.93-0.99)	.004
Major CVD	2020	0.94 (0.92-0.97)	<.001
Composite	2674	0.96 (0.94-0.98)	<.001
Low ω-3 fish			
Event			
Total mortality	1877	1.01 (0.96-1.06)	.78
Major CVD	2020	1.03 (0.98-1.08)	.27
Composite	2674	1.02 (0.98-1.06)	.40
Shellfish			
Event			
Total mortality	1877	1.01 (0.93-1.10)	.76
Major CVD	2020	0.99 (0.91-1.07)	.72
Composite	2674	0.98 (0.92-1.05)	.53



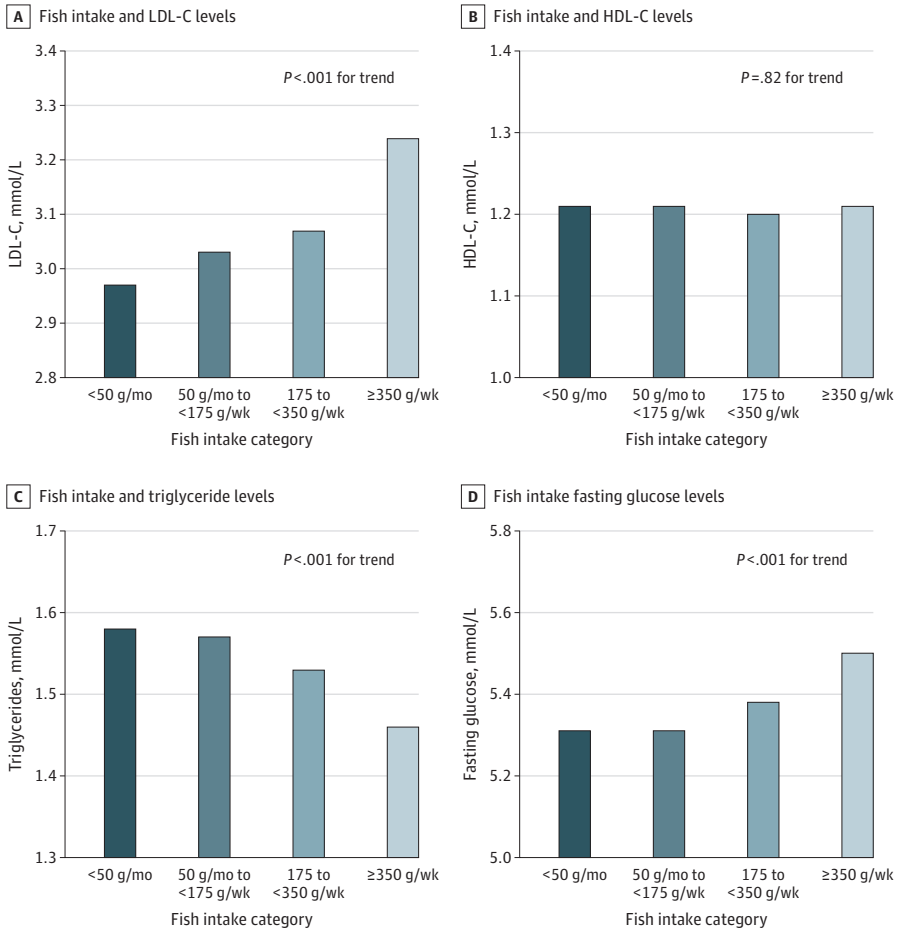
Data are adjusted for age, sex, study center (random effect), body mass index, educational level, smoking status, physical activity, alcohol intake, history of diabetes, cardiovascular disease (CVD), cancer, use of statin or antihypertension medication, and intake of fruit, vegetables, red meat, poultry, and dairy. Fish with highest ω-3 levels included herring, mackerel, sable, salmon, tuna (steak), and sardine. Other fish with high ω-3 levels included anchovy, bluefish, oyster, tuna (can), salmon (can), and trout. Fish with lowest ω-3 levels included bass, barramundi, bream, flathead, flounder, perch, snapper, octopus, sword fish, tile fish, and shark. Shellfish included crab, lobster, scallop, and mussel.[30] HR represents hazard ratio.

and mackerel), at least twice a week for CVD prevention.[1,2,31-33] High-dose fish oil has been shown to lower triglyceride levels in people with severe hypertriglyceridemia.[6,7] Furthermore, short-term trials showed that 2 servings of fatty fish per week (roughly 112 g [4 oz] each) decreased triglyceride levels by 11.4% but also slightly increased LDL-C levels compared with the control diet.[34,35] Our findings are consistent with this information, both among people with and among persons without vascular disease (8% decrease in triglyceride level with approximately 2 standard servings of fish per week but with slightly higher LDL-C level). The increase in LDL-C level associated with fish intake may not suggest an increased CVD risk because this risk may be offset by the positive effects on lipoproteins.[36] Our finding of higher blood glucose levels associated with higher fish intake is consistent with some trial data for patients with diabetes,[37] but other trials of fish or fish oil consumption have been neutral regarding this factor.[38] Cohort studies of fish intake and incident diabetes have shown variable results.[39,40] Cooking methods, mercury levels, and the presence of polychlorinated biphenyls or other environmental contaminants in fish are potential factors associated with the different findings across studies,[41] but further work is needed in this area. Given that there are associations with CVD risk markers, some of which may be protective and others harmful, and that some fish may contain contaminants,[42,43] studying the association of fish intake with outcome events is essential to inform recommendations for populations.

To our knowledge, there are no primary prevention trials on fish intake and CVD outcomes. Some prospective cohort studies among mostly healthy people have found an inverse association between fish intake and CVD mortality, whereas others do not.[44] A recent umbrella review of cohort studies found modest protective associations of fish consumption with fatal coronary heart disease (ie, summary relative risks ranging from 2% to 15% lower risk).[14] Compared with fatal cardiac events, fish consumption has weaker associations with nonfatal cardiac events and stroke.[14,44] However, those meta-analyses were not based on combining individual data from each study and thus were not able to fully adjust for all potential confounders. In PURE, which covers fish intake in numerous world regions in which various amounts and types of fish are consumed, we found no significant association of fish intake with outcome events. In analyses by geographic region, we found considerable heterogeneity across geographic regions, but associations were neutral in most regions except for China and Africa, where protective associations between fish intake and composite events were detected. Taken together, the results suggest that higher fish consumption may be modestly associated with CVD outcomes or mortality in generally healthy populations.

Our findings of favorable associations of fish intake with CVD events and mortality among patients with vascular disease are consistent with the DART-1 (Diet and Reinfarction) trial,[45] but not the DART 2 study[46] or 2 recent meta-analyses of randomized clinical trials of fish oil supplementation for high-risk individuals, which showed that fish oil (approximately 1 g/d) had no association with CVD outcomes or total mortality.[8,9] More recently, in 2018, 2 trials of a 1-g/d ω-3 formulation found no significant effect of supplementation on major CVD, but there was significant lowering of fatal myocardial infarction, total coronary heart disease,[12] and fatal CVD.[11] In a 2019 meta-analysis[10] that included those new trials,[11,12] individuals who received ω-3 supplementation had significantly better CVD outcomes, even after excluding the recent REDUCE-IT randomized clinical trial of patients with elevated triglyceride levels that used a much higher dose of fish oil (4 g daily).[13] In our study, CVD risk was lowest with a moderate amount of fish (ie, at least 175 g/wk, or approximately 2 servings/wk), with no further apparent decrease in risk with higher fish intake (ie, >350 g/wk, or >3-4 servings/wk). Similarly, previous cohort studies of mostly generally healthy populations showed that approximately 2 or more

Figure 3. Mean Levels of Cardiovascular Risk Markers by Amount of Fish Intake in the Prospective Urban Rural Epidemiology (PURE) Trial (n = 147 541)



Data adjusted for age, sex, study center (random effect), body mass index, educational level, smoking status, physical activity, alcohol intake, urban vs rural location, history of diabetes, cardiovascular disease, cancer, use of statin or antihypertension medication, and intake of fruit, vegetables, red meat, poultry, dairy, and total energy. LDL-C represents low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

servings/wk (150 g/wk) is associated with the lowest CVD risk.[14,44] On this basis, 2 servings of fish per week may be the minimal amount of fish needed to reach maximum benefit (an amount consistent with current recommendations for CVD prevention),[1,2,31-33] with little additional benefit with higher intakes among patients with vascular disease. As expected in ORIGIN, for which we collected information on types of fish, consumption of fish with higher amounts of ω-3 fats was strongly associated with a lower risk of major CVD, whereas consumption of other types of fish was found to be neutral. These findings are compatible with trials showing favorable effects of oily fish intake on CVD risk markers.[6] In addition, fish may have selective antiarrhythmic effects and accompanying protection against sudden cardiac death.[3,4,8] Some[47] but not all[48,49] trials of patients with vascular disease found that fish oil use results in a lower risk of sudden cardiac death. In our cohorts of patients with vascular disease, we found protective associations of fish intake (mainly from high ω-3 fish) with sudden death (HR, 0.79; 95% CI, 0.63-0.99, comparing >350 g/wk vs <50 g/mo). Collectively, a possible modest cardiovascular benefit (ie, approximately 10%-15% risk lowering) was found to be associated with consuming an equivalent of at least 175 g (2 servings) of fish weekly and with similar protection for more than 350 g (approximately 4 servings) weekly for secondary prevention. However, our findings require confirmation from randomized clinical trials evaluating the effects of increasing fish consumption (especially oily fish) on the clinical outcomes of people with vascular disease.

Limitations

The first potential limitation of this study is that diet was self-reported, and variations in reporting may lead to random errors that could dilute real associations between fish intake and clinical outcomes. Second, we were not able to consider cooking methods, how the fish was consumed (with sauces, smoked, salted, etc), or contaminants in fish, which may also affect the results. Furthermore, we were not able to conduct a separate assessment of oily fish in PURE, which could at least partly explain the overall null findings. Third, in observational studies, the possibility of residual confounding cannot be completely ruled out (eg, fish intake may be a proxy for poverty or access to health care). However, our results persisted despite extensive adjustments for all known confounders, including the use of 4 markers of socioeconomic status (educational level, wealth, urban vs

rural location, and geographic location). In addition, we adjusted for study center as a random effect, which takes into account socioeconomic factors and clustering by community, leading to comparisons within countries (eAppendix in the Supplement). Lastly, some misclassification of fish intake cannot be ruled out because we did not have repeated measures of diet in all studies, and a full-length FFQ was used only in PURE. However, the ORIGIN study, in which we conducted repeated diet assessments at 2 years, showed similar results based on the first vs second diet assessments, indicating that misclassification of fish intake during follow-up was not a major factor in our findings (eTable 3 in the Supplement).

Conclusions

In summary, this study found that a minimal fish intake of 175 g (approximately 2 servings) weekly was associated with lower risk of major CVD events and total mortality among high-risk individuals or patients with existing vascular disease but not in the general population.

ARTICLE INFORMATION

Accepted for Publication: December 18, 2020.

Published Online: March 8, 2021. doi:10.1001/jamainternmed.2021.0036

Correction: This article was corrected on May 3, 2021, to fix an error in an author affiliation.

Author Affiliations: Madras Diabetes Research Foundation and Dr. Mohan's Diabetes Specialities Centre, Chennai, India (D. Mohan, V. Mohan); Population Health Research Institute, Hamilton Health Sciences and McMaster University, Hamilton, Canada (Mente, Dehghan, Rangarajan, Hu, Teo, Gerstein, S. Yusuf); Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada (Mente, Teo, Gerstein, S. Yusuf); Department of Medicine, McMaster University, Hamilton, Ontario, Canada; (O'Donnell, Teo, Gerstein, S. Yusuf); HRB-Clinical Research Facility, NUI Galway, Ireland (O'Donnell); Université Laval Institut Universitaire de Cardiologie et de Pneumologie de Québec, Québec, Canada, G1V 4G5 (Dagenais); Department of Medicine, University of Ottawa, Ottawa, Ontario, Canada (Wielgosz); Faculty of Health Sciences, and Department of Biomedical Physiology & Kinesiology, Simon Fraser University, Vancouver, British Columbia, Canada (Lear); State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Disease, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, China (Wei); Estudios Clinicos Latinoamerica ECLA, Rosario, Santa Fe, Argentina (Diaz); International Research Centre, Hospital Alemao Oswaldo Cruz, Sao Paulo, Brazil, Universidade Santo Amaro (UNISA), Sao Paulo, SP Brazil (Avezum); Masira Research Institute, Medical School, Santander University (UDES), Colombia (Lopez-Jaramillo); Universidad de La Frontera, Francisco Salazar, Temuco, Chile (Lanas); St John's Research Institute, Koramangala, Bangalore, India (Swaminathan); School of Public Health, Postgraduate Institute of Medical Education and Research, Chandigarh, India (Kaur); Health Action by People, Amrita Institute of Medical Sciences, Trivandrum, Kerala, India (Vijayakumar); Eternal Heart Care Centre and Research Institute, Rajasthan University of Health Sciences, Jaipur, India (Gupta); Wroclaw Medical University, Department of Internal Medicine, 4th Military Hospital, Wroclaw, Poland (Szuba); Department of Community Health Sciences and Medicine, Aga Khan University, Karachi Pakistan (Iqbal); Independent University, Bangladesh, Bashundhara, Dhaka, Bangladesh (R. Yusuf); Isfahan Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran (Mohammadifard); Institute for Community and Public Health, Birzeit University, Birzeit, Palestine (Khatib); Advocate Research Institute, Advocate Health Care, Chicago, Illinois (Khatib); Universiti Teknologi MARA, Sungai Buloh, Selangor, Malaysia, UCSI University, Cheras, Selangor, Malaysia (Yusoff); Cardiology Department, Ankara University Medical School, Ankara, Turkey (Gulec); Department of Molecular and Clinical Medicine, Sahlgrenska Academy, University of Gothenburg and Sahlgrenska University Hospital/Östra Hospital, Gothenburg, Sweden (Rosengren); Hatta Hospital, Dubai Health Authority, Dubai Medical University, Dubai, United Arab Emirates (Yusufali); Centre of Excellence for Nutrition, Faculty of Health Sciences, Potchefstroom, South Africa (Wentzel-Viljoen); Physiology Department, College of Health Sciences, University of Zimbabwe, Harare, Zimbabwe (Chifamba); University of the Philippines, Ermita, Manila, Philippines (Dans); Department of Cardiac Sciences, King Fahad Cardiac Center, College of Medicine, King Saud University, Riyadh, Saudi Arabia (Alhabib); Department of Medicine, Etherington Hall, Queen's University, Kingston, Ontario, Canada (Yeates).

Author Contributions: Drs D. Mohan and Mente are co–first authors. Drs D. Mohan and Mente had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Mente, Dehghan, O'Donnell, V. Mohan, Khatib, Chifamba, Dans, S. Yusuf.
Acquisition, analysis, or interpretation of data: D. Mohan, Mente, Rangarajan, O'Donnell, Hu, Dagenais, Wielgosz, Lear, Wei, Diaz, Avezum, Lopez-Jaramillo, Lanas, Swaminathan, Kaur, Krishnapillai, Gupta, Szuba, Iqbal, R. Yusuf, Mohammadifard, Khatib, Yusoff, Gulec, Rosengren, Yusufali, Wentzel-Viljoen, Alhabib, Yeates, Teo, Gerstein, S. Yusuf.
Drafting of the manuscript: D. Mohan, Mente, Dehghan, Dans.
Critical revision of the manuscript for important intellectual content: Rangarajan, O'Donnell, Hu, Dagenais, Wielgosz, Lear, Wei, Diaz, Avezum, Lopez-Jaramillo, Lanas, Swaminathan, Kaur, Krishnapillai, V. Mohan, Gupta, Szuba, Iqbal, R. Yusuf, Mohammadifard, Khatib, Yusoff, Gulec, Rosengren, Yusufali, Wentzel-Viljoen, Chifamba, Alhabib, Yeates, Teo, Gerstein, S. Yusuf.
Statistical analysis: Mente, Dehghan, Hu, Wei, Khatib.
Obtained funding: O'Donnell, Lear, Lanas, Rosengren, Yusufali, Alhabib, Yeates.
Administrative, technical, or material support: Rangarajan, Dagenais, Wielgosz, Diaz, Lanas, Swaminathan, Krishnapillai, Gupta, Yusoff, Gulec, Yusufali, Wentzel-Viljoen, Alhabib, S. Yusuf.
Supervision: Rangarajan, Wielgosz, Diaz, Kaur, V. Mohan, Gupta, Szuba, Iqbal, R. Yusuf, Khatib, Yusufali, Chifamba, Alhabib, Yeates, Teo, S. Yusuf.

Conflict of Interest Disclosures: Dr Diaz reported receiving grants from Amgen and Sanofi; recieiving personal fees from Sanofi; and receiving grants from Amarin outside the submitted work. Dr Szuba reported receiving grants from the Polish Ministry of Science and Higher Education and from the Population Health Research Institute during the conduct of the study. Dr Gulec reported receiving personal fees from Amgen, Astra Zeneca, Boehringer Ingelheim, Daichii Sankyo, Menarini, Pfizer, and Recordati outside the submitted work. Dr Yusufali reported receiving grants from Sheikh Hamdan bin Rashid AlMakhtoum Medical Research Award during the conduct of the study. Dr Gertstein reported recieving grants from Sanofi during the conduct of the study; grants and personal fees from AstraZeneca, Lilly, Novo Nordisk and Sanofi; and receiving personal fees from Abbot, Boehringer Ingelheim, Kowa Pharmaceuticals America Inc, and Merck & Co outside the submitted work. Dr S. Yusuf reported recieving support from the Mary W Burke endowed chair of the Heart and Stroke Foundation of Ontario. No other disclosures were reported.

Funding/Support: Dr S. Yusuf is supported by the Marion W Burke endowed chair of the Heart and Stroke Foundation of Ontario. The PURE study is an investigator-initiated study that is funded by the Population Health Research Institute, Hamilton Health Sciences Research Institute (HHSRI), the Canadian Institutes of Health Research, Heart and Stroke Foundation of Ontario, Support from Canadian Institutes of Health Research's Strategy for Patient Oriented Research, through the Ontario SPOR Support Unit, as well as the Ontario Ministry of Health and Long-Term Care and through unrestricted grants from several pharmaceutical companies (with major contributions from AstraZeneca [Canada], Sanofi-Aventis [France and Canada], Boehringer Ingelheim [Germany and Canada], Servier, and GlaxoSmithKline), and additional contributions from Novartis and King Pharma and from various national or local organisations in participating countries. These include: Argentina: Fundacion ECLA (Estudios Clínicos Latino America) ; Bangladesh: Independent University, Bangladesh and Mitra and Associates; Brazil: Unilever Health Institute, Brazil; Canada: This study was supported by an unrestricted grant from Dairy Farmers of Canada and the National Dairy Council (US), Public Health Agency of Canada and Champlain Cardiovascular Disease Prevention Network; Chile: Universidad de La Frontera [DI13-PE11]; China: National Center for Cardiovascular Diseases and ThinkTank Research

Center for Health Development; Colombia: Colciencias (grant 6566-04-18062 and grant 6517-777-58228); India: Indian Council of Medical Research; Malaysia: Ministry of Science, Technology and Innovation of Malaysia (grants 100-IRDC/BIOTEK 16/6/21 [13/2007] and 07-05-IFN-BPH 010), Ministry of Higher Education of Malaysia (grant 600-RMI/LRGS/5/3 [2/2011]), Universiti Teknologi MARA, Universiti Kebangsaan Malaysia (UKM-Hejim-Komuniti-15-2010); occupied Palestinian territory: the United Nations Relief and Works Agency for Palestine Refugees in the Near East, occupied Palestinian territory; International Development Research Centre, Canada; Philippines: Philippine Council for Health Research and Development; Poland: Polish Ministry of Science and Higher Education (grant 290/W-PURE/2008/0), Wroclaw Medical University; Saudi Arabia: Saudi Heart Association, Dr.Mohammad Alfagih Hospital, The Deanship of Scientific Research at King Saud University (Research group RG -1436-013), Riyadh; Saleh Hamza Serafi Chair for Research of Coronary Heart Disease, Umm AlQura University, Makkah, Saudi Arabia; South Africa: The North-West University, SA and Netherlands Programme for Alternative Development, National Research Foundation, Medical Research Council of South Africa, The South Africa Sugar Association, Faculty of Community and Health Sciences; Sweden: Grants from the Swedish state under the Agreement concerning research and education of doctors; the Swedish Heart and Lung Foundation; the Swedish Research Council; the Swedish Council for Health, Working Life and Welfare, King Gustaf V's and Queen Victoria Freemason's Foundation, AFA Insurance; Turkey: Metabolic Syndrome Society, AstraZeneca, Sanofi Aventis; United Arab Emirates: Sheikh Hamdan Bin Rashid Al Maktoum Award For Medical Sciences and Dubai Health Authority, Dubai.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information: The PURE, ONTARGET, TRANSCEND, and ORIGIN investigators are as follows. An asterisk denotes a national coordinator, and a hashtag denotes deceased person. **PURE Project Office Staff, National Coordinators, Investigators, and Key Staff: Project office (Population Health Research Institute, Hamilton Health Sciences and McMaster University, Hamilton, Canada):** S. Yusuf* (Principal Investigator), S. Rangarajan (Program Manager); K.K. Teo, S.S. Anand, C.K. Chow, M. O'Donnell, A. Mente, D. Leong, A. Smyth, P. Joseph, M. Duong, R. D'Souza, M. Walli-Attaei, S. Islam (Statistician), W. Hu (Statistician), C. Ramasundarahettige (Statistician), P. Sheridan (Statistician), S. Bangdiwala, L. Dyal, B. Liu (Biometric Programmer), C. Tang (Biometric Programmer), X. Yang (Biometric Programmer), R. Zhao (Biometric Programmer), L. Farago (ICT), M. Zarate (ICT), J. Godreault (ICT), M. Haskins (ICT), M. Jethva (ICT), G. Rigitano (ICT), A. Vaghela (ICT), M. Dehghan (Nutrition Epidemiologist), A. Aliberti, A. Reyes, A. Zaki, B. Connolly, B. Zhang, D. Agapay, D. Krol, E. McNeice, E. Ramezani, F. Shifaly, G. McAlpine, I. Kay, J. Rimac, J. Swallow, M. Di Marino, M. Jakymyshyn, M(a). Mushtaha, M(o). Mushtaha, M. Trottier, N. Aoucheva, N. Kandy, P. Mackie, R. Buthool, R. Patel, R. Solano, S. Gopal, S. Ramacham, S. Trottier. **Core Laboratories**: G. Pare, M. McQueen, S. Lamers, J. Keys (Hamilton), X. Wang (Beijing, China), A. Devanath (Bangalore, India). **Argentina:** R. Diaz*, A. Orlandini, P. Lamelas, M.L. Diaz, A. Pascual, M. Salvador, C. Chacon; **Bangladesh:** O. Rahman*, R. Yusuf*, S.A.K.S. Ahmed, T. Choudhury, M. Sintaha, A. Khan, O. Alam, N. Nayeem, S.N. Mitra, S. Islam, F. Pasha; **Brazil:** A. Avezum*, C.S. Marcilio, A.C. Mattos, G.B. Oliveira; **Canada:** K. Teo*, S. Yusuf*, Sumathy Rangarajan, A. Arshad, B. Bideri, I. Kay, J. Rimac, R. Buthool, S. Trottier, G. Dagenais, P. Poirier, G. Turbide, A.S. Bourlaud, A. LeBlanc De Bluts, M. Cayer, I. Tardif, M. Pettigrew, S. Lear, V. de Jong, A.N. Saidy, V. Kandola, E. Corber, I. Vukmirovich, D. Gasevic, A. Wielgosz, A. Pipe, A. Lefebvre, A. Pepe, A. Auclair, A. Prémont, A.S. Bourlaud; **Chile:** F. Lanas*, P. Serón, M.J. Oliveros, F. Cazor, Y. Palacios; **China:** Liu Lisheng*, Li Wei*, Chen Chunming#, Zhao Wenhua. Hu Bo, Yin Lu, Zhu Jun, Liang Yan, Sun Yi, Wang Yang, Deng Qing, Jia Xuan, He Xinye, Zhang Hongye, Bo Jian, Wang Xingyu, Liu Xu, Gao Nan, Bai Xiulin, Yao Chenrui, Cheng Xiaoru, Wang Chuangshi, Li Sidong, Liu Weida, Lang Xinyue, Liu Xiaoyun, Zhu Yibing, Xie Liya, Liu Zhiguang, Ren Yingjuan, Dai Xi, Gao Liuning, Wang Liping, Su yuxuan, Han Guoliang, Song Rui, Cao Zhuangni, Sun Yaya, Li Xiangrong, Wang Jing, Wang Li, Peng Ya, Li Xiaoqing, Li Ling, Wang Jia, Zou Jianmei, Gao Fan, Tian Shaofang, Liu Lifu, Li Yongmei, Bi Yanhui, Li Xin, Zhang Anran, Wu Dandan, Cheng ying, Xiao Yize, Lu Fanghong, Li Yindong, Hou Yan, Zhang Liangqing, Guo Baoxia, Liao Xiaoyang, Chen Di, Zhang Peng, Li Ning, Ma Xiaolan, Lei Rensheng, Fu Minfan, Liu Yu, Xing Xiaojie, Yang Youzhu, Zhao Shenghu, Xiang Quanyong, Tang Jinhua, Liu Zhengrong, Qiang Deren, Li Xiaoxia, Xu Zhengting, Aideeraili.Ayoupu, Zhao Qian; **Colombia:** P. Lopez-Jaramillo*, P.A. Camacho-Lopez, M. Perez, J. Otero-Wandurraga, D. I Molina, C. Cure-Cure, J.L. Accini, E. Hernandez, E. Arcos, C. Narvaez, A. Sotomayor, F. Manzur, H. Garcia, G. Sanchez, F. Cotes, A. Rico, M. Duran, C. Torres; **India: Bangalore -** P. Mony *, M. Vaz*, S. Swaminathan, A.V. Bharathi, K. Shankar, A. V. Kurpad, K.G. Jayachitra, H.A.L. Hospital, A.R. Raju, S. Niramala, V. Hemalatha, K. Murali, C. Balaji, A. Janaki, K. Amaranadh, P. Vijayalakshmi, **Chennai** - V. Mohan*, R.M. Anjana, M. Deepa, K. Parthiban, L. Dhanasekaran, S.K. Sundaram, M. Rajalakshmi, P. Rajaneesh, K. Munusamy, M. Anitha, S. Hemavathy, T. Rahulashankiruthiyayan, D. Anitha, R. Dhanasekar, S. Sureshkumar, D. Anitha, K. Sridevi, **Jaipur** - R. Gupta, R.B. Panwar, I. Mohan, P. Rastogi, S. Rastogi, R. Bhargava, M. Sharma, D. Sharma, **Trivandrum** - V. Raman Kutty, K. Vijayakumar, S. Nair, Kamala R., Manu M.S., Arunlal A.R., Veena A., Sandeep P. Kumar, Leena Kumari, Tessi R., Jith S., K. Ajayan, G. Rajasree, A.R. Renjini, A. Deepu, B. Sandhya, S. Asha, H.S. Soumya, **Chandigarh**- R. Kumar, M. Kaur, P.V.M. Lakshmi, V. Sagar J.S. Thakur, B. Patro, R. Mahajan, A. Josh, G. Singh, K. Sharma, P. Chaudary, **Iran:** R. Kelishadi*, A. Bahonar, N. Mohammadifard, H. Heidari, **Kazakhstan:** K. Davletov*, B. Assembekov, B. Amirov; **Kyrgyzstan:** E. Mirrakhimov*, S. Abilova, U. Zakirov, U. Toktomamatov; **Malaysia: UiTM -** K. Yusoff*, T.S. Ismail, K. Ng, A. Devi, N. Mat-Nasir, A.S. Ramli, M.N.K. Nor-Ashikin, R. Dasiman, M.Y. Mazapuspavina, F. Ariffin, M. Miskan, H. Abdul-Hamid, S. Abdul-Razak, N. Baharudin, N.M.N. Mohd-Nasir, S.F. Badlishah-Sham, M.S. Mohamed-Yassin, M. Kaur, M. Koshy, F.A. Majid, N.A. Bakar, N. Zainon, R. Salleh, S.R. Norlizan, N.M. Ghazali, M. Baharom, H. Zulkifli, R. Razali, S. Ali, C.W.J.C.W. Hafar, F. Basir; **UKM** - Noorhassim Ismail, M.J. Hasni, M.T. Azmi, M.I. Zaleha, R. Ismail, K.Y. Hazdi, N. Saian, A. Jusoh, N. Nasir, A. Ayub, N. Mohamed, A. Jamaludin, Z. Rahim; **Occupied Palestinian Territory:** R. Khatib*, U. Khammash, R. Giacaman; **Pakistan:** R. Iqbal*, R. Khawaja, I. Azam, K. Kazmi; **Peru:** J. Miranda*, A. Bernabe Ortiz, W. Checkley, R.H. Gilman, L. Smeeth, R.M. Carrillo, M. de los Angeles, C. Tarazona Meza; **Philippines:** A. Dans*, H.U. Co, J.T. Sanchez, L. Pudol, C. Zamora-Pudol, L.A. M Palileo-Villanueva, M.R. Aquino, C. Abaquin, S.L. Pudol, K. Manguiat, S. Malayang; **Poland:** W. Zatonski*, A. Szuba, K. Zatonska, R. Ilow#, M. Ferus, B. Regulska-Ilow, D. Różańska, M. Wolyniec; **Saudi Arabia:** K.F. AlHabib*, M. Alshamiri, H.B. Altaradi, O. Alnobani, N. Alkamel, M. Ali, M. Abdulrahman, R. Nouri; **South Africa:** L. Kruger*, A. Kruger#, P. Bestra, H. Voster, A.E. Schutte, E. Wentzel-Viljoen, F.C. Eloff, H. de Ridder, H. Moss, J. Potgieter, A. Roux, M. Watson, G. de Wet, A. Olckers, J.C. Jerling, M. Pieters, T. Hoekstra, T. Puoane, R. Swart*, E. Igumbor, L. Tsolekile, K. Ndayi, D. Sanders, P. Naidoo, N. Steyn, N. Peer, B. Mayosi#, B. Rayner, V. Lambert, N. Levitt, T. Kolbe-Alexander, L. Ntyintyane, G. Hughes, J. Fourie, M. Muzigaba, S. Xapa, N. Gobile, K. Ndayi, B. Jwili, K. Ndibaza, B. Egbujie; **Sweden** A. Rosengren*, K. Bengtsson Boström, A. Rawshani, A. Gustavsson, M. Andreasson, L. Wirdemann; **Tanzania:** K. Yeates*, M. Oresto, N. West **Turkey:** A. Oguz*, N. Imeryuz, Y. Altuntas, S. Gulec, A. Temizhan, K. Karsidag, K.B.T. Calik, A.K. Akalin, O.T. Caklili, M.V. Keskinler, K. Yildiz; **United Arab Emirates:** A.H. Yusufali, F. Hussain, M.H.S. Abdelmotagali, D.F. Youssef, O.Z.S. Ahmad, F.H.M. Hashem, T.M. Mamdouh, F.M. AbdRabbou, S.H. Ahmed, M.A. AlOmairi, H.M. Swidan, M. Omran, N.A. Monsef; **Zimbabwe:** J. Chifamba*, T. Ncube, B. Ncube, C. Chimhete, G.K. Neya, T. Manenji, L. Gwaunza, V. Mapara, G. Terera, C. Mahachi, P. Murambiwa, R. Mapanga, A. Chinhara. **ONTARGET/TRANSCEND Office Staff, National Coordinators, Investigators, and Key Staff:** Current members of the Operations Committee are denoted by an asterisk. Previous members of the Operations Committee are denoted by a dagger. NC denotes National Coordinator, and NL National Leader. *Steering Committee:* S. Yusuf (Chair and Principal Investigator),* P. Sleight,* C. Anderson,* K. Teo,* I. Copland,* B. Ramos,† L. Richardson,* J. Murphy,* M. Haehl,* L. Hilbrich,† R.Svaerd,* K. Martin,† D. Murwin,* T. Meinicke,† A. Schlosser,* G. Schmidt,† R. Creek,* H. Schumacher,* M. Distel,† B. Aubert, J.Pogue, L. Dyal, R. Schmieder, T. Unger, R. Asmar, G. Mancia, R. Diaz, E. Paolasso, L. Piegas, A. Avezum, G. Dagenais, E. Cardona Munoz, J. Probstfield, M. Weber, J. Young, R. Fagard, P. Jansky, J. Mallion, J. Mann, M. Böhm, B. Eber, N.B. Karatzas, M. Keltai, B.Trimarco, P. Verdecchia, A. Maggioni, F.W.A. Verheugt, N.J. Holwerda, L. Ceremuzynski, A. Budaj, R. Ferreira, I. Chazova, L. Rydén, T.L. Svendsen, K. Metsärinne, K. Dickstein, G. Fodor, P. Commerford, J. Redon, T.R. Luescher, A. Oto, A. Binbrek, A. Parkhomenko, G. Jennings, L.S. Liu, C.M. Yu, A.L. Dans, R. Shah, J.-H. Kim, J.-H. Chen, S. Chaithiraphan. *Data and*

Safety Monitoring Board: J. Cairns (Chair), L. Wilhelmsen, J. Chalmers, J. Wittes, M. Gent, C.H. Hennekens. *Adjudication Committee:* G. Dagenais (Chair), N. Anderson, A. Avezum, A. Budaj, G. Fodor, M. Keltai, A. Maggioni, J. Mann, A. Parkhomenko, K. Yusoff, P. Auger, V. Bernstein, E. Lonn, A. Panju, I. Anand, J.T. Bigger, P. Linz, J. Healey, C. Held, C. McGorrian, M. Rokoss, J. Villar. *Substudies/Publication Committee:* P. Sleight (Chair), C. Anderson, R. Creek, A. Dans, R. Diaz, R. Fagard, J. Probstfield, R. Svaerd, K. Teo, T. Unger, S. Yusuf. *Coordinating Centers:* Hamilton: K. Teo, I. Copland, B. Ramos, A. McDonald, J. Pogue, L. Dyal, R. Afzal, F. Zhao, S. Yusuf; Oxford: P. Sleight, L. Richardson; Auckland: C. Anderson, J. Murphy. *Sites and Principal Investigators by Country: Argentina*: R. Diaz (NC), E. Paolasso (NL), R.A. Ahuad Guerrero, M. Amuchastegui, H.P. Baglivo, M. Bendersky, J. Bono, B. Bustos, A. Caccavo, L.R. Cartasegna, C.R. Castellanos, M.A. Cipullo, P. Crunger, C.A. Cuneo, M. Focaccia, J.J. Fuselli, E. Hasbani, M.A. Hominal, J. Humphreys, F. Inserra, C.R. Killinger, E. Kuschnir, C.R. Majul, O.D. Manuale, G. Martinez, E.M. Marzetti, R. Nordaby, A.D. Orlandini, J.C. Pomposiello, G.M. Rodríguez, J. Salas, O.A. Salomone, R.A. Sanchez, C. Serra, M.L. Vico; *Australia*: G.L.R. Jennings (NC), J.V. Amerena, L.F. Arnolda, G.M. Aroney, P.E. Aylward, C.F. Bladin, J.C. Bridgeman, B.R. Chambers, A.J. Corbett, D.S. Crimmins, D.B. Cross, L. Davies, S.M. Davis, G.A. Donnan, D.S. Eccleston, J.H. Frayne, R. Hendriks, G.K. Herkes, A.T. Hill, I.M. Jeffery, J.A. Karrasch, G. Koshy, T.H. Marwick, D.A. Owensby, M.W. Parsons, D.M. Rees, A. Russell, R. Schwartz, B. Singh, P.L. Thompson, J.H. Waites, W.F. Walsh, D.L. Walters, R.W. Watts, A.P. Whelan; *Austria*: M. Böhm (NC), B.E. Eber (NL), J.B. Bonelli, P. Dolliner, J.H. Hohenecker, G.S. Steurer, W.W. Weihs; Belgium: R. Fagard (NC), I. Bekaert, C. Brohet, P. Chaumont, P. Cheron, V. Crasset, J.-P. Degaute, P. Dendale, K. Dujardin, S. Elshot, S. Hellemans, M. Herssens, G. Heyndrickx, P. Laloux, H. Lesseliers, P. Noyens, M. Quinonez, F. Stammen, H. Striekwold, J. Thoeng, W. Van Mieghem, G. Vanhooren, G. Vervoort, M. Vrolix, B. Wollaert; *Brazil*: L. Piegas (NC), A. Avezum (NL), J.A.M. Abrantes, D. Armaganijan, J.C. Ayoub, L.C. Bodanese, A.C. Carvalho, M. Coutinho, J.P. Esteves, R.J.S. Franco, P.C.B.V. Jardim, J.F. Kerr Saraiva, P.E. Leães, L.N. Maia, J.A. Marin-Neto, R.L. Marino, D. Mion, Jr., J.R. Moreira, Jr., W. Oigman, R.C. Pedrosa, E.A. Pelloso, F.L. Plavnik, C.A. Polanczyk, Á. Rabelo, Jr., S. Rassi, G. Reis, A.B. Ribeiro, J.M. Ribeiro, J.C. Rocha, P.R.F. Rossi, R.D. Santos, J.C.E. Tarastchuk, M.N. Villalón; *Canada*: K. Teo (NC), G. Dagenais (NC), B. Abramson, M. Arnold, T. Ashton, P. Auger, I. Bata, K. Bayly, J. Beauchef, A. Bélanger, V. Bernstein, R. Bhargava, A.W. Booth, S. Bose, M. Boulianne, M. Cameron, Y.K. Chan, C. Constance, P. Costi, D. Dion, J. Douketis, D. Fell, J.P. Giannoccaro, A. Glanz, G. Gosselin, D. Gould, S. Goulet, F. Grondin, M. Gupta, G. Gyenes, J.W. Heath, V.A. Heath, A. Hess, J.G. Hiscock, G. Hoag, G. Honos, J. Imrie, R. Kuritzky, C. Lai, A. Lalani, A. Lamy, P. LeBouthillier, H. Lochnan, E. Lonn, B. Lubelsky, A. Mackey, M. Meunier, A. Milot, L.B. Mitchell, S. Nawaz, M. Omichinski, A. Panju, C. Pilon, D. Pilon, P. Polasek, G. Proulx, T. Rebane, A.J. Ricci, D.W. Rupka, É. Sabbah, D. Savard, N.K. Sharma, D. Shu, R. St. Hilaire, F. St. Maurice, R. Starra, B. Sussex, T. Szaky, P. Talbot, K.-W. Tan, T.B. To, S. Tobe, R. Tytus, R. Vexler, P. Whitsitt, V. Woo; *China*: L. Liu (NC), X. Bai, X. Chen, J. Feng, S. Fu, Y. Ge, L. Gong, Z. He, J. Huang, Y. Jiang, L. Li, Q.H. Li, Y. Liao, Z. Lu, F. Lu, S. Ma, F. Niu, C. Pan, F. Qian, X. Shi, N. Sun, M. Sun, G. Sun, J. Wang, S. Wang, Y. Wang, Z. Wu, X. Yan, X. Yang, H. Yang, X. Ye, S. Yuan, T. Zhang, C. Zhang, F. Zhang, S. Zhang, D. Zhao, B. Zheng, H.Y. Zhou, S. Zhou, J. Zhu; *Czech Republic*: P. Janský (NC), V. Dedek, J. Dvorák, R. Holaj, J. Kotouš, E. Pederzoliová, M. Polák, J. Povolný, K. Smetana, J. Špác; *Denmark*: T.L. Svendsen (NC), L. Götzsche, H.F. Juhl, K. Koelendorf, P. Lund, F. Pedersen, O.L. Perdersen, T. Pindborg, L.H. Rasmussen, S.L. Rasmussen, K. Thygesen, C. Tuxen; *Finland*: K. Metsärinne (NL), R. Antikainen, M. Jääskivi, I. Kantola, M. Kastarinen, P. Kohonen-Jalonen, A. Koistinen, E. Lehmus, R. Nuuttila, M.-L. Tuominen, H. Ylihärsilä; France: J. Mallion (NC), N. Abenhaim, J. Allix, L. Boucher, M. Bourgoin, A. Boye, N. Breton, D. Cadinot, A. Campagne, J. Churet, G. Constantin, E. De Sainte Lorette, A. El Sawy, G. Etchegarray, S. Farhat, F. Lacoin, T. Latte, C. Magnani, D. Pineau-Valenciennes, M. Pithon, A. Quéguiner, J. Sicard, G. Sorbe, D. Taminau, H. Vilarem, J.Y. Vogel; *Germany*: H.H. Ebert, S. Genth-Zotz, N. Hermanns, C. Holzer, J. Minnich, D. Schimkus, M. Boehm (NC), J. Mann (NC), B. Brado, G. Claus, U. Dietz, R. Griebenow, T. Haak, K. Hahn, R. Hampel, H. Heitzer, G. Holle, T. Horacek, J. Jordan, C. Klein, R. Kolloch, S. Ludewig, W. Motz, T. Muenzel, H.P. Nast, M. Nauck, H. Nebelsieck, K. Rybak, H. Samer, T. Schaefer, J. Scholze, B. Schulze, Schleppinghoff, R. Schmieder, B. Schwaab, U. Sechtem, W. Sehnert, E. Steinhagen-Thiessen, G. Stenzel, P. Trenkwalder, B. Wedler, J. Zippel; *Greece*: N. Karatzas (NC), A. Achimastos, E. Diamantopoulos, A. Efstratopoulos, M. Elisaf, H. Karvounis, D. Mentzikof, D. Mytas, D. Papadogiannis, V. Pyrgakis, C. Stefanadis, D. Symeonidis, A. Tsoukas, I. Vogiatzis, S. Voyaki, C. Zamboulis; *Hong Kong*: C.-M. Yu (NC), C.K.H. Chan, L. Lam, Y.K. Lau, J. Sanderson, J. Wong, E.B. Wu, C.S. Yue; Hungary: M. Keltai (NC), I. Czuriga, I. Édes, C.S. Farsang, Á. Kalina, K. Karlócai, K. Keltai, M. Kozma, Z. László, V. Nagy, A. Papp, G.Y. Polák, I. Préda, A. Rónaszéki, M. Sereg, K. Simon, S. Sonkodi, J. Szegedi, S. Timár, K. Tóth, G.Y. Vándorfi, A. Vértes; Ireland: J. Feely, V.M.G. Maher, A.V. Stanton, P. Sullivan; *Italy*: B. Trimarco (NC), P. Verdecchia (NC), A. Maggioni (NL), E. Agabiti Rosei, G.B. Ambrosio, M. Bentivoglio, A. Branzi, P. Cavallo Perin, M. Chiariello, V. Cirrincione, R. Ferrari, R. Gattobigio, E. Giovannini, D. Giugliano, A. Lacchè, R. Lauro, G. Lembo, G. Marchetti, L. Moretti, L. Pancaldi, L. Partemi, S. Pede, G. Pettinati, G. Reboldi, R. Ricci, G. Rosiello, F. Rozza, M.G. Sardone, E.V. Scabbia, G. Selvetella, L. Tavazzi, P. Terrosu, A. Venco, A. Vetrano, M. Volpe, G. Zilio; Malaysia: T. Ismail, R.P. Shah, M. Singaraveloo, W.A. Wan Ahmad, Z. Yusof, K. Yusoff, I. Zainal Abidin, R. Zambahari; *Mexico*: E. Cardona Munoz (NC), L. Alcocer Diaz, S. Pascoe-Gonzalez, R. Arriaga Nava, G. De La Peña Topete, L.A. Elizondo Sifuentes, H.R. Hernández García, J. Illescas-Diaz, M.A. Macías Islas, J.A. Noriega Arellano, R. Olvera Ruiz, J.Z. Parra Carrillo, G. Velasco Sánchez, M. Vidrio Velásquez; *the Netherlands*: F.W.A. Verheugt (NC), N.J. Holwerda (NL), D.C.G. Basart, A.J.M. Boermans, H.A. Bosker, K.P. Bouter, C.P. Buiks, W.A. de Backer, J. J. de Graaf, J.H.M. Deppenbroek, F.D. Eefting, F.C.N.M. Gunneweg, H.R. Michels, D. Poldermans, G. Schrijver, M.I. Sedney, T. Slagboom, J.G. Smilde, G.E.M.G. Storms, R.M. Tjon, P.F.M.M. van Bergen, G.J.M. van Doesburg, L.H.J. van Kempen, H.F.C.M. van Mierlo, A. Veerman, F.A.A.M. Vermetten, A. Wester; *New Zealand*: W. Bagg, J. Benatar, R.J. Coxon, R.N. Doughty, D.H. Friedlander, R.A. Luke, P.L. Nairn, Y. Ratnasabapathy, A.M. Richards, G.P. Singh, R.A.H. Stewart, R.W. Troughton, H.D. White, M. Williams, S.P. Wong; Norway: K. Dickstein (NL), N. Bogale, J.O. Lier, J.E. Otterstad, P.K. Rønnevik, S. Skeie, P.O. Walle; *Philippines*: A.L. Dans (NC), M.T.B. Abola, J.C. Añonuevo, J.M. Jaro, D.R. Marañon, V.L. Mendoza, D.R. Morales, E.P. Pacheco, E.B. Reyes, A.A. Roxas, M.B. Sedurante; *Poland*: L. Ceremuzynski (NC), A. Budaj (NC), Z. Binio, M. Bronisz, P. Buszman, T. Czerski, M. Dalkowski, J. Gessek, A. Gieroba, K. Janik, M. Janion, T. Kawka-Urbanek, R. Klabisz, M. Krauze-Wielicka, S. Malinowski, P. Miekus, J. Mormul, M. Ogorek, G. Opolski, M. Skura, M. Szpajer, M. Tendera, T. Waszyrowski, M. Wierzchowiecki, B. Zalska; *Portugal*: R. Ferreira (NC), R. Capucho, C. Correia, L. Cunha, J.M. Ferro, V. Gama Ribeiro, V. Gil, P. Marques da Silva, M. Oliveira Carrageta, R. Sebra Gomes, M. Veloso Gomes; *Russia*: I. Chazova (NC), F. Ageev, Y. Belenkov, A. Ivleva, Y. Karpov, M. Shestakova, E. Shlyakhto, S. Shustov, B. Sidorenko; Singapore: H.M. Chang, B. Kwok; *Slovakia*: G. Fodor (NC), A. Dukát, J. Gonsorcík, M. Hranai, J. Lietava, D. Pella, R. Rybar, L. Ruffini; South Africa: P. Commerford (NC), F. Bonnici, B. Brown, A.J. Dalby, G.J. Gibson, L. Herbst, J. King, E. Klug, M. Middle, D. P. Naidoo, M. Pretorius, G. Podgorski, N. Ranjith, K. Silwa-Hahnle, H. Theron; *South Korea*: J.H. Kim (NC), S.C. Chae, N.S. Chung, K.P. Hong, M.H. Jeong, H.J. Kang, J.J. Kim, M.H. Kim, H.S. Seo, E.K. Shin; *Spain*: J. Redón (NC), J. Abellán, P. Aranda, V. Barrios, C. Calvo, M. De La Figuera, E. De Teresa, R. Durá, F. Escobar, F. Fernandez-Cruz, E. Galve, J. Garcia-Puig, B. Gil-Extremera, R. Gomis, O. Gonzalez-Albarran, J.R. González-Juanatey, A. Llacer, L. López-Bescós, J. Oliván, A. Picó, A. Pose, A. Roca-Cusachs, L.M. Ruilope; *Sweden*: L. Rydén (NC), A. Alvång, P.-Å. Boström, M. Dellborg, U.-B. Ericsson, J. Herlitz, T. Juhlin, K. Pedersen, B. Sträng, B. Sundqvist, B.-O. Tengmark, G. Ulvenstam, B. Westerdahl, L. Winberg; *Switzerland*: T.R. Luescher (NC), I. Baumgartner, P. Dubach, A. Gallino, T. Moccetti, G. Noll, A. Nordmann, H. Rickli, H. Schläpfer, K. Weber; *Taiwan*: J.-H. Chen (NC), T.H. Chao, C.Y. Chen, J.J. Cheng, H.C. Chiou, C.C. Fu, M. Fu, W.T. Lai, Y.H. Li, L.M. Lien, C.D. Tsai, J.H. Wang, P.S. Yeh; *Thailand*: S. Chaithiraphan (NC), T. Chantadansuwan, K. Jirasirirojanakorn, R. Krittayaphong, P. Laothavorn, N. Mahanonda, S. Sitthisook, S. Tanomsup, S. Tansuphaswadikul, P. Tatsanavivat, S. Yamwong; *Turkey*: A. Oto (NC), M. Akin, N.T. Caglar, A. Ergin, H. Müderrisoglu, A. Oguz, Z. Ongen, V. Sansoy, T. Tetiker, A. Uysal; *Ukraine*: A. Parkhomenko (NC), E. Amosova, O. Cherkasova, Y. Dykun, G. Dzyak, A. Galystska, O. Grishyna, O. Jaremenko, L. Kononenko, E. Koval, V. Kovalenko, V. Netyazhenko, T. Pertseva, A. Prokhorov, G. Radchenko, Y.U. Rudyk, Y. Sirenko, A. Skarzhevsky; *United Arab Emirates:* A.S. Binbrek (NC), A.A.R. Al Hajiri, E. Al Hatou, A.A.S. Al-Sousi, M. Alomairi, I. Maqsood Wajib; *United Kingdom:* P. Sleight (NC), A.A.J. Adgey, R. Andrews, S.G. Ball, D.H. Barer, A.H. Barnett, A.B. Bridges, V. Bryson,

A.S. Cowie, A.J. De Belder, R. Donnelly, C.M. Francis, J. Furnace, S.K. Glen, N. Gough, A.M. Heagerty, P.R. Jackson, S.H.D. Jackson, E. Joyce, D.J. McEneaney, A.J. Moriarty, D.L. Murdoch, J.P. O'Hare, W.J. Penny, C.J. Reid, J. Tilley, J.P. Vora, J. Webster, B. Williams; *United States:* J. Probstfield (NC), M. Weber (NC), J. Young (NC), I. Ahmed, I.S. Anand, J.L. Anderson, J.S. Aponte Pagán, J. Barzilay, J.N. Basile, P.F. Bass III, S.S. Blumenthal, W.J. Bommer, D.F. Brautigam, C.D. Brown, N. Brown, J.D. Byrum, A.A. Carr, J. Chinn, D. Chiu, N.R. Cho, J.O. Ciocon, P.J. Colón-Ortíz, J.B. Cruz, W.D. Dachman, G.M. Dolson, S.G. Dorfman, W. Drummond, C. East, F. Eelani, H.S. Ellison, J.V. Felicetta, M.H. Fishbach, R.W. Force, S.J. Giddings, M.C. Goldberg, S. Goldman, R. Gomez Adrover, S.L. Goss, S.P. Graham, C.B. Granger, M.M. Greenspan, R.H. Grimm, G.B. Habib, M.R. Hagen, P.D. Hart, T.J. Hartney, M.A. Henriquez, J.J. Holland, B.J. Hoogwerf, M. Hossfeld, A.K. Jacobson, M.J. Jelley, T.V. Jones, R.A. Kaplan, D.G. Karalis, L.A. Katz, D.J. Kereiakes, M. Khan, R.M. Kipperman, M.J. Kozinn, J.G. Kozlowski, E.W. Lader, C. Landau, J.S. Landzberg, D. Laughrun, S.J. Lewis, C.S. Liang, M.C. Limacher, P.E. Linz, T.S. Lo, F. Lopez-Arostegui, R.R. Maddox, P.R. Mahrer, M.S. Maurer, D.K. McGuire, A.D. Mercando, J.H. Mersey, M. Meyer, A.N. Mooss, P. Narayan, S. Oparil, D.N. Padhiar, A.L. Phillips, M. Prisant, N. Qureshi, M.P. Raghuwanshi, R.R. Randall, T.M. Retta, R.E. Ringrose, A.A. Rizvi, M.D. Rizvi, M.G. Saklayen, S. Sastrasinh, I.K. Savani, A. Schlau, H.S. Schultz, M.J. Schweiger, R.D. Smith, M. Sosa-Padilla, D. Streja, T.P. Stuver, D.C. Subich, F.C. Sulak, W.A. Swagler III, M. Taitano, J.A. Tavarez-Valle, E.M. Taylor, M.L. Tuck, W.B. White, W.J. Wickemeyer, T.B. Wiegmann, P.A. Zee, X.Q. Zhao. **ORIGIN Office Staff, National Coordinators, Investigators, and Key Staff:** *Operations committee:* H. Gerstein (Co-chair and Co-PI), S. Yusuf (Co-chair and Co-PI), L. Rydén (European Co-chair), J. Bosch (Project Director), L. Richardson (European Project Office), G. Dagenais, R. Diaz, P Johnston, A. Maggioni, J Probstfield, A. Ramachandran, M. Riddle, R. Vige. *Steering committee:* H. Gerstein (Co-chair and Co-PI), S. Yusuf (co-chair and co-PI), L. Rydén (European co-chair), K. Birkeland, J. Bosch (project director), A. Budaj, E. Cardona, I. Chazova, P. Commerford, G. Dagenais, R. Diaz, L. Danilova, M. Davies, R. Fernando, G. Fodor, R. Gilbert, R. Gomis, N. Hâncu, M. Hanefeld, P. Hildebrandt, P. Johnston, G. Kacerovsky-Bielesz, M. Keltai, J.H. Kim, H. Krum, H. Kültürsay, F. Lanas, B.S. Lewis, E. Lonn, P. López-Jaramillo, A. Maggioni, J. Marin-Neto, M. Marre, R McKelvie, M. McQueen, I. Mendoza, C. Morillo, C. Pan, V. Pīrāgs, J. Probstfield, V. Profozic, A. Ramachandran, R. Ratner, M. Riddle, L. Richardson (European Project Office), J. Rosenstock, G.A. Spinas, S. Sreenan, I. Stoel, M. Syvänne, R. Vige, J.F. Yale. *Event adjudication committee:* G. Dagenais (chair), R. McKelvie (co-chair), A. Avezum, M.C. Bahit, P. Bogaty, L. Bordeleau, C. Chacón, M. Corson, G. Fodor, W.L. Harper, D. Halon, P. Hildebrandt, P Magloire, J. Mann, C. Morillo, V. Pavlova, Z. Punthakee, J. Silva, M. Syvänne, B. Tsang, N. Yakubovich. *Substudy and publications committee:* A. Maggioni (co-chair), J. Probstfield (co-chair), P. Commerford, M. Davies, R. Gilbert, P. Johnston, J. Marin-Neto, M. McQueen; *Glycemia management committee:* H. Gerstein, M. Hanefeld, P. Johnston, A. Ramachandran, R. Ratner, M. Riddle, J. Rosenstock, J.F. Yale; *Global project office:* A. Abdallah, S. Ahmad, J. Bosch, J. Chandra, R. Chandra, T. Cukierman-Yaffee, L. Dyal, H. Gerstein, H. Jung, L. Joldersma, L. MacRae, S. MacRae, S. Malik, A. Mead, F. Pasha, J. Pazmino-Canizares, J. Pogue, K. Pohl, L. Richardson, A. Sakalas, J. Tyrwhitt, S. Yusuf. *Site investigators by country: Argentina*: R. Diaz, R. Ahuad Guerrero, A. Alebuena, N. Alvarez, M. Alzogaray, M. Amuchastegui, M. Andres, M. Angos, H. Baglivo, M. Barbieri, F. Bassi, F. Bello, J. Bono, M. Bustamante Labarta, B. Bustos, A. Caccavo, M. Calveira, A. Camino, M. Cantero, M. Capozzi, M. Cardone, L. Cartasegna, A. Cassetari, R. Castellanos, R. Chavez Caballero, M. Cipullo, A. Contreras, J. Coria, F. Corinaldesi, G. Costa, C. Crespo, M. Cruz, J. Cuello, C. Cuneo, I. Del Corro, R. Diez, C. Dituro, A. Dominguez, A. Facta, C. Faingold, M. Farah, A. Fares Taie, A. Fernandez, A. Ferrari, N. Ferrari, C. Garcia Monteverde, M. Garrido, C. Giachello, M. Gonzalez, N. Gutierrez, L. Guzman, P. Guzman, E. Hasbani, R. Henquin, A. Hershon, A. Hirschon Alvarez Prado, M. Hominal, A. Hrabar, H. Imposti, M. La Grutta, P. Lanchiotti, L. Lobo Marquez, R. Lopez Santi, J. Lowenstein, M. Lugo, M. Luqueci, S. Mainini, C. Majul, R. Manzano, S. Manzur, G. Marcucci, M. Marino, F. Massari, N. Mendez, M. Molina, O. Montaña, M. Mulazzi, L. Nardone, I. Odetto, A. Orlandini, A. Oviedo, O. Paez, A. Parnas, F. Risso Patron, C. Pedernera, M. Pelagagge, M. Plastino, P. Polari, J. Pomposiello, A. Porta, A. Prado, M. Quiroz, A. Ramirez, C. Rodriguez, M. Rodriguez, R. Ronderos, L. Sago, A. Sanchez, R. Sanchez, A. Sandrin, P. Schygiel, V. Sernia, I. Sinay, T. Smith Casabella, A. Sosa Liprandi, M. Sosa Liprandi, L. Soso, G. Sposetti, D. Stisman, P. Streitenberger, G. Suarez, H. Tonin, M. Ulla, J. Valdez, M. Vico, A. Villamil, A. Villarino, A. Viscaya Castro, V. Visco, D. Vogel, F. Waisman, C. Zaidman; *Australia*: H. Krum, J. Amerena, A. Applebe, P. Aylward, M. Binnekamp, I. Bruce, C. Burdeniuk, R. Burnet, P. Colman, D. Colquhoun, S. Davis, F. De Looze, C. De Pasquale, M. D'Emden, H. Eaton, A. Farshid, S. Foulanos, J. Galanos, G. Gordon, M. Guhu, J. Ho, I. Jeffery, G. Jerums, M. Kwan, J. Lefkovits, S. Luu, R. MacIsaac, J. Marjason, V. Mohabbati, A. Nankervis, D. O'Neal, N. Perera, A. Poynten, A. Rahman, S. Razak, T. Roberts, M. Sebastian, R. Simpson, G. Soldatos, D. Sullivan, H. Teede, F. Tiong, D. Topliss, D. Torpy, K. Waddell-Smith, J. Waites, J. Wenman, A. Whelan, L. Williams, B. Yeap, W. Yeow, G. Yong; *Austria*: G. Kacerovsky-Bielesz, S. Aczel, N. Azimy, P. Bertha, J. Blocher, C. Bohnel, H. Brath, J. Breuss, A. De Campo, H. Drexel, Y. Ettmuller, A. Feder, C. Feinboeck, E. Gulz, M. Hofmann, F. Hoppichler, H. Jahnel, V. Jankovic, T. Kann, T. Kathrein, T. Kotter, E. Kratz, E. Kreuzwieser, C. Loreck, B. Ludvik, T. Marte, K. Mellitzer, S. Nistler, G. Placher-Sorko, R. Prager, P. Rein, M. Riedl, C. Säly, G. Schernthaner, E. Schichka, C. Seidlhofer, M. Sonnenfeld, H. Stefan, K. Steiner, B. Thomas, H. Toplak, K. Urstoger, B. Vetter, A. Vonbank, W. Waldschutz, F. Wallner, F. Winkler; *Belarus*: L. Danilova, D. Goncharik, I. Lazareva, N. Lichorad, A. Mrochek, N. Murashko, D. Radyuk, A. Ramanovski, S. Sudzhaeva, V. Sujayeva, N. Yarashevich; *Bermuda*: G. Campbell, S. Marshall, A. West; *Brazil*: J. Marin-Neto, F. Abreu, M. Alves, J. Ayoub-Aidar, M. Barros, J. Barros-Silveira, M. Blacher, E. Costa, F. Costa, C. Daltro, J. Delana, F. Eliaschewitz, C. Facanha, G. Feitosa, J. Figueiredo, A. Forti, D. Franco, M. Franken, F. Freire, V. Garcia, A. Gouvea-Neto, S. Grofallo, N. Kanedlai, J. Kerr-Saraiva, R. Ladeira, P. Leaes, M. Lemos, F. Lima, M. Lima Filho, L. Macedo, E. Manenti, J. Marin-Neto, O. Monte, A. Mossman, F. Mothe, O. Mouco, M. Moyses Golbert, L. Nasser Hissa, M. Nasser-Hissa, J. Nicolau, L. Nigro Maia, T. Ninno, C. Nunes, C. Oliveira, O. Oliveira, R. Passos da Silva, J. Pericles-Esteves, L. Rabelo, A. Rabelo-Alves Jr., S. Rassi, R. Rech, F. Roldan, J. Salles, C. Sampaio, A. Seabra, N. Sealissi, A. Seixas, R. Sena, I. Shehadeh, M. Teixeira, H. Turin, C. Vicente Serrano Jr., M. Vidigal, M. Vilela, B. Wajchenberg; *Canada*: G. Dagenais, E. Lonn, C. Abbott, A. Abu-Bakare, J. Ardilouze, E. Auersperg, A. Bailey, G. Bailey, J. Baillargeon, C. Beaurivage, J. Belair, A. Belanger, D. Bellabarba, J. Berlingieri, F. Bernier, R. Bhargava, T. Bhesania, W. Booth, S. Bose, M. Boulianne, S. Bourgeois, D. Breton, R. Brossoit, J. Buithieu, J. Campeau, B. Carlson, A. Carpentier, R. Cavalcanti, J. Cha, P. Chagnon, Y. Chan, C. Chessex, J. Chiasson, S. Chouinard, D. Clayton, J. Conway, J. Crepeau, D. Cudmore, G. D'Ignazio, G. Doig, M. Dominguez, F. Dube, R. Dumas, R. Dupuis, I. Dyrda, D. Eddy, D. Eiley, H. Fox, S. Fratesi, S. Gallant, C. Garceau, N. Garfield, C. Germain, S. Glazer, G. Gosselin, D. Gould, G. Grills, J. Halle, P. Hardin, W. Harper, J. Heath, V. Heath, M. Hivert, K. Ho, G. Houde, I. Hramiak, A. Hutchinson, T. Huynh, R. Ilie-Haynes, S. Imran, A. Islam, M. Iwanochko, C. Jones, C. Joyce, I. Kirouac, R. Kumar, M. Lamothe, M. Langlois, C. Lauzon, M. Lavoie, R. Leader, S. Lecours, S. Lepage, H. Lochnan, P. Ma, S. Malik, A. McLean, S. Mecci, P. Mehta, M. Mercier, D. Miller, A. Morisset, S. Nawaz, W. Nisker, G. Nyomba, D. O'Keefe, J. Palardy, P. Parekh, T. Paul, P. Perron, M. Pesant, R. Phillips, G. Pruneau, I. Quintin, K. Raby, C. Richard, G. Rosenfeld, D. Saulnier, J. Shaban, A. Shah, D. Shu, R. Sigal, M. Silverman, J. Singh, W. Sivucha, A. Skamene, D. Sliwowicz, R. Smith, R. St. Hilaire, D. Steinson, B. Sussex, K. Tan, R. Tannous, A. Telner, P. Theroux, C. Tsoukas, G. Tsoukas, J. van Buuren, N. Van Rossum, R. Vexler, S. Vizel, W. Warnica, M. Weingert, R. Wilson, R. Wilson, W. Wong, V. Woo, J. Yale; *Chile*: F. Lanas, M. Acevedo, C. Alwyn, E. Baier, S. Baier, R. Galloso, R. Lahsen, G. Lorenas, A. Montecinos, M. Montecinos, P. Pineda, F. Pollak, J. Sapunar, V. Serrano, B. Stockins, P. Varleta, J. Yovanovich, F. Zambra; *China*: C. Pan, J. Ba, Y. Bao, Y. Bi, S. Bu, B. Chen, H. Chen, H. Chen, J. Chen, L. Chen, L. Chen, M. Chen, Y. Chen, Y. Chen, J. Cui, M. Dong, P. Feng, Z. Feng, C. Gao, F. Gao, X. Gao, Z. Gao, Y. Gong, L. Guang, X. Guo, F. Han, X. Han, X. Hou, R. Hu, L. Jl, J. Jia, W. Jia, X. Jiao, X. Jin, J. Kuang, M. Li, Q. Li, X. Li, Y. Li, Y. Ling, F. Liu, Z. Liu, B. Lu, J. Lu, Z. Lu, X. Lv, G. Ning, Y. Peng, Y. Ren, Y. Shao, Y. Shi, X. Shu, H. Sun, L. Sun, X. Sun, K. Tang, H. Tian, H. Tian, C. Wang, F. Wang, L. Wang, Q. Wang, W. Wang, X. Wang, Y. Wang, Y. Wang, J. Wen, C. Wu, H. Wu, H. Wu, J. Wu, M. Wu, X. Xing, Y. Xue, L. Yan, S. Yan, H. Yang, N. Yang, W. Yang, Z. Yang, J. Yao, J. Yao, L. Yao, D. Yu, H. Yu, M. Yu, X. Yu, L. Yuan, M. Yuan, S. Yuan, W. Yuan, Y. Yuan, Z. Yuan, T. Zeng, J. Zhang, R. Zhang, X. Zhang, X. Zhang, L. Zhao, B. Zheng, J. Zheng, J. Zheng, W. Zhou, N. Zhu, Y. Zhu, D. Zou, J. Zou; *Colombia*: P. Lopez-Jaramillo, C. Morillo, J.L. Accini, R. Bohorquez, R. Botero, C. Cure, M. Figueredo, E. Hernandez, W. Kattah, A. Llamas, L. Orozco, L. Pava, M. Perez, M. Pineda, A. Quintero, R. Quiros, M. Urina, S. Velez: *Croatia*: V. Profozic, V. Altabas,

I. Baotic, M. Berkovic, V. Goldoni, T. Kerum, G. Mirosevic, D. Tarle, I Vidovic, V. Zjacic-Rotkvic; *Denmark*: P. Hildebrandt, R. Abbas, H. Andersen, S. Auscher, L. Baumbach, H. Brockstedt, P. Christensen, M. Christiansen, K. Clemmensen, K. Egstrup, G. Gislason, D. Haar, K. Hansen, P. Heden Andersen, K. Helleberg, K. Hermansen, J. Holmer, J. Jeppesen, I. Klausen, T. Koustrup-Sonder, T. Krarup, S. Lerche, H. Lervang, B. Linde, P. Lund, S. Lund, S. Madsbed, J. Molvig, C. Orskov, O. Ostergaaard, H. Perrild, A. Pietraszek, N. Ralfkjaer, H. Roenne, J. Rokkedal Nielsen, M. Seibaek, H. Soendergaard, L. Sorensen, L. Sundahl Mortensen, C. Torp-Pedersen, C. Tuxen, S. Urhammer, E. Vadstrup; *Estonia*: V. Pirags, A. Ambos, A. Janson, P. Rudenko, L. Viitas; *Finland*: M. Syvänne, S. Aranko, M. Badeau, J. Eriksson, H. Haapamäki, O. Kajander, A. Kuusisto, S. Luukkonen, J. Mäkelä, S. Nieminen, L. Niskanen, J. Ripatti, S. Ruotsalainen, J. Saltevo, K. Sävelä, J. Strand, T. Valle, A. Virkamäki; *France*: M. Marre, E. Aboud, L. Alavoine, A. Bekherraz, P. Bohme, H. Bourezane, B. Catargi, G. Charpentier, A. Clergeot, J. Courreges, T. Delmas, F. Duengler, C. Feknous, D. Gendre, B. Guerci, S. Hadjadj, V. Kerlan, N. Laguerre, J. Le Potier, F. Lombardo, E. Malville, R. Marechaud, C. Mattei, J. Moreira, A. Penfornis, C. Petit, J. Pinel, X. Piquel, D. Raccah, Y. Reznik, A. Rod, N. Roudaut, E. Rousseau, F. Schillo, B. Schmitt, E. Sonnet, F. Torremocha, F. Travert, C. Vanhoute, M. Vimeux; *Germany*: M. Hanefeld, R. Abdollahnia, A. Adamidou, S. Arslan, B. Bach-Kliegel, B. Bartusch, N. Bauer, T. Bieler, H. Blankenfeld, U. Boeckmann, K. Busch, R. Butzer, M. Chenchanna-Merzhaeuser, R. Denger, C. Deutsch, S. Diessel, I. Donati-Hirsch, M. Dornisch, K. Enghofer, T. Fleig, T. Forst, M. Frommherz, K. Goeller, J. Habbig, S. Hadziselimovic, A. Hamann, T. Hampel, S. Heger, C. Helmes, C. Hoffman, C. Hohberg, P. Humpert, A. Kamke, W. Kamke, P. Kindermann, C. Klein, D. Klein, A. Koehler, A. Kuehn, K. Langer, S. Limmer, A. Loew, A. Maimer, C. Marck, G. Meier, M. Methner-Friederich, W. Metzler, K. Meyer, N. Miftari, J. Milde, J. Minnich, M. Molkewehrum, M. Morcos, C. Mueller-Hoff, M. Nguyen, M. Nishwitz, J. Oldenburg, P. Ott, K. Pauli, B. Pauly, A. Pfeiffer, A. Pfuetzner, U. Pischa, R. Radke, P. Reismann, M. Riemer, H. Rochlitz, G. Rudofsky, S. Ruhla, A. Sammler, F. Schaper, K. Schiemenz, G. Scholz, P. Schumm-Draeger, T. Segiet, A. Segner, J. Seissler, S. Spahn, U. Stier, G. Tonon, S. von Amelunxen, C. von Schacky, B. Wilhelm, K. Wilhelm, K. Witt, S. Wuechner-Hofmann; *Hungary*: M. Keltai, M. Baranyai, Z. Birkus, I. Foldesi, Z. Gaal, E. Harcsa, K. Hati, Z. Hohmann, I. Istenes, I. Jozsef, E. Juhasz, P. Kempler, B. Keresztes, K. Keresztes, P. Kis-Gombos, I. Kovacs, T. Kozma, Z. Laszlo, E. Noori, G. Nyirati, Z. Papp, J. Patkay, F. Poor, P. Pusztai, Z. Putz, E. Rigo, M. Sereg, K. Simon, A. Somogyi, J. Sumegi, A. Szabo, J. Szabo, S. Szigeti, D. Szilveszter, M. Tarko, C. Varga, L. Varga Szabo, P. Voros; *India*: A. Ramachandran, Arathi, S. Aravind, M. Badgandi, M. Balaji, V. Balaji, S. Chamukuttan, Devi Manduva, S. Fatima, B. Ganapathy, O. George, P. George, M. Jaffar, P. Jain, P. Kamath, V. Karthik, G. Koshy, L. Krishnan, H. Kumar, P. Lal, A. Mithal, S. Modi, V. Mohan, V. Moses, R. Oomen, P. Pais, P. Pati, S. Pendsey, P. Rai, R. Rajagopal, M. Ramu, U. Ranjit, P. Rao, V. Senthil, V. Seshaiah, B. Sethi, P. Shah, R. Sharma, S. Shetty, A. Shobha, R. Siddharth, G. Sridhar, K. Sudeep, C. Sunil, S. Sunitha, S. Suresh, N. Thomas, A. Vageesh; *Ireland*: S. Sreenan, Z. Anwer, J. Barton, L. Behan, M. Bell, M. Cullen, S. Dineen, M. Draman Yusof, F. Dunne, J. Gibney, T. Hussain, M. Khan, B. Kinsley, P. Kyithar, F. Lavin, A. McGowan, C. McGurk, A. Mirza, B. Mohammadi, T. O'Brien, J. O'Connell, D. O'Halloran, D. O'Shea, G. Roberts, G. Tomkin, W. Wan Mahmood; *Israel*: B.S. Lewis, R. Abramod-Ness, F. Adawi, B. Aharon, M. Backer, A. Beniashvili, A. Berliner, L. Bloch, D. Bugelman, A. Butnaru, O. Cohen, Y. Cohen, M. Frenkel, M. Glant, B. Gustava, H. Guttman, S. Halabi, D. Halon, I. Harman-Boehm, J. Ilany, B. Karkabi, N. Khader, A. Khaskia, Y. Khudyak, E. Klainman, N. Kogan, D. Lender, I. Levin, T. Mardi, A. Marmor, M. Mosseri, D. Nabriski, M. Omary, S. Orlovsky, D. Peres, M. Quasim, I. Raz, M. Remesnik, O. Rogowski, I. Rozenfeld, D. Scharr, I. Shnifer, T. Shuster, R. Solomon, H. Steiner, D. Tzivoni, N. Wolfson, Z. Yossef, D. Zahger, D. Zeltser, R. Zimlichman; *Italy*: A. Maggioni, Aina, C. Ariatti, R. Bonetti, F. Cacciatore, F. Calcinaro, G. Corona, P. De Maria, S. Del Prato, G. Derosa, G. Di Pasquale, A. Falorni, R. Fanelli, D. Fedele, G. Filorizzo, R. Fogari, G. Furgi, A. Ghio, C. Giorda, G. Gregori, G. Iannuzzi, A. Lapolla, B. Luciano, P. Lucotti, A. Maggi, L. Marafetti, T. Marchese, G. Martino, S. Marzotti, R. Miccoli, L.D. Monti, L. Moretti, M. Palvarini, R. Petacchi, F. Piarulli, P.M. Piatti, S. Rudi, F. Santeusanio, G. Sesti, E. Setola, A. Sforza, E. Shehaj, M. Veniani, G. Viviani, E. Zigoura; *Korea*: J.H. Kim, S. Chae, D. Cho, E. Cho, Y. Cho, Y. Choi, M. Chung, E. Hong, Y. Hong, M. Jeong, B. Kim, D. Kim, H. Kim, I. Kim, J. Kim, J. Kim, P. Kim, S. Kim, S. Kim, B. Koo, S. Kwok, H. Kwon, J. Lee, J. Lee, J. Lim, S. Oh, J. Ohn, C. Park, H. Park, K. Park, K. Seung, H. Son, J. Woo, K. Yoon; *Latvia*: V. Pirags, B. Ansmite, I. Balcere, A. Bumbure, K. Ducena, A. Lejnieks, I. Rasa, R. Ritenberga, M. Romanova, I. Salmina, S. Steina; *Lithuania*: V. Pirags, J. Badariene, S. Gailiuniene, S. Grigonis, R. Juskiene, Z. Petrulioniene, G. Sakalyte, T. Stasiunas, M. Sulskiene, B. Urbonaite, R. Zarankiene, R Ziukaite; *Mexico*: E. Cardona, R. Arechavaleta, T. Beltran-Jaramillo, C. Calvo-Vargas, C. Campillo-Cardenas, D. Cardona, J. Carmona-Huerta, M. Cedano-Limon, M. Comellas-De Armas, C. Dominguez, J. Gomez-Cruz, R. Gonzalez-Perez, J. Illescas, S. Jimenez-Ramos, A. Lopez-Alvarado, E. Marquez-Rodriguez, G. Martinez, S. Pascoe, O. Plascencia Vazquez, H. Rodriguez, M. Ruiz-Cornejo, G. Velasco-Sanchez, M. Vidrio-Velazquez, E. Villeda-Espinosa; *Netherlands*: I. Stoel, E. Badings, G. Bartels, P. Bruggink-Andre de la Porte, E. Bruijns, J. Cornel, P. De Milliano, M. De Mulder, J. De Swart, A. Derks, A. Dirkali, J. Droste, M. Galjee, R. Hautvast, W. Hermans, N. Holwerda, B. Ilmer, M. Kofflard, J. Kooistra-Huizer, M. Kurvers, J. Langerveld, C. Leenders, A. Liem, D. Lok, D. Neumann, P. Nierop, K. Plomp, J. Posma, C. Reichert, H. Roeters Van Lennep, E. Ronner, S. Said, L. Takens, V. Umans, A.A. Van der Sluis, C. Van der Zwaan, J. Van Dobbenburgh, A. Van Es, M. Van Hessen, R. Van Mechelen, A. Van Miltenburg-Van Zijl, L. Van Zeijl, M. Veerhoek, E. Viergever, E.E. Weijers, F. Willems; *Norway*: K. Birkeland, I. Blix, J. Cooper, A. Debowska, K. Erichsen, J. Fossum, E. Gjertsen, V. Grill, S. Gudnason, K. Hoye, H. Istad, J. Winther, R. Joakimsen, R. Jorde, I. Larsen, B. Mella, J. Otterstad, K. Risberg, K. Skare, S. Skeie, L. Sommervoll, A. Tandberg, R. Whitfield, C. Wium; *Philippines*: R. Fernando, E. Cunanan, E. Fernando-Catindig, M. Gomez, C. Jaring, F. Lantion-Ang, M. Licaros, J. Lim, M. Lim-Abrahan, E. Madronio, A. Panelo, J. Raboca, G. Ramos, S. Tugna; *Poland*: A. Budaj, E. Aksamit-Bialoszewska, E. Bandurska-Stankiewicz, M. Baranska, A. Bronisz, M. Bronisz, W. Chrustowski, B. Cieslak, L. Czupryniak, B. Drazkowicz-Gozdzik, A. Galuszka-Bilinska, M. Gmytrasiewicz, K. Janik, K. Jedynasty, G. Kania, T. Kawka-Urbanek, I. Kinalska, K. Kincel, U. Kleszczewska, J. Kruszewski, J. Loba, J. Malicka, M. Mielecka-Kincel, A. Milczarczyk, D. Milosz, A. Mrowczynska, M. Mytnik, A. Nowakowski, P. Nowakowski, L. Oleskowska, E. Omelanczuk-Wiech, M. Pawlowski, A. Poplawska, M. Rucinska, M. Rucinski, J. Rutkowska, M. Saryusz-Wolska, K. Siewko, M. Sikora-Frac, J. Stecka-Wierzbicka, M. Swiatkowski, R. Swierczynski, M. Szpajer, K. Szymkowiak, J. Tarach, U. Tarasiewicz, D. Wiatr, P. Wojewoda, H. Woszczak-Marcinkowska, J. Zadrozny; *Romania*: N. Hancu, A. Albota, C. Bala, D. Barbonta, G. Botnariu, O. Bradescu, M. Busegeanu, M. Bzduch, D. Catrinoiu, R. Caziuc, A. Cerghizan, D. Cheta, A. Cif, D. Ciomos, D. Cosma, G. Creteanu, I. Crisan, R. Danciulescu, C. Dobjanschi, R. Dodan, L. Duma, I. Ferariu, T. Ghenes, G. Ghise, M. Graur, M. Ilinca, R. Marton, N. Mindrescu, A. Morosanu, M. Morosanu, M. Mota, V. Nafornita, G. Negrisan, S. Nicodim, A. Nicolau, C. Nita, A. Onaca, C. Panus, N. Pletea, C. Pop, L. Pop, B. Popa, G. Roman, M. Rosu, N. Sandu, V. Serban, A. Sima, L. Stamoran, M. Strugariu, G. Suciu, I. Szilagyi, G. Vacaru, I. Veresiu, A. Vlad; *Russia*: I. Chazova, T. Adasheva, F. Ageev, N. Akhmedganov, A. Akinina, A. Alexandrov, L. Ambatiello, A. Ametov, A. Ausheva, L. Babaeva, A. Babenko, E. Balyasnikova, B. Bart, J. Belova, L. Berstein, I. Bondarenko, E. Bondarev, O. Bulkina, N. Chernikova, B. Chumak, T. Deeva, O. Demicheva, T. Demidova, E. Doskina, A. Duganova, N. Dzhaiani, I. Egorova, O. Ettinger, S. Feofanova, T. Fofanova, P. Galaktionov, N. Gavrilova, S. Gilyarevsky, N. Gnidkina, A. Golubev, N. Gornyakova, S. Grigorova, E. Grineva, V. Gurevich, N. Irtuganov, L. Ivanova, N. Jaiani, M. Kalashnikova, Y. Karpov, Y. Khalimov, G. Khorocheva, E. Kirillova, J. Kistner, Z. Kobalava, I. Kochergina, T. Kravchenko, K. Krylov P. Kulkova, I. Kuparev, E. Kurbanova, T. Lysenko, A. Markovich, I. Martyanova, T. Martynyuk, M. Masiinvets, E. Mavlyavieva, E. Maychuk, G. Melnichenko, M. Mikhailusova, A. Mkrtumyan, V. Mychka, D. Nebieridze, E. Nesterova, V. Orlov, V. Orlova, Y. Orlova, F. Papov, I. Patroucherva, N. Petunina, S. Pirozhinskaya, S. Podachina, S. Postnikova, O. Pshikova, L. Rogova, B. Romashevskiy, N. Runikhina, I. Sadulayeva, A. Safaryan, E. Sakovich, T. Saprikina, V. Sargsyan, O. Semikozova, E. Shkolnik, A. Shubina, S. Shustov, I. Sinitsina, E. Solovyeva, G. Storogakov, O. Stovpyuk, A. Sussekov, M. Telnova, A. Temirov, V. Terekhov, S. Tereschenko, T. Tiourina, V. Tolkacheva, U. Tsoy, S. Urazgyldeeva, Y. Vasyuk, N. Vinnitskay, E. Voevodina, A. Volkova, V. Zadionchenko, A. Zalevskaya, T. Zhelninova, N. Zhukova, A. Zilov; *Slovakia*: G. Fodor, J. Bernatova, T. Duris, I. Markova, E. Martinka, L. Michalova, P. Minarik, L. Peter, K. Raslova, D. Silvia, M. Subadova, J. Tisonova, B. Vohnout; *South Africa*: P. Commerford, M. Adam, A. Badat, A. Bester, F. Bester, L. Blacking, D. Bouwer, B. Brice, S. Cassimjee, T. Cronje, J. Deftereos, L. Distiller,

G. Ellis, O. Forster, M. Fulat, M. Gani, G. Gibson, S. Hansa, N. Hendricks, L. Herbst, J. Hitzeroth, B. Joffe, C. Kelbe, D. Kelbe, J. King, B. Kramer, S. Landau, N. Levitt, S. Meyer-Nell, R. Moore, D. Muller, H. Nell, M. Omar, H. Randeree, M. Seeber, Seedat, D. Segynu, M. Siebert, E. Van Den Berg, P. Van Der Walt, C. Van Dyk, F. Van Niekerk, L. Van Zyl, H. Wellman *Spain*: R. Gomis, V. Bertomeu, M. Botella, M. Buño, A. Calle, J. Cano Perez, M. Coves, J.G. Juanatey, R. Garcia-Mayor, S. Gaztambide, A. Gippini, I. Goikolea, J. Gonzalez, N. Hillman, V. Lopez Garcia Aranda, I. Magueda, J. Mato, P. Mazon, P. Morillas, A. Novials, L. Pallardo, L. Perez, J. Rodriguez, L. Romero, E. Sagarra, L. Shamagian, A. Soto, H. Torrealday, R. Valero; *Sweden*: L. Rydén, S. Agergaard, S. Agewall, K. Andersson, O. Bergstrom, M. Bjornstedt Bennermo, J. Blomgren, K. Boman, G. Brohall, C. Cherfan, C. Dahlen, A. Dotevall, P. Enander, U. Ericsson, P. Hallgren, A. Hansson, L. Henareh, P. Henriksson, J. Herlitz, J. Holmqvist, G. Jarevi, C. Linderfalk, L. Jonasson, S. Jovinge, J. Kalen, M. Kilstrup, M. Leosdotir, J. Leppert, B. Linde, J. Ljungberg, B. Löfdahl, P. Lundman, C. LysellBergstrom, U. Mathiesen, L. Mellbin, S. Mörner, D. Nathanson, L. Nilsson, M. Peterson, S. Quittenbaum, A. Rosengren, B. Ryttberg, S. Scheel, K. Svensson, Å. Tenerz, P. Vasko, A. Waldenström, M. Wieloch; *Switzerland*: G. Spinas, M. Braendle, B. Felix, P. Gerber, T. Moccetti, N. Pitteloud; *Turkey*: H. Kultursay, A. Aydinalp, M. Balci, M. Cayli, E. Hatipoglu, H. Ilkova, M. Kayikcioglu, M. Koc, H. Muderrisoglu, R. Sari, F. Saygili, K. Tekin, N. Tutuncu, B. Yurekli; *United Kingdom:* M. Davies, A. Adler, A. Ali, Balasubramanian, P. Bandypadhyay, O. Barakat, A. Barnett, L. Borthwick, Brookes, J. Burton, J. Cecil, S. Chaterjee, J. Clark, D. Collinson, S. Collinson, W. Crasto, R. Donnelly, J. du Plessis, S. Egan, A. Ellery, R. Evans, J. Ewing, C. Fox, M. Gibson, T. Hall, E. Higgs, M. Hollway, E. Hughes, N. Jackson, H. Jalihawi, G. Jones, H. Knights, S. Korsheed, R. Kumar Singh, D. Laithwaite, I. Lawrence, J. Litchfield, G. Manning, P. McNally, M. Millar-Craig, I. Mohammed, R. Narayanan, G. Nayani, A. Norris, J. Purohit, M. Quinn, Ramtoola, J. Randall, R. Rea, J. Reckless, T. Richardson, D. Robertson, A. Robinson, K. Salem, M. Sampson, M. Savage, J. Shaker, T. Srinivasan, I. Tracy, J. Tringham, A. Viljoen, A. Ward, H. Waterhouse, N. Wijenaike, P. Wiles; *United States of America:* J. Probstfield, M. Riddle, A. Ahmann, I. Ahmed, A. Alam, R. Arakaki, S. Asad, S. Banarer, H. Baum, K. Belew, R. Bergenstal, M. Bethel, C. Boyer, S. Catton, P. Challans, B. Childs, R. Christian, S. Clement, R. Cuddihy, G. Dailey III, G. Damberg, C. De Bold, J. De Lemos, D. Donovan, J. Dudl, J. Dunbar, S. Ebner, R. Failor, M. Feinglos, G. Flaker, M. Freiburghaus, K. Furlong, D. Gardner, E. Gillespie, R. Goland, R. Goldberg, A. Gotham, R. Guthrie, M. Hamaty, I. Hirsch, S. Jabbour, M. Janci, B. Javorsky, S. Jones, V. Kamana, M. Kashyap, S. Kaufman, P. Kearns, A. Khera, B. Klopfenstein, W. Kniffen, P. Kringas, A. Licata, C. LopezJimenez, M. Madden, C. Marx, A. McCall, J. McCallum, S. McFarlane, D. McGuire, J. Melish, L. Meneghini, S. Miller, B. Miranda-Palma, R. Mitchell, C. Nasr, J. Nelson, P. Niblack, E. Nylen, K. Osei, A. Pandey, V. Papademetriou, M. Pilar Solano, R. Ratner, J. Rosenstock, L. Sameshima, V. Savarese, J. Schnure, D. Schuster, J. Shin, A. Taylor, P. Thomson, M. Ting-Ryan, D. Trence, A. Vo, K. Weiland, K. Wells, P. Wu, M. Zimering, R. Zimmerman *Venezuela*: I. Mendoza, P. Ascanio, I. Brajkovich, E. Carrillo, J. Coll, K. Gonzalez, N. Gonzalez, E. Jimenez, R. Lopez, D. Marante, I. Morr, M. Paolillo, D. Perche, M. Portillo, H. Valbuena, M. Velarde, G. Vergara.

REFERENCES

1. World Health Organization. Population nutrient intake goals for preventing diet-related chronic diseases. Accessed December 15, 2019. https://www.who.int/nutrition/topics/5_population_nutrient/en/

2. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140(11):e596-e646. doi:10.1161/CIR.0000000000000678

3. Kimmig LM, Karalis DG. Do omega-3 polyunsaturated fatty acids prevent cardiovascular disease? a review of the randomized clinical trials. *Lipid Insights*. 2013;6:13-20. doi:10.4137/LPI.S10846

4. Gebauer SK, Psota TL, Harris WS, Kris-Etherton PM. n-3 Fatty acid dietary recommendations and food sources to achieve essentiality and cardiovascular benefits. *Am J Clin Nutr*. 2006;83(6)(suppl):1526S-1535S. doi:10.1093/ajcn/83.6.1526S

5. Tørris C, Småstuen MC, Molin M. Nutrients in fish and possible associations with cardiovascular disease risk factors in metabolic syndrome. *Nutrients*. 2018;10(7):E952. doi:10.3390/nu10070952

6. Mozaffarian D, Wu JH. Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. *J Am Coll Cardiol*. 2011;58(20):2047-2067. doi:10.1016/j.jacc.2011.06.063

7. Wu JH, Mozaffarian D. ω-3 Fatty acids, atherosclerosis progression and cardiovascular outcomes in recent trials: new pieces in a complex puzzle. *Heart*. 2014;100(7):530-533. Published online January 23, 2014. doi:10.1136/heartjnl-2013-305257

8. Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. *JAMA*. 2012;308(10):1024-1033. doi:10.1001/2012.jama.11374

9. Abdelhamid AS, Brown TJ, Brainard JS, et al. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2018;7:CD003177.

10. Hu Y, Hu FB, Manson JE. Marine omega-3 supplementation and cardiovascular disease: an updated meta-analysis of 13 randomized controlled trials involving 127 477 participants. *J Am Heart Assoc*. 2019;8(19):e013543. doi:10.1161/JAHA.119.013543

11. Bowman L, Mafham M, Wallendszus K, et al; ASCEND Study Collaborative Group. Effects of n-3 fatty acid supplements in diabetes mellitus. *N Engl J Med*. 2018;379(16):1540-1550. doi:10.1056/NEJMoa1804989

12. Manson JE, Cook NR, Lee IM, et al; VITAL Research Group. Marine n-3 fatty acids and prevention of cardiovascular disease and cancer. *N Engl J Med*. 2019;380(1):23-32. doi:10.1056/NEJMoa1811403

13. Bhatt DL, Steg PG, Miller M, et al; REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. 2019;380(1):11-22. doi:10.1056/NEJMoa1812792

14. Jayedi A, Shab-Bidar S. Fish consumption and the risk of chronic disease: an umbrella review of meta-analyses of prospective cohort studies. *Adv Nutr*. 2020;11(5):1123-1133. doi:10.1093/advances/nmaa029

15. Yusuf S, Islam S, Chow CK, et al; Prospective Urban Rural Epidemiology (PURE) Study Investigators. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey. *Lancet*. 2011;378(9798):1231-1243. doi:10.1016/S0140-6736(11)61215-4

16. Corsi DJ, Subramanian SV, Chow CK, et al. Prospective Urban Rural Epidemiology (PURE) study: baseline characteristics of the household sample and comparative analyses with national data in 17 countries. *Am Heart J*. 2013;166(4):636-646.e4. doi:10.1016/j.ahj.2013.04.019

17. Chow CK, Teo KK, Rangarajan S, et al; PURE (Prospective Urban Rural Epidemiology) Study investigators. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. *JAMA*. 2013;310(9):959-968. doi:10.1001/jama.2013.184182

18. Teo K, Lear S, Islam S, et al; PURE Investigators. Prevalence of a healthy lifestyle among individuals with cardiovascular disease in high-, middle- and low-income countries: the Prospective Urban Rural Epidemiology (PURE) study. *JAMA*. 2013;309(15):1613-1621. doi:10.1001/jama.2013.3519

19. Yusuf S, Rangarajan S, Teo K, et al; PURE Investigators. Cardiovascular risk and events in 17 low-, middle-, and high-income countries. *N Engl J Med*. 2014;371(9):818-827. doi:10.1056/NEJMoa1311890

20. Yusuf S, Teo KK, Pogue J, et al; ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008;358(15):1547-1559. doi:10.1056/NEJMoa0801317

21. Yusuf S, Teo K, Anderson C, et al; Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. *Lancet*. 2008;372(9644):1174-1183. doi:10.1016/S0140-6736(08)61242-8

22. Gerstein HC, Bosch J, Dagenais GR, et al; ORIGIN Trial Investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med*. 2012;367(4):319-328. doi:10.1056/NEJMoa1203858

23. Bosch J, Gerstein HC, Dagenais GR, et al; ORIGIN Trial Investigators. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. *N Engl J Med*. 2012;367(4):309-318. doi:10.1056/NEJMoa1203859

24. Mente A, Dehghan M, Rangarajan S, et al; Prospective Urban Rural Epidemiology (PURE) study investigators. Association of dietary nutrients with blood lipids and blood pressure in 18 countries: a cross-sectional analysis from the PURE study. *Lancet Diabetes Endocrinol*. 2017;5(10):774-787. doi:10.1016/S2213-8587(17)30283-8

25. Dehghan M, Mente A, Zhang X, et al; Prospective Urban Rural Epidemiology (PURE) study investigators. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study. *Lancet*. 2017; 390(10107):2050-2062. doi:10.1016/S0140-6736(17)32252-3

26. Burke DL, Ensor J, Riley RD. Meta-analysis using individual participant data: one-stage and two-stage approaches, and why they may differ. *Stat Med*. 2017;36(5):855-875. doi:10.1002/sim.7141

27. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188. doi:10.1016/0197-2456(86)90046-2

28. Groll A, Hastie T, Tutz G. Selection of effects in Cox frailty models by regularization methods. *Biometrics*. 2017;73(3):846-856. doi:10.1111/biom.12637

29. Dehghan M, Mente A, Rangarajan S, et al; Prospective Urban Rural Epidemiology (PURE) study investigators. Association of dairy intake with cardiovascular disease and mortality in 21 countries from five continents (PURE): a prospective cohort study. *Lancet*. 2018;392(10161):2288-2297. doi:10.1016/S0140-6736(18)31812-9

30. National Institutes of Health, Office of Dietary Supplements. Omega 3 fatty acids. Accessed March 15, 2020. https://ods.od.nih.gov/factsheets/Omega3FattyAcids-HealthProfessional/

31. Brownie S, Muggleston H, Oliver C. The 2013 Australian dietary guidelines and recommendations for older Australians. *Aust Fam Physician*. 2015;44(5):311-315.

32. U.S. Department of Health. Dietary guidelines for Americans 2015–2020, eighth edition. Published December 2015. Accessed January 2021. https://health.gov/our-work/food-nutrition/previous-dietary-guidelines/2015

33. Piepoli MF, Hoes AW, Agewall S, et al; ESC Scientific Document Group. 2016 European guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J*. 2016;37(29):2315-2381. doi:10.1093/eurheartj/ehw106

34. Rajaram S, Haddad EH, Mejia A, Sabaté J. Walnuts and fatty fish influence different serum lipid fractions in normal to mildly hyperlipidemic individuals: a randomized controlled study. *Am J Clin Nutr*. 2009;89(5):1657S-1663S. doi:10.3945/ajcn.2009.26736S

35. Raatz SK, Johnson LK, Rosenberger TA, Picklo MJ. Twice weekly intake of farmed Atlantic salmon (Salmo salar) positively influences lipoprotein concentration and particle size in overweight men and women. *Nutr Res*. 2016;36(9): 899-906. doi:10.1016/j.nutres.2016.06.011

36. Theobald HE, Chowienczyk PJ, Whittall R, Humphries SE, Sanders TA. LDL cholesterol-raising effect of low-dose docosahexaenoic acid in middle-aged men and women. *Am J Clin Nutr*. 2004;79(4):558-563. doi:10.1093/ajcn/79.4.558

37. Karlström BE, Järvi AE, Byberg L, Berglund LG, Vessby BO. Fatty fish in the diet of patients with type 2 diabetes: comparison of the metabolic effects of foods rich in n-3 and n-6 fatty acids. *Am J Clin Nutr*. 2011;94(1):26-33. doi:10.3945/ajcn.110.006221

38. Chen C, Yu X, Shao S. Effects of omega-3 fatty acid supplementation on glucose control and lipid levels in type 2 diabetes: a meta-analysis. *PLoS One*. 2015;10(10):e0139565. doi:10.1371/journal.pone.0139565

39. Wallin A, Di Giuseppe D, Orsini N, Patel PS, Forouhi NG, Wolk A. Fish consumption, dietary long-chain n-3 fatty acids, and risk of type 2 diabetes: systematic review and meta-analysis of prospective studies. *Diabetes Care*. 2012;35(4): 918-929. doi:10.2337/dc11-1631

40. Forouhi NG, Misra A, Mohan V, Taylor R, Yancy W. Dietary and nutritional approaches for prevention and management of type 2 diabetes. *BMJ*. 2018;361:k2234. doi:10.1136/bmj.k2234

41. Nanri A, Mizoue T, Noda M, et al; Japan Public Health Center-based Prospective Study Group. Fish intake and type 2 diabetes in Japanese men and women: the Japan Public Health Center-based Prospective Study. *Am J Clin Nutr*. 2011;94(3): 884-891. doi:10.3945/ajcn.111.012252

42. Sheehan MC, Burke TA, Navas-Acien A, Breysse PN, McGready J, Fox MA. Global methylmercury exposure from seafood consumption and risk of developmental neurotoxicity: a systematic review. *Bull World Health Organ*. 2014;92(4):254-269F. doi:10.2471/BLT.12.116152

43. Sioen I, De Henauw S, Van Camp J, Volatier JL, Leblanc JC. Comparison of the nutritional-toxicological conflict related to seafood consumption in different regions worldwide. *Regul Toxicol Pharmacol*. 2009;55(2):219-228. doi:10.1016/j.yrtph.2009.07.003

44. Mozaffarian D. Dietary and policy priorities for cardiovascular disease, diabetes, and obesity: a comprehensive review. *Circulation*. 2016;133(2): 187-225. doi:10.1161/CIRCULATIONAHA.115.018585

45. Burr ML, Fehily AM, Gilbert JF, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet*. 1989;2(8666):757-761. doi:10.1016/S0140-6736(89)90828-3

46. Burr ML, Ashfield-Watt PA, Dunstan FD, et al. Lack of benefit of dietary advice to men with angina: results of a controlled trial. *Eur J Clin Nutr*. 2003;57(2):193-200. doi:10.1038/sj.ejcn.1601539

47. Casula M, Soranna D, Catapano AL, Corrao G. Long-term effect of high dose omega-3 fatty acid supplementation for secondary prevention of cardiovascular outcomes: a meta-analysis of randomized, placebo controlled trials. *Atheroscler Suppl*. 2013;14(2):243-251. Published correction appears in *Atheroscler Suppl*. 2014;233(1):122. doi:10.1016/S1567-5688(13)70005-9

48. Hooper L, Thompson RL, Harrison RA, et al. Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: systematic review. *BMJ*. 2006;332(7544):752-760. doi:10.1136/bmj.38755.366331.2F

49. Marik PE, Varon J. Omega-3 dietary supplements and the risk of cardiovascular events: a systematic review. *Clin Cardiol*. 2009;32(7): 365-372. doi:10.1002/clc.20604

Invited Commentary

Fish, Cardiovascular Disease, and Mortality—What Is the Global Evidence?

Dariush Mozaffarian, MD, DrPH

Fish and shellfish (hereafter referred to as fish) are major sources of the dietary long-chain ω-3 fatty acids eicosapentaenoic acid (20:5n-3) and docosahexaenoic acid (22:6n-3) and also contain other nutrients, such as vitamin D, riboflavin, iodine, calcium, phosphorus, magnesium, potassium, zinc, and iron. The summed results of observational studies of fish intake, randomized clinical trials of fish oil supplements, and associated mechanistic and experimental studies suggest that regular fish consumption may decrease the incidence of myocardial infarction (MI) and coronary heart disease (CHD), with more uncertain effects on stroke, total cardiovascular disease (CVD), or other composite events, such as all-cause mortality.[1-3] Yet, these summed findings obscure the inconsistent results of individual clinical trials, which have raised uncertainty and controversy about health benefits. Proposed explanatory factors for the heterogeneity have included dose, type of fish (oily vs white), methods for preparation of fish (baked or grilled vs fried), background fish consumption, underlying participant risk, outcome (eg, fatal CHD vs combined CVD events), and even presence of trace contaminants such as mercury or

Multimedia

Related article page 631