Epidemiology

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

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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.

Clinical Perspective p 458

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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450
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. 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” 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) 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 predominately white European continental ancestry and a total of 3,582 incident cases of CHD (including 1,089 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 3,785 CHD cases) to those in the previous review of Western studies. Thus, in aggregate, 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. 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 8,888 male and 9,681 female participants without a history of myocardial infarction (72% response rate). Nurses admin-}

Sarwar et al Triglycerides and Coronary Heart Disease

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 hematomatological measurements involved standard assays, as previously described. 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 (Stat 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.

Results of studies were combined using inverse variance-weighted estimates. In the Western populations, the large majority of participants in the studies included both male and female participants adjusted risk estimates for gender. Because this review was restricted to studies based in general populations (ie, in cohorts not selected on the basis of preexisting disease) using search, abstraction, and data synthesis methods that have been described previously 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 general populations (ie, in cohorts not selected on the basis of preexisting disease) using search, abstraction, and data synthesis methods that have been described previously 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.

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 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, $\chi^2=106$) in individuals in the top third compared with those in the bottom third of baseline log-triglyceride concentrations (corresponding to tertile cutoffs of 1.28 and 0.87 mmol/L). The odds ratio fell to 1.43

### TABLE 1. Baseline Characteristics of Study Populations

<table>
<thead>
<tr>
<th>Characteristic CHD Cases</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reykjavik study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>2459</td>
<td>3969</td>
</tr>
<tr>
<td>Age, y</td>
<td>55.8±9.3</td>
<td>55.7±9.1</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>1774 (72)</td>
<td>2743 (69)</td>
</tr>
<tr>
<td>Current cigarette smoker, n (%)</td>
<td>962 (39)</td>
<td>1266 (32)</td>
</tr>
<tr>
<td>History of diabetes, n (%)</td>
<td>83 (3)</td>
<td>63 (2)</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>4.6±1.1</td>
<td>4.5±0.8</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26±3.9</td>
<td>25±3.7</td>
</tr>
<tr>
<td>Nonmanual occupation, n (%)</td>
<td>703 (40)</td>
<td>1227 (42)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>146±22</td>
<td>141±20</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>89±11</td>
<td>87±11</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>2.8±0.85</td>
<td>2.9±0.86</td>
</tr>
<tr>
<td>Total serum cholesterol, mmol/L</td>
<td>6.8±1.18</td>
<td>6.4±1.14</td>
</tr>
<tr>
<td>Serum triglycerides, mmol/L</td>
<td>1.19±0.79</td>
<td>1.03±0.62</td>
</tr>
<tr>
<td>Log, triglycerides</td>
<td>0.18±0.46</td>
<td>0.030±0.44</td>
</tr>
<tr>
<td>EPIC-Norfolk study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>1123</td>
<td>2206</td>
</tr>
<tr>
<td>Age, y</td>
<td>65.4±7.8</td>
<td>65.3±7.8</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>717 (64)</td>
<td>1388 (63)</td>
</tr>
<tr>
<td>Current cigarette smoker, n (%)</td>
<td>170 (15)</td>
<td>179 (8)</td>
</tr>
<tr>
<td>History of diabetes, n (%)</td>
<td>73 (7)</td>
<td>40 (2)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27±3.9</td>
<td>26±3.5</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>94.3±11.8</td>
<td>91.3±11.4</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>144±19</td>
<td>139±18</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>86±12</td>
<td>84±11</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>2.3±0.74</td>
<td>2.4±0.75</td>
</tr>
<tr>
<td>Total serum cholesterol, mmol/L</td>
<td>6.50±1.24</td>
<td>6.31±1.16</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.3±0.4</td>
<td>1.4±0.4</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>4.3±1.0</td>
<td>4.1±1.0</td>
</tr>
<tr>
<td>Serum triglycerides, mmol/L</td>
<td>2.20±1.21</td>
<td>1.90±1.17</td>
</tr>
<tr>
<td>Log, triglycerides</td>
<td>0.29±0.22</td>
<td>0.22±0.22</td>
</tr>
</tbody>
</table>

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; and FEV₁, forced expiratory volume in 1 second.
TABLE 2. Baseline Correlates of Log Triglycerides Levels in Controls

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Reykjavik Study</th>
<th>t Value*</th>
<th>EPIC-Norfolk Study</th>
<th>t Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>54.8 ± 8.5</td>
<td></td>
<td></td>
<td>65.0 ± 8.0</td>
<td>0.01</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>847 (64)</td>
<td>0.09</td>
<td>428 (65)</td>
<td>0.09</td>
</tr>
<tr>
<td>Questionnaire</td>
<td></td>
<td>0.6</td>
<td>467 (66)</td>
<td>5.0*</td>
</tr>
<tr>
<td>Current cigarette smokers, n (%)</td>
<td>395 (30)</td>
<td>3.4</td>
<td>480 (64)</td>
<td>10.1*</td>
</tr>
<tr>
<td>History of diabetes, n (%)</td>
<td>23 (2)</td>
<td>3.6</td>
<td>12 (2)</td>
<td>4.8¶</td>
</tr>
<tr>
<td>Nonmanual occupation, n (%)</td>
<td>520 (40)</td>
<td>6.5†</td>
<td>330 (61)</td>
<td>3.4</td>
</tr>
<tr>
<td>Education beyond high school, n (%)</td>
<td>366 (28)</td>
<td>4.5</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Home owner, n (%)</td>
<td>1134 (86)</td>
<td>9.3</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Lives in apartment block, n (%)</td>
<td>644 (49)</td>
<td>14.3</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physical measurements</th>
<th>Reykjavik Study</th>
<th>t Value*</th>
<th>EPIC-Norfolk Study</th>
<th>t Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.2 ± 3.4</td>
<td>20.9†</td>
<td>25.1 ± 3.2</td>
<td>17.5†</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>NA</td>
<td>9.3</td>
<td>36.4 ± 3.1</td>
<td>19.5†</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>138.7 ± 19.2</td>
<td>9.4†</td>
<td>136.8 ± 17.8</td>
<td>9.6†</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>85.6 ± 10.1</td>
<td>11.3†</td>
<td>81.3 ± 10.5</td>
<td>10.1†</td>
</tr>
<tr>
<td>FEV1, L</td>
<td>2.9 ± 0.86</td>
<td>3.1</td>
<td>2.4 ± 0.8</td>
<td>5.0*</td>
</tr>
<tr>
<td>Protein or sugar in urine, n (%)</td>
<td>34 (2.8)</td>
<td>1.4</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood sample</th>
<th>Reykjavik Study</th>
<th>t Value*</th>
<th>EPIC-Norfolk Study</th>
<th>t Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>6.20 ± 1.09</td>
<td>15.4†</td>
<td>5.9 ± 1.0</td>
<td>25.5†</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>NA</td>
<td>14.2†</td>
<td>6.3 ± 1.0</td>
<td>24.1†</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>NA</td>
<td>2.0</td>
<td>4.2 ± 0.9</td>
<td>27.5†</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>1.0 ± 3.0</td>
<td>10.2†</td>
<td>1.0 ± 0.2</td>
<td>9.9*</td>
</tr>
<tr>
<td>Fasting blood glucose, mmol/L</td>
<td>4.5 ± 0.6</td>
<td>4.0†</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Serum uric acid, μmol/L</td>
<td>277.0 ± 61.5</td>
<td>20.4†</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hemoglobin, mmol/L</td>
<td>8.9 ± 0.8</td>
<td>13.2†</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hematocrit, n (%)</td>
<td>43.6 (3.5)</td>
<td>5.7†</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate, mmmol/L</td>
<td>6.0 ± 2.7</td>
<td>3.9†</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>von Willebrand factor, U/mL†</td>
<td>99.5 ± 66.7</td>
<td>2.5</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td>44.9 ± 4.2</td>
<td>3.4</td>
<td>1.6</td>
<td>NA</td>
</tr>
</tbody>
</table>

| 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*

<table>
<thead>
<tr>
<th>CHD Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted for Age, Gender, and Period</td>
<td>Adjusted for Age, Gender, Period, and Smoking</td>
</tr>
<tr>
<td>Top Third</td>
<td>Middle Third</td>
</tr>
<tr>
<td>Reykjavik study</td>
<td></td>
</tr>
<tr>
<td>All individuals</td>
<td>927</td>
</tr>
<tr>
<td>Men</td>
<td>693</td>
</tr>
<tr>
<td>Women</td>
<td>234</td>
</tr>
<tr>
<td>EPIC-Norfolk study</td>
<td></td>
</tr>
<tr>
<td>All individuals</td>
<td>497</td>
</tr>
<tr>
<td>Men</td>
<td>327</td>
</tr>
<tr>
<td>Women</td>
<td>170</td>
</tr>
</tbody>
</table>

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.

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: \( \chi^2_{\text{gender}} = 0.85, P = 0.65 \); EPIC-Norfolk study: \( \chi^2_{\text{gender}} = 0.87, P = 0.35 \), 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 suggested 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 study 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 (\( \chi^2 = 93.5; P < 0.001; I^2 = 64\% \); 95% CI, 48 to 74), with only a relatively small part of it explained by geographical location (\( \chi^2_{\text{location}} = 14.4; P < 0.001 \), sample size (\( \chi^2 = 11.0; P = 0.001 \), and inclusion...
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 ($\chi^2_{1} = 3.0; P = 0.22$), 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 $\chi^2$ 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.
First, in contrast to previous suggestions, 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 $\chi^2$ 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 $\approx 1.7$ (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. 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, and this issue requires further investigation in more detailed analyses (described below). Also, in contrast to previous suggestions based on much sparser data, 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...
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.\(^9\) 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.\(^{40–44}\) 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.

**References**

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 individuals with usual triglyceride levels 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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