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Triglycerides and the Risk of Coronary Heart Disease 10 158 Incident Cases Among 262 525 Participants in 29 Western Prospective Studies

Nadeem Sarwar, MPhil; John Danesh, DPhil; Gudny Eiriksdottir, MSc; Gunnar Sigurdsson, PhD;
Nick Wareham, PhD; Sheila Bingham, PhD; S. Matthijs Boekholdt, PhD;
Kay-Tee Khaw, MBBChir; Vilmundur Gudnason, PhD

Background—Many epidemiological studies have reported on associations between serum triglyceride concentrations and the risk of coronary heart disease, but this association has not been reliably quantified. In the present study, we report 2 separate nested case-control comparisons in 2 different prospective, population-based cohorts, plus an updated meta-analysis of 27 additional prospective studies in general Western populations.

Methods and Results—Measurements were made in a total of 3582 incident cases of fatal and nonfatal coronary heart disease and 6175 controls selected from among the 44 237 men and women screened in the Reykjavik and the European Prospective Investigation of Cancer (EPIC)-Norfolk studies. Repeat measurements were obtained an average of 4 years apart in 1933 participants in the EPIC-Norfolk Study and an average of 12 years apart in 379 participants in the Reykjavik study. The long-term stability of log-triglyceride values (within-person correlation coefficients of 0.64 [95% CI, 0.60 to 0.68] over 4 years and 0.63 [95% CI, 0.57 to 0.70] over 12 years) was similar to those of blood pressure and total serum cholesterol. After adjustment for baseline values of several established risk factors, the strength of the association was substantially attenuated, and the adjusted odds ratio for coronary heart disease was 1.76 (95% CI, 1.39 to 2.21) in the Reykjavik study and 1.57 (95% CI, 1.10 to 2.24) in the EPIC-Norfolk study in a comparison of individuals in the top third with those in the bottom third of usual log-triglyceride values. Similar overall findings (adjusted odds ratio, 1.72; 95% CI, 1.56 to 1.90) were observed in an updated meta-analysis involving a total of 10 158 incident coronary heart disease cases from 262 525 participants in 29 studies.

Conclusions—Available prospective studies in Western populations consistently indicate moderate and highly significant associations between triglyceride values and coronary heart disease risk. Because these associations depend considerably on levels of established risk factors, however, further studies are needed to help assess the nature of any independent associations. (*Circulation*. 2007;115:450-458.)

Key Words: coronary disease ■ epidemiology ■ lipids ■ meta-analysis ■ triglycerides

Triglycerides are lipid fractions used for energy storage that are both intrinsically synthesized in the liver and derived from external sources through uptake in the intestine.

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These fractions are transported primarily in very-low-density lipoproteins and chylomicrons and are stored mainly in adipose tissue.¹ Many epidemiological studies have reported associations between serum triglyceride concentrations and the risk of coronary heart disease (CHD),²⁻²⁸ but their relevance to disease remains uncertain. The first of 2 previous

attempts to synthesize the available data was a meta-analysis reported in 1996 of published data from 17 prospective studies in Western populations, involving a total of 2900 CHD end points.²⁹ It reported relative risks, adjusted for several established risk factors, of 1.14 (95% CI, 1.05 to 1.28) in men and 1.37 (95% CI, 1.13 to 1.66) in women per 1-mmol/L increase in triglycerides, suggesting that triglyceride concentrations are twice as strongly associated with cardiovascular disease risk in women than in men.²⁹ The validity of these observations, however, was limited by the inclusion of only a few hundred female patients, by lack of

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From the Department of Public Health and Primary Care, University of Cambridge (N.S., J.D., K.-T.K.), MRC Epidemiology Unit (N.W.), MRC Dunn Nutrition Unit, and MRC Centre for Nutrition and Cancer Prevention and Survival (S.B.), Cambridge, England; Icelandic Heart Association, Kopavogur, Iceland (G.E., G.S., V.G.); and Academic Medical Center, Amsterdam, the Netherlands (S.M.B.).

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Correspondence to Professor John Danesh, Department of Public Health and Primary Care, University of Cambridge, Strangeways Research Laboratory, Wort's Causeway, Cambridge, CB1 8RN, UK. E-mail john.danesh@phpc.cam.ac.uk

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correction for within-person variability in triglyceride values (ie, for regression dilution bias), and by inconsistent adjustment for possible confounding factors across different published studies. A more recent, nonoverlapping meta-analysis involved individual data from 26 prospective studies in Asian and Pacific populations.³⁰ It reported a relative risk for CHD, adjusted consistently for several established risk factors, of 1.80 (95% CI, 1.49 to 2.19) in a comparison of individuals in the top fifth compared with those in the bottom fifth of long-term (“usual”) triglyceride values, concluding that triglycerides are an “independent determinant”³⁰ of CHD risk. That review, however, lacked information on some possible confounders (such as fasting glucose concentrations) and involved a total of about 850 CHD cases, which may be too few to characterize reliably the associations of triglycerides under different circumstances. It is also uncertain to what extent its findings could be applied to individuals in Western populations (who may have lipid profiles different from those in Asian populations), reinforcing the latest conclusion from the American National Cholesterol Education Program-Adult Treatment Panel (NCEP-ATP III)³¹ that there is insufficient evidence to regard triglycerides as an independent coronary risk factor in Western populations.

To help quantify more reliably than previously possible the association of long-term circulating triglyceride concentrations with CHD risk, we report primary data on triglyceride concentrations from 2 prospective cohort studies: the Reykjavik study and the European Prospective Investigation of Cancer (EPIC)-Norfolk study, which together comprise 44 237 Western middle-aged men and women of predominantly white European continental ancestry and a total of 3582 incident cases of CHD (including 1089 female cases), more CHD cases than reported in either previous meta-analysis. Serial triglyceride measurements were made in subsets of participants in each study, enabling cohort-specific adjustment for regression dilution bias. Furthermore, to help put these new data in context, we have updated the previous literature-based meta-analysis of prospective studies in Western populations, adding 12 more studies (involving an additional 3785 CHD cases) to those in the previous review of Western studies.²⁹ Thus, in aggregate, the present report includes information from a total of >10 000 CHD cases from 29 Western prospective studies involving a total of >260 000 participants. The present report focuses on the potential etiological association of circulating triglycerides with CHD risk; the question of any value of its measurement in risk prediction will be addressed separately.

Methods

Participants in the Reykjavik and EPIC-Norfolk Studies

The Reykjavik and the EPIC-Norfolk studies, initiated in 1967 and 1993, respectively, have each been described in detail previously.^{32,33} All men born between 1907 and 1934 and all women born between 1908 and 1935 who were resident in Reykjavik, Iceland, and its adjacent communities on December 1, 1966, were identified in the national population register and then invited to participate in the Reykjavik study during 5 stages of recruitment between 1967 and 1991, yielding 8888 male and 9681 female participants without a history of myocardial infarction (72% response rate). Nurses admin-

istered questionnaires, made physical measurements, recorded an ECG, performed spirometry, and collected fasting venous blood samples. All participants have been monitored subsequently for cause-specific mortality and for cardiovascular morbidity, with a loss to follow-up of only ≈0.6% to date. A total of 2459 men and women had major coronary events between the beginning of follow-up and December 31, 1995, yielding mean durations of follow-up among CHD cases of 17.5 years (SD, 8.7 years) and 20.6 years (SD, 8.2 years) among controls. Among men, 1073 CHD deaths and 701 nonfatal myocardial infarctions were recorded; 385 CHD deaths and 300 nonfatal myocardial infarctions were recorded among women. Deaths from CHD were ascertained from central registers on the basis of a death certificate with *International Classification of Diseases, 9th Revision*, codes 410 to 414; the diagnosis of nonfatal myocardial infarction was based on Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) criteria. We selected 3969 controls “frequency” matched to cases on calendar-year of recruitment, gender, and age in 5-year bands from among participants who had survived to the end of the study period without a myocardial infarction. The National Bioethics Committee and the Data Protection Authority of Iceland approved the study protocol, and participants provided informed consent.

The EPIC-Norfolk study enrolled 25 668 men and women (45% response rate) identified through general practice registers who were 45 to 79 years of age at a screening visit during which demographic, nutritional, lifestyle, anthropometric, and metabolic information and nonfasting venous blood samples were obtained. All participants had been flagged for cause-specific mortality by the UK Office of National Statistics and linked with the ENCORE database (East Norfolk Health Authority) for hospital discharge diagnosis codes recorded throughout England and Wales. Trained nosologists coded the underlying cause of death or hospital admission according to *International Classification of Diseases, 9th Revision*, criteria, with fatal CHD defined as a death certificate with codes 410 to 414 and nonfatal CHD as a hospital admission with the underlying cause coded 410 to 414. Detailed review of clinical records according to MONICA criteria confirmed such diagnoses in 38 of 39 CHD deaths and in all 26 nonfatal CHD events randomly selected in a validation substudy conducted in 1996. Between 1993 and 2003, 1138 incident cases of CHD (including 785 nonfatal CHD events) were recorded. We selected 2276 controls individually matched to cases by age (in 5-year bands), gender, and date of screening (± 3 months) who had survived to the censoring date free of cardiovascular disease. The study was approved by the Norwich District Health Authority Ethics Committee, and all participants provided written informed consent.

Laboratory Methods

In both prospective studies, laboratory measurements were carried out in fresh samples (ie, before the diagnosis of CHD and therefore without knowledge of disease status). In the Reykjavik study, serum triglyceride concentrations were measured by fluorimetry using a Technicon (Cranesville, Pa) autoanalyzer in strict accordance with the Cooperative Triglycerides Standardization Program. In the EPIC-Norfolk study, serum triglyceride concentrations were measured by an enzymatic method (RA10000, Bayer, Wuppertal, Germany). Other biochemical and hematological measurements involved standard assays, as previously described.^{32,33} Measurements were made in pairs of samples in 1933 participants in the EPIC-Norfolk study collected at a mean interval of ≈4 years apart and in pairs of samples in 379 participants in the Reykjavik study collected at a mean interval of ≈12 years apart. Because these resurvey intervals were approximately the midpoints of the recorded mean follow-up durations in each study, they should provide optimum intervals for quantification of regression dilution (see below).

Statistical Methods

Case-control comparisons were made by unmatched logistic regression fitted by unconditional maximum likelihood, adjusted for the matching variables (Stata Corp, College Station, Tex). Values of serum triglycerides were log-transformed to achieve approximately symmetrical distributions. Primary analyses were prespecified to be

by thirds of log-triglyceride values in the controls (with subsidiary analyses involving other cutoff points such as comparisons by 1-mmol/L increases or by extreme fifths to enable comparisons with previous meta-analyses). All analyses of the 2 cohorts involved within-study comparisons (ie, cases and controls were only directly compared within each prospective study) to avoid potential biases; this approach also was applied to the meta-analysis described below. Correction for regression dilution was made by dividing the regression coefficients (and their standard errors) that related risk to measurements of baseline log-triglyceride concentrations by the regression dilution factor calculated from resurvey measurements made in each cohort.³⁴ Meta-analysis was done of studies published before January 2005 with >1 year's follow-up in approximately general populations (ie, in cohorts not selected on the basis of preexisting disease) using search, abstraction, and data synthesis methods that have been described previously³⁵ and with nonfatal myocardial infarction or CHD death as end points. All studies that included both male and female participants adjusted risk estimates for gender. Because this review was restricted to studies based in Western populations, the large majority of participants in the contributing studies were of white European continental ancestry. Results of studies were combined using inverse variance-weighted averages of log odds ratios. A regression dilution correction factor of 0.6 (derived from the resurveys in the present studies) was applied to the studies identified in the meta-analysis. Heterogeneity was assessed by standard χ^2 tests and the I^2 statistic, which describes the percentage of variation in the log odds ratios that is attributable to genuine differences across studies rather than random error.³⁶ Subsidiary analysis by random-effects regression models with restricted maximum likelihood estimation (ie, "meta-regression") was conducted to test whether any observed sources of heterogeneity could be accounted for by other recorded study characteristics. Odds ratios are given with 95% CIs, and 2-sided probability values are used.

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

Results

The mean age at CHD event among cases was 70.2 ± 9.7 years in the Reykjavik study and 74.6 ± 8.0 years in the EPIC-Norfolk study. In both studies, there were highly significant differences between cases and controls with respect to established coronary risk factors such as smoking, body mass index, blood pressure, and serum lipid concentrations (Table 1). The mean triglyceride concentrations in controls were substantially higher in the EPIC-Norfolk study (1.90 ± 1.17 mmol/L or 0.22 ± 0.22 for log-triglycerides) than in the Reykjavik study (1.03 ± 0.62 mmol/L or 0.03 ± 0.44 for log-triglycerides), reflecting mainly the recruitment of non-fasting participants in EPIC-Norfolk.

Baseline Associations and Within-Person Variation of Triglyceride Values

Among controls in each study, log-triglycerides were highly significantly associated with male gender, cigarette smoking, body mass index, blood pressure, and C-reactive protein ($P < 0.001$ for each; Table 2). In 1933 individuals who provided paired blood samples in the EPIC-Norfolk study at a mean interval of ≈ 4 years, the within-individual correlation coefficient value for triglycerides was 0.64 (95% CI, 0.60 to 0.68), which was similar to the long-term consistency recorded for total cholesterol (0.60; 95% CI, 0.56 to 0.63), low-density lipoprotein cholesterol (0.58; 95% CI, 0.54 to 0.62), systolic blood pressure (0.61; 95% CI, 0.58 to 0.65), and diastolic blood pressure (0.50; 95% CI, 0.46 to 0.53) but

TABLE 1. Baseline Characteristics of Study Populations

Characteristic	CHD Cases	Controls	P
Reykjavik study			
n	2459	3969	...
Age, y	55.8 ± 9.3	55.7 ± 9.1	Matched
Male, n (%)	1774 (72)	2743 (69)	Matched
Current cigarette smoker, n (%)	962 (39)	1266 (32)	<0.001
History of diabetes, n (%)	83 (3)	63 (2)	<0.001
Fasting glucose, mmol/L	4.6 ± 1.1	4.5 ± 0.8	<0.001
Body mass index, kg/m ²	26 ± 3.9	25 ± 3.7	<0.001
Nonmanual occupation, n (%)	703 (40)	1227 (42)	0.15
Systolic blood pressure, mm Hg	146 ± 22	141 ± 20	<0.001
Diastolic blood pressure, mm Hg	89 ± 11	87 ± 11	<0.001
FEV ₁ , L	2.8 ± 0.85	2.9 ± 0.86	0.002
Total serum cholesterol, mmol/L	6.82 ± 1.18	6.40 ± 1.14	<0.001
Serum triglycerides, mmol/L	1.19 ± 0.79	1.03 ± 0.62	<0.001
Log _e triglycerides	0.18 ± 0.46	0.030 ± 0.44	<0.001
EPIC-Norfolk study			
n	1123	2206	...
Age, y	65.4 ± 7.8	65.3 ± 7.8	Matched
Male, n (%)	717 (64)	1388 (63)	Matched
Current cigarette smoker, n (%)	170 (15)	179 (8)	<0.001
History of diabetes, n (%)	73 (7)	40 (2)	<0.001
Body mass index, kg/m ²	27 ± 3.9	26 ± 3.5	<0.001
Waist circumference, cm	94.3 ± 11.8	91.3 ± 11.4	<0.001
Systolic blood pressure, mm Hg	144 ± 19	139 ± 18	<0.001
Diastolic blood pressure, mm Hg	86 ± 12	84 ± 11	<0.001
FEV ₁ , L	2.3 ± 0.74	2.4 ± 0.75	<0.001
Total serum cholesterol, mmol/L	6.50 ± 1.24	6.31 ± 1.16	<0.001
HDL cholesterol, mmol/L	1.3 ± 0.4	1.4 ± 0.4	<0.001
LDL cholesterol, mmol/L	4.3 ± 1.0	4.1 ± 1.0	<0.001
Serum triglycerides, mmol/L	2.20 ± 1.21	1.90 ± 1.17	<0.001
Log _e triglycerides	0.29 ± 0.22	0.22 ± 0.22	<0.001

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; and FEV₁, forced expiratory volume in 1 second.

somewhat lower than that recorded for high-density lipoprotein (HDL) cholesterol (0.71; 95% CI, 0.69 to 0.74) in the same participants. In 379 individuals who provided paired blood samples in the Reykjavik study at a mean interval of ≈ 12 years, the within-individual correlation coefficient value for triglycerides was 0.63 (95% CI, 0.57 to 0.70), which again was similar to the long-term consistency recorded for total cholesterol (0.60; 95% CI, 0.54 to 0.66), systolic blood pressure (0.66; 95% CI, 0.60 to 0.72), and diastolic blood pressure (0.53; 95% CI, 0.46 to 0.60) in the same participants.

Triglycerides and Incident CHD

In the Reykjavik study, the odds ratio for CHD adjusted for age, gender, and calendar period was 2.04 (95% CI, 1.78 to 2.32; Wald test statistic, $\chi_1^2 = 106$) in individuals in the top third compared with those in the bottom third of baseline log-triglyceride concentrations (corresponding to tertile cut-offs of 1.28 and 0.87 mmol/L). The odds ratio fell to 1.43

TABLE 2. Baseline Correlates of Log Triglycerides Levels in Controls

	Reykjavik Study						EPIC-Norfolk Study					
	Bottom Third (n=1239)	Middle Third (n=1239)	Top Third (n=1240)	Pearson Correlation Coefficient	t Value* (Age, Gender, Period Adjusted)	t Value* (Further Adjusted†)	Bottom Third (n=773)	Middle Third (n=706)	Top Third (n=727)	Pearson Correlation Coefficient	t Value† (Age, Gender, Period Adjusted)	t Value† (Further Adjusted‡)
Demographic												
Age, y	54.8±8.5	56.2±9.2	56.6±9.7	0.09	0.6	3.4	65.0±8.0	65.7±7.6	65.3±7.7	0.01	0.8	1.6
Male, n (%)	847 (64)	886 (67)	966 (73)	0.08	4.8¶	6.4¶	428 (55)	467 (66)	493 (68)	0.09	5.0¶	10.1¶
Questionnaire												
Current cigarette smokers, n (%)	395 (30)	432 (33)	436 (33)	0.03	3.6¶	6.5¶	60 (8)	61 (9)	58 (8)	0.00	0.1	1.3
History of diabetes, n (%)	23 (2)	18 (1)	25 (2)	0.01	0.7	1.1	12 (2)	12 (2)	16 (2)	0.04	1.8	1.0
Nonmanual occupation, n (%)	520 (40)	557 (42)	603 (46)	0.06	3.7¶	4.2¶	480 (64)	433 (63)	430 (61)	-0.03	0.9	0.4
Education beyond high school, n (%)	366 (28)	378 (29)	430 (33)	0.04	1.8	3.4	96 (13)	91 (13)	88 (12)	-0.04	1.3	0.4
Home owner, n (%)	1134 (86)	1135 (86)	1106 (84)	-0.01	-1.5	-1.1	NA	NA	NA
Lives in apartment block, n (%)	644 (49)	689 (52)	675 (51)	0.02	0.6	-0.3	NA	NA	NA
Physical measurements												
Body mass index, kg/m ²	24.2±3.4	25.4±3.7	27.0±3.8	0.33	20.5¶	19.3¶	25.1±3.2	26.3±3.2	27.6±3.6	0.29	17.8¶	16.5¶
Waist circumference, cm	NA	NA	NA	86.8±10.9	91.8±10.9	91.3±11.4	0.32	19.5¶	8.1¶
Systolic blood pressure, mm Hg	138.7±19.2	141.7±19.7	146.4±20.6	0.15	9.4¶	3.4¶	136.8±17.8	139.1±18.0	142.5±16.8	0.16	9.6¶	3.6
Diastolic blood pressure, mm Hg	85.6±10.1	87.3±10.5	90.2±11.0	0.17	11.3¶	5.3¶	81.3±10.5	83.6±11.3	86.2±11.0	0.18	10.1¶	3.8¶
FEV ₁ , L	2.9±0.86	2.9±0.86	2.8±0.9	-0.03	-3.4	-3.1§	2.4±0.8	2.4±0.7	2.4±0.7	-0.02	5.6¶	3.1
Protein or sugar in urine, n (%)	34 (2.6)	25 (1.9)	50 (3.8)	0.03	1.6	1.4	NA	NA	NA
Blood sample												
Total cholesterol, mmol/L	6.20±1.09	6.46±1.12	6.67±1.19	0.19	15.4¶	14.2¶	5.9±1.0	6.3±1.0	6.8±1.2	0.37	25.5¶	24.1¶
LDL cholesterol, mmol/L	NA	NA	NA	3.9±1.0	4.2±0.9	4.2±1.1	0.18	26.6¶	27.6¶
HDL cholesterol, mmol/L	NA	NA	NA	1.6±0.4	1.3±0.4	1.2±0.3	-0.43	33.3¶	29.1¶
C-reactive protein, mg/L†	1.0±3.0	1.3±3.0	1.7±3.0	0.18	10.2¶	4.0¶	1.0±0.2	1.7±0.2	3.1±1.4	0.06	9.9	4.6¶
Fasting blood glucose, mmol/L	4.5±0.6	4.5±0.7	4.7±0.9	0.14	8.3¶	4.5§	NA	NA	NA
Serum uric acid, μmol/L	277.0±61.5	298.5±64.5	328.1±74.3	0.33	20.4¶	13.2¶	NA	NA	NA
Hemoglobin, mmol/L	8.9±0.8	9.1±0.8	9.2±0.8	0.18	12.2¶	5.7¶	NA	NA	NA
Hematocrit, n (%)	43.6 (3.5)	44.4 (3.6)	45.0 (3.5)	0.17	10.2¶	3.6	NA	NA	NA
Erythrocyte sedimentation rate, mm/h†	6.0±2.7	6.0±2.7	6.7±2.7	0.03	5.6¶	2.8¶	NA	NA	NA
von Willebrand factor, IU/dL†	99.5±66.7	99.5±66.7	99.5±66.7	0.06	2.5	1.2	NA	NA	NA
Albumin, g/L	44.9±4.2	45.0±4.4	45.8±4.9	0.06	3.4	1.6	NA	NA	NA

LDL indicates low-density lipoprotein; HDL, high-density lipoprotein; FEV₁, forced expiratory volume in 1 second; and NA, not available.

*Derived from regression of log-triglyceride concentration on each characteristic separately. For categorical variables, the z value is reported.

†Adjusted for age, gender, period of recruitment, systolic blood pressure, total cholesterol, body mass index, diabetes history, smoking (never, former, or current and number of cigarettes per day), except analysis of diastolic blood pressure was not adjusted for systolic blood pressure.

‡Factor log-transformed for analysis and presented as geometric mean±SD.

§P<0.01; ||P<0.001; ¶P<0.0001.

(95% CI, 1.23 to 1.65; $\chi^2=21$) after further adjustment for smoking and several other established coronary risk factors, including fasting glucose and total serum cholesterol concentration (Table 3); after correction for regression dilution, the

odds ratio was 1.76 (95% CI, 1.39 to 2.21). In the EPIC-Norfolk study, the odds ratio for CHD adjusted for age, gender, and calendar period was 1.95 (95% CI, 1.63 to 2.33; Wald test statistic, $\chi^2=52.7$) in individuals in the top third

TABLE 3. Relative Odds of CHD Among Patients Who Had Log-Triglyceride Levels in the Top Third of the Distribution of Values for Controls Compared With Those Who Had Values in the Bottom Third of the Same Distribution*

	CHD Cases			Controls			Odds Ratio (95% CI)†			Adjusted for Age, Gender, Period, Smoking, and Other Established Risk Factors, Including HDL Cholesterol
	Top Third	Middle Third	Bottom Third	Top Third	Middle Third	Bottom Third	Adjusted for Age, Gender, and Period	Adjusted for Age, Gender, Period, and Smoking	Adjusted for Age, Gender, Period, Smoking, and Other Established Risk Factors	
Reykjavik study										
All individuals	927	783	618	1239	1239	1240	2.04 (1.78–2.32)	1.99 (1.75–2.28)	1.43 (1.23–1.65)	NA
Men	693	542	410	775	819	913	2.06 (1.76–2.41)	2.04 (1.74–2.39)	1.51 (1.27–1.80)	NA
Women	234	241	208	288	409	514	2.05 (1.61–2.61)	1.92 (1.50–2.46)	1.24 (0.94–1.62)	NA
EPIC-Norfolk study										
All individuals	497	354	272	773	706	727	1.95 (1.63–2.33)	1.94 (1.62–2.33)	1.52 (1.24–1.89)	1.31 (1.06–1.62)
Men	327	221	169	428	467	493	1.70 (1.35–2.13)	1.70 (1.35–2.14)	1.33 (1.04–1.72)	1.16 (0.89–1.52)
Women	170	133	103	345	239	234	2.47 (1.83–3.33)	2.45 (1.81–3.31)	1.88 (1.34–2.63)	1.59 (1.11–2.28)

NA indicates not available.

The adjusted odds ratios for CHD in the Reykjavik study with the use of alternative comparisons were as follows: 1.63 (95% CI, 1.25 to 1.97) for the top fifth vs the bottom fifth of the distribution, 1.52 (95% CI, 1.33 to 1.73) for a 1-log unit increase in baseline log-triglyceride concentration, and 1.27 (95% CI, 1.16 to 1.39) per 1-mmol/L increase in baseline triglyceride concentration. The adjusted odds ratio for CHD in the EPIC-Norfolk study with the use of alternative comparisons were as follows: 1.72 (95% CI, 1.20 to 2.87) for the top fifth vs the bottom fifth of the distribution, 1.58 (95% CI, 1.32 to 1.89) for a 1-log unit increase in baseline log triglyceride concentration, and 1.19 (95% CI, 1.08 to 1.32) per 1-mmol/L increase in baseline triglyceride concentration.

*Cut points for top and bottom thirds of log-triglyceride levels were 0.25 and -0.14 (exponentiated to 1.28 and 0.87 mmol/L) in the Reykjavik study and 0.30 and 0.11 (exponentiated to 2.00 and 1.33 mmol/L) in the EPIC-Norfolk study, respectively.

†Period refers to calendar-year of recruitment. Adjustment for smoking status was performed by categorizing individuals into never smokers, current smokers, and former smokers on the basis of self-report. Other established risk factors in the Reykjavik study included total cholesterol, systolic blood pressure, body mass index, fasting glucose, and history of diabetes. Systolic blood pressure was calculated by taking the mean of 2 separate systolic blood pressure measurements on the same clinic visit. In the EPIC-Norfolk study, other established risk factors included LDL cholesterol, systolic blood pressure, body mass index, and history of diabetes. After further adjustment for C-reactive protein in the principal comparison of extreme thirds of log triglycerides, the odds ratios were 1.39 (95% CI, 1.20 to 1.61) in the Reykjavik study and 1.28 (95% CI, 1.03 to 1.59) in the EPIC-Norfolk study. (The odds ratio was 1.47 [95% CI, 1.20 to 1.80] when omitting adjustment for HDL cholesterol in the EPIC-Norfolk study.) After adjustment for waist circumference instead of body mass index in the EPIC-Norfolk study, the odds ratio was 1.29 (95% CI, 1.04 to 1.60). (The odds ratio was 1.50 [95% CI, 1.22 to 1.83] when omitting adjustment for HDL cholesterol.)

compared with those in the bottom third of baseline log-triglyceride concentrations (corresponding to tertile cutoffs of 2.00 and 1.33 mmol/L). The odds ratio fell to 1.52 (95% CI, 1.24 to 1.89; $\chi^2=15.0$) after further adjustment for smoking and several other established coronary risk factors, including low-density lipoprotein cholesterol, and fell still further to 1.31 (95% CI, 1.06 to 1.62; $\chi^2=5.1$) after additional adjustment for HDL cholesterol (Table 3). After correction for regression dilution, the odds ratio was 1.57 (95% CI, 1.10 to 2.24). In both the Reykjavik and EPIC-Norfolk studies, additional adjustment for C-reactive protein made little difference to the adjusted odds ratios (see Table 3 legend). Similar findings were observed in each of the studies when cutoff levels were varied (eg, involving comparisons of extreme fifths, a 1 log-unit increase, or per 1-mmol/L increase in triglyceride values; see Table 3 legend). Although women had somewhat smaller odds ratios than did men in the Reykjavik study (and vice versa in the EPIC-Norfolk study), the CIs around the gender-specific odds ratios were all overlapping, and there was no evidence of an interaction between gender and triglycerides (Reykjavik study: $\chi^2=0.85$, $P=0.65$; EPIC-Norfolk study: $\chi^2=0.87$, $P=0.35$), prompting further investigation of this issue in the combined analysis of all 29 prospective studies in Western populations (see below). Analysis across fifths of log-triglycerides sug-

gested an approximately log-linear association with CHD risk (data available on request), although larger numbers based on data pooling are needed to make this relationship distinct (see Discussion).

Updated Meta-Analysis

We identified 29 published prospective reports on triglycerides and CHD (including the present Reykjavik and EPIC-Norfolk studies) in Western populations, with a total of 10 158 CHD cases (weighted mean age at entry, 56.8 years; weighted mean follow-up, 12.1 years; Table 4 and Figure 1), plus an additional 31 prospective studies that are known to have recorded triglyceride values and cardiovascular outcomes but have not yet specifically reported their triglyceride findings (see the online Data Supplement). A combined analysis of the 29 available studies yielded an adjusted odds ratio of 1.72 (95% CI, 1.56 to 1.90) in a comparison of extreme thirds of usual triglyceride values (all but 1 study⁸ reported adjustment for at least age, sex, smoking, and lipid concentrations, and most also adjusted for blood pressure). There was evidence of heterogeneity between the findings of the 29 available published studies ($\chi^2_{28}=93.5$; $P<0.001$; $I^2=64\%$; 95% CI, 48 to 74), with only a relatively small part of it explained by geographical location ($\chi^2_1=14.4$; $P<0.001$), sample size ($\chi^2_1=11.0$; $P=0.001$), and inclusion

TABLE 4. Characteristics of 27 Previously Published Prospective Studies in Western Populations (Plus the 2 Present Studies) of Triglycerides and CHD

Study	Location	Population Source/ Sampling Method*	Time of Baseline Survey	Total Participants, n	CHD Cases, n	Age Range, y	Male %	Mean Follow-Up, y	Mean (SD) Triglycerides of Controls, mmol/L	Triglyceride Assay			
										Fasted at Baseline	Source	Type	Sample State at Analysis
Reykjavik ³²	Iceland	Population register/complete	1967–1991	18 569	2459	33–59	48	20	1.03 (0.62)	Yes	Technicon	Fluorometry	Fresh
EPIC-Norfolk ³³	UK	GP lists/complete	1993–1998	25 638	1123	39–79	45	8	1.90 (1.17)	No	Bayer	Enzymatic	Fresh
ARIC ²	USA	Household listings/random	1987–1989	12 339	725	45–64	56	10	Men: 1.44 (0.73) Women: 1.30 (0.66)	Yes	NS	Enzymatic	Frozen (–70°C)
Framingham ³	USA	Population register/random	1968	5505	612	30–74	46	14	Men: 1.31 (0.75) Women: 1.03 (0.6)	Yes	NS	NS	Fresh
CDSNC† ^{4,5}	Norway	Population screening/complete	1974–1978	62 081	564	35–49	51	14.6	NS	No	Technicon	Nonenzymatic	Fresh
Malmö ⁶	Sweden	Census registers/complete	1974–1983	12 510	446	46–49	100	10	1.3 (NS)	Yes	NS	NS	Fresh
CHS ⁷	USA	Medicare lists/random	1989–1993	4885	436	>65	40	7.5	Men: 1.55 (0.86) Women: 1.56 (0.80)	Yes	NS	NS	Fresh
MRFIT ⁸	USA	Occupational/complete	1973	6340	426	35–57	100	6.1	1.99 (NS)	Yes	NS	NS	Fresh
BRHS ⁹	UK	GP lists/random	1978–1980	5675	324	40–59	100	7.5	2.03 (1.34)	No	NS	NS	NS
SPS ¹⁰	Sweden	Health register/complete	1961–1962	6224	306	15–79	56	14	NS	Yes	NS	NS	NS
PHS ¹¹	USA	Occupational/complete	1982	14 916	266	40–84	100	7	1.75 (1.20)	No	Roche	Enzymatic	Frozen (–80°C)
WCGS ¹²	USA	Occupational/complete	1961–1962	3154	257	39–59	100	8.5	1.65 (0.95)	Yes	NS	NS	NS
NHS ¹³	USA	Occupational/complete	1989–1990	32 826	234	30–55	0	8	1.24 (0.84–1.68) [¶]	No	Hitachi	Enzymatic	Frozen (LN)
CMS ¹⁴	Denmark	Occupational/complete	1985–1986	2906	229	53–74	100	8	NS	Yes	Boehringer	Enzymatic	Fresh
North Karelia ¹⁵	Finland	Population register/random	1972	4057	211	30–59	100	7	1.54 (0.97)	Yes	Technicon	Enzymatic	Frozen (–80°C)
LRCFUS ¹⁶	USA	Population register/random	1972–1976	7505	201	>30	55	12.2	NS	Yes	Technicon	Fluorometry	Fresh
PROCAM ¹⁷	Germany	Occupational/complete	1981–1986	4559	186	40–65	100	6	1.52 (NS)	Yes	Boehringer	Enzymatic	Fresh
NPHSII ¹⁸	UK	GP list/complete	1989–1994	2345	163	50–61	100	6	1.80 (0.95)	No	WAKO	Enzymatic	Frozen (–80°C)
Paris ¹⁹	France	Occupational/complete	1967–1972	6999	157	43–53	100	11.4	1.52 (1.22)	Yes	NS	Fluorometry	Fresh
Caerphilly§ ²⁰	UK	Electoral rolls/complete	1979–1983	2512	153	45–59	100	5	NS	Yes	NS	Enzymatic	Fresh
Honolulu ²¹	USA	Service record/complete	1980–1982	3571	149	>60	100	12	1.77 (1.17)	Yes	NS	Enzymatic	Fresh
Rome ²²	Italy	Occupational/complete	1979–1981	3007	107	46–65	100	10	1.76 (1.17)	Yes	In house	Enzymatic	Fresh
Uppsala ²³	Sweden	Population register/complete	1970–1973	1175	106	50‡	100	10	1.76 (1.19)	Yes	Technicon	Enzymatic	Fresh
Speedwell§ ²⁰	UK	GP list/complete	1979–1982	2348	98	45–49	100	3.2	NS	Yes	NS	Enzymatic	Fresh
Suami ²⁴	Finland	Insurance enrollees/complete	1965–1966	1648	68	50–53	100	7	1.72 (1.16)	Yes	In house	NS	Fresh
Evans County ²⁵	USA	Population register/random	1967–1969	905	52	50–79	49	4.5	NS	Yes	NS	NS	Fresh
Goteborg 1913 ²⁶	Sweden	Population register/complete	1963	790	44	50	100	10	1.24 (0.72)	Yes	NS	NS	NS
NAS ²⁷	USA	Employee records/complete	1963–1970	1086	30	21–81	100	4	NS	Yes	In house	Nonenzymatic	Fresh
Goteborg ²⁸ Women	Sweden	Population register/random	1968–1969	1450	26	58–80	0	20	1.53 (0.66)	Yes	NS	NS	NS

NS indicates not specified; GP, general practitioner; LN, liquid nitrogen; ARIC, Atherosclerosis Risk in Communities; CDSNC, Cardiovascular Disease Study in Norwegian Counties; CHS, Cardiovascular Health Study; BRHS, British Regional Heart Study; SPS, Stockholm Prospective Study; PHS, Physicians' Health Study; WCGS, Western Collaborative Group Study; NHS, Nurses Health Study; CMS, Copenhagen Male Study; LRCFUS, Lipid Research Clinic Follow Up Study; NPHS II, Northwick Park Heart II; and NAS, Normative Ageing Study.

*Random sampling method involved invitation of randomly selected subgroup of eligible persons. Complete sampling involved invitation of all eligible persons.

†Different participants reported separately from same population cohort.

‡Mean age.

§Results published were combined for these 2 studies.

¶ Median (interquartile range).

of adjustment for HDL cholesterol ($\chi^2_1=6.4$; $P=0.01$). Other recorded study characteristics, such as population sampling framework ($\chi^2_1=1.4$; $P=0.23$), mean duration of follow-up ($\chi^2_1=0.1$; $P=0.77$), gender of participants ($\chi^2_1=0.08$; $P=0.77$), fasting status ($\chi^2_1=0.7$; $P=0.42$), sample state at analysis ($\chi^2_2=3.0$; $P=0.22$), and assay method ($\chi^2_2=5.3$; $P=0.07$) did not explain much of the overall heterogeneity, as is evident in the small fraction of the χ^2 value for heterogeneity associated with these study characteristics (Figure 2). In a meta-regression to assess whether any of the potentially important sources of heterogeneity (such as geographical location of the study) could be explained by

the other recorded study characteristics, only heterogeneity attributable to study size remained statistically significant ($P=0.012$).

Discussion

The present data on triglyceride concentrations and future risk of CHD involve 262 525 participants and 10 158 CHD cases in 29 Western prospective studies, including new primary data on 3582 of the CHD cases derived from 44 237 participants. These findings have suggested several implications for the development of disease prevention strategies.

Risk ratio (95% CIs) (top third vs. bottom third)

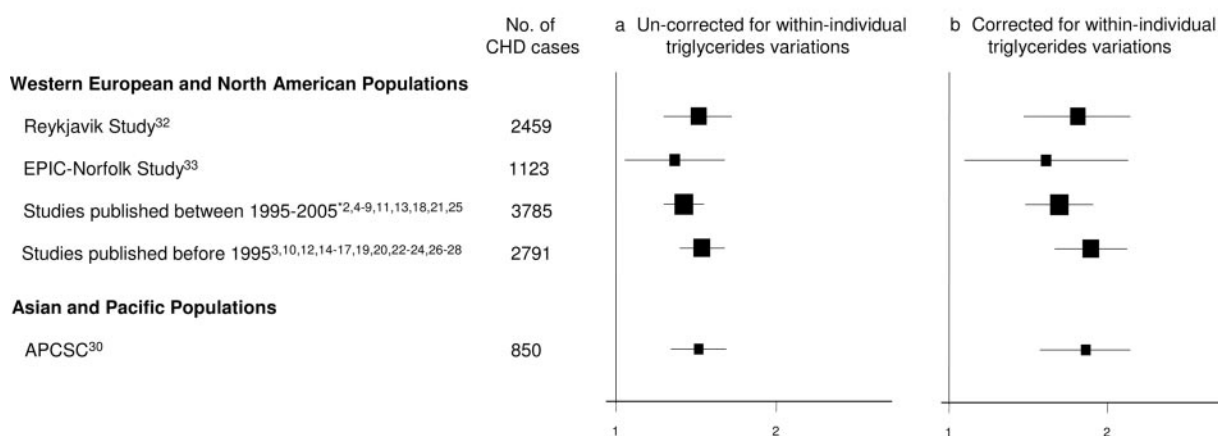


Figure 1. Available prospective studies of triglycerides and CHD in essentially general populations. APCSC indicates Asian and Pacific Cohort Studies Collaboration. *Includes 3 studies that were published before 1995 but were not included in the previous review.^{4,5,9,25}

First, in contrast to previous suggestions,³⁷ our new primary data demonstrate that the year-to-year and decade-to-decade consistencies of triglyceride values within individuals are similar to those for blood pressure and other serum lipid concentrations. Second, although there is consistent evidence that raised circulating triglyceride levels are associated with increased CHD risk, adjustment for established coronary risk factors, especially HDL cholesterol, substantially attenuated the magnitude of this association (evident by the sharp decline in the χ^2 on adjustment of risk estimates for such factors in both the Reykjavik and EPIC-Norfolk Studies). Third, the combined odds ratio for CHD in Western populations, adjusted for several established risk factors, was ≈ 1.7 (95% CI, 1.6 to 1.9) in individuals with usual triglyceride values in the top third of the population compared with those in the bottom third, which is very similar to the combined odds ratio previously reported in Asian and Pacific populations.³⁰ Fourth, the available data indicate that the impact of

triglycerides on CHD risk is similar in men and women. This finding contrasts with previous suggestions that the hazard is substantially greater in women,²⁹ and this issue requires further investigation in more detailed analyses (described below). Also, in contrast to previous suggestions based on much sparser data,³⁸ the present data suggest no important differences in the strength of associations between triglycerides and CHD in studies of fasting participants compared with studies of nonfasting participants. Finally, the present data suggest that the somewhat weaker association noted between triglycerides and CHD risk in North American than in European populations is probably accounted for largely by differences in study sample size, but this may require further investigation.

The potential limitations of the present report merit consideration. It was not possible to adjust consistently for possible confounding factors in the updated meta-analysis of 27 available prospective studies because the present review

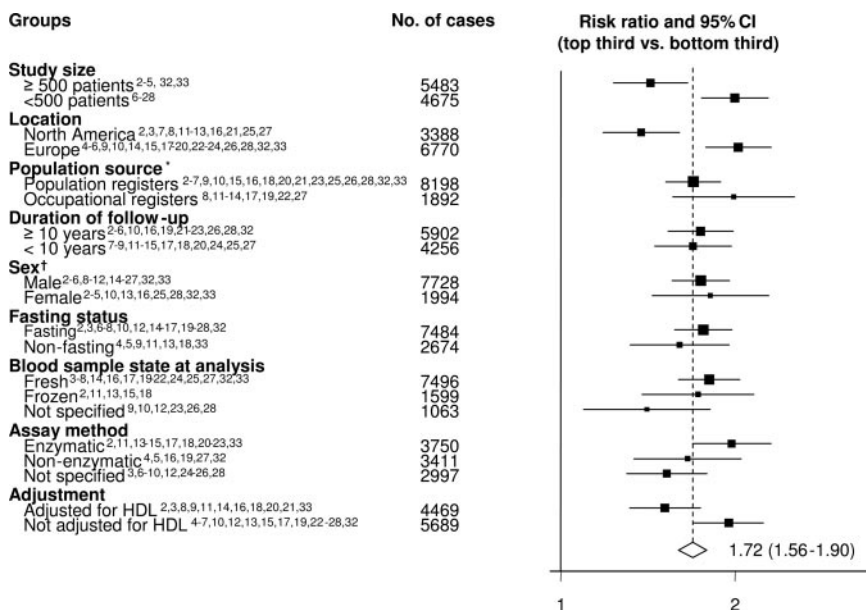


Figure 2. Studies of the risk of CHD in individuals in the top vs bottom third of usual log-triglyceride values grouped according to several study characteristics. Pooled estimate presented was calculated using a fixed effects model. Using a random effects model yielded a risk ratio of 1.86 (1.56–2.21). *Results from 1 study not shown that used insurance plan enrollees to identify study population.²⁴ †Results from 1 study not shown that did not report risk estimates separately for men and women.⁷

was based on variably adjusted data reported in the published literature. Nor was entirely consistent adjustment possible in the 2 cohorts for which primary data were available because the Reykjavik study recorded fasting blood glucose values but not serum lipid subtypes, whereas the reverse was the case in the EPIC-Norfolk study. So, although Figure 1 does not suggest major variations in adjusted risk estimates between triglycerides and CHD reported in different sets of studies, more detailed pooling of these studies, perhaps on the basis of individual participant data, is required to help make assessments about the nature of any independent associations and to investigate the impact of triglycerides on CHD risk under different circumstances (such as at different ages, at different levels of triglycerides, and at different levels of established risk factors and of emerging risk markers). For example, detailed pooling of available study data (involving, when available, information on lipid subtypes and markers of insulin sensitivity) would help to distinguish the effects of triglycerides on CHD risk from those of other lipid fractions (notably HDL cholesterol) and markers of insulin sensitivity, a relevant consideration because disorders of low-density lipoprotein/triglyceride metabolism reduce HDL concentrations and are related to markers of insulin resistance.³⁹ Future syntheses should also aim at encompassing the few dozen prospective studies that have recorded triglyceride values (because of the widespread availability of assays for these lipids) and cardiovascular disease outcomes but have not yet specifically reported their triglyceride findings (see the online Data Supplement). Further research also is required to determine whether circulating triglyceride levels are likely to be causally involved in CHD. Data from available randomized trials of interventions that lower levels of triglycerides (eg, fibrate medications) cannot provide unbiased etiological insight into the relevance of triglycerides to CHD because these interventions influence several lipid components rather than selectively lowering triglyceride concentrations.^{40–43} The integration of evidence from epidemiological and genetic association studies (ie, mendelian randomization) may help to determine the nature of this association,⁴⁴ although it remains to be established whether variants in genes presently known to influence triglyceride levels such as the *APOA5* gene are sufficiently specific for such purposes as they also importantly influence levels of other circulating lipid subfractions (such as HDL cholesterol).^{45,46}

Conclusions

In the largest and most comprehensive epidemiological assessment so far in Western populations, moderately strong associations were consistently observed between triglyceride concentrations and CHD risk, as well as moderately high levels of reproducibility in triglyceride values within individuals over time. These data renew the importance of further investigations to help assess the nature of any independent associations between triglycerides and CHD.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Despite many investigations of circulating triglyceride levels and the risk of coronary heart disease (CHD), their relevance to CHD remains uncertain. We report new data from 2 large prospective studies involving a total of 3582 CHD cases and 44 237 middle-aged men and women, plus a meta-analysis of 27 previously published studies based in Western populations, involving a total of 10 158 incident CHD cases and 262 525 participants. In contrast to previous suggestions, our data demonstrate that the year-to-year and decade-to-decade consistencies of triglyceride levels within individuals are similar to those for blood pressure and total cholesterol. Although elevated circulating triglyceride levels are associated with increased CHD risk, adjustment for established cardiovascular risk factors, especially high-density lipoprotein cholesterol, substantially attenuates the magnitude of this association. The combined odds ratio for CHD in Western populations, adjusted for several established risk factors, is ≈ 1.7 (95% CI, 1.6 to 1.9) in individuals with usual triglyceride values in the top third of the population compared with those in the bottom third. Available data indicate consistent, moderate, and highly significant associations between triglyceride levels and CHD risk, but because these associations appear to depend considerably on levels of established risk factors, there is a need for further studies to help assess causality.

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