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Nonfasting Triglycerides and Risk of Myocardial Infarction, Ischemic Heart Disease, and Death in Men and Women

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HYPERTRIGLYCERIDEMIA IS A heterogeneous disorder with an unclear association with atherosclerosis.¹⁻⁴ Patients with high triglyceride levels of more than 25 mmol/L (>2212.4 mg/dL) and the familial chylomicronemia syndrome rarely develop atherosclerosis,⁴ perhaps because their plasma lipoprotein particles are too large to enter into the arterial intima.^{5,6} However, patients with moderate hypertriglyceridemia and conditions like familial hypertriglyceridemia, familial combined hyperlipidemia, the metabolic syndrome, and remnant hyperlipidemia often develop premature atherosclerosis.^{1,4} With moderate hypertriglyceridemia, chylomicron remnants and very low-density lipoprotein remnants are present in plasma. These smaller triglyceride-rich lipoproteins penetrate the arterial intima⁷ and appear to be preferentially trapped within the arterial wall.^{8,9}

Triglycerides are routinely measured in the fasting state excluding remnant lipoproteins; however, except for the first hours in the early morning, most individuals are in the nonfasting state most of the time. Atherosclerosis may be a postprandial phenomenon in which remnant lipoproteins play a

See also pp 309 and 336.

Context Elevated nonfasting triglycerides indicate the presence of remnant lipoproteins, which may promote atherosclerosis.

Objective To test the hypothesis that very high levels of nonfasting triglycerides predict myocardial infarction (MI), ischemic heart disease (IHD), and death.

Design, Setting, and Participants A prospective cohort study of 7587 women and 6394 men from the general population of Copenhagen, Denmark, aged 20 to 93 years, followed up from baseline (1976-1978) until 2004.

Main Outcome Measures Hazard ratios (HRs) for incident MI, IHD, and total death according to baseline nonfasting triglyceride level categories of 1 to 1.99 mmol/L (88.5-176.1 mg/dL), 2 to 2.99 mmol/L (177.0-264.6 mg/dL), 3 to 3.99 mmol/L (265.5-353.0 mg/dL), 4 to 4.99 mmol/L (354.0-441.6 mg/dL), and 5 mmol/L or more (\geq 442.5 mg/dL) vs triglyceride levels of less than 1 mmol/L (<88.5 mg/dL).

Results With increasing levels of nonfasting triglycerides, levels of remnant lipoprotein cholesterol increased. During a mean follow-up of 26 years, 1793 participants (691 women and 1102 men) developed MI, 3479 (1567 women and 1912 men) developed IHD, and 7818 (3731 women and 4087 men) died. For MI, among women, the age-adjusted HRs and multifactorially adjusted HRs (aHRs) for each respective category per 1-mmol/L increase in nonfasting triglyceride levels were 2.2 (aHR, 1.7), 4.4 (aHR, 2.5), 3.9 (aHR, 2.1), 5.1 (aHR, 2.4), and 16.8 (aHR, 5.4); for both, *P* for trend < .001. For MI, among men, the values were 1.6 (aHR, 1.4), 2.3 (aHR, 1.6), 3.6 (aHR, 2.3), 3.3 (aHR, 1.9), and 4.6 (aHR, 2.4); for both, *P* for trend < .001. For IHD, among women, the values were 1.7 (aHR, 1.4), 2.8 (aHR, 1.8), 3.0 (aHR, 1.8), 2.1 (aHR, 1.2), and 5.9 (aHR, 2.6); for both, *P* for trend < .001. For IHD, among men, the values were 1.3 (aHR, 1.1), 1.7 (aHR, 1.3), 2.1 (aHR, 1.3), 2.0 (aHR, 1.2), and 2.9 (aHR, 1.5); *P* for trend < .001 for age-adjusted and *P* for trend = .03 for multifactorially adjusted. For total death, among women, the values were 1.3 (aHR, 1.3), 1.7 (aHR, 1.6), 2.2 (aHR, 2.2), 2.2 (aHR, 1.9), and 4.3 (aHR, 3.3); for both, *P* for trend < .001. For total death, among men, the values were 1.3 (aHR, 1.2), 1.4 (aHR, 1.4), 1.7 (aHR, 1.5), 1.8 (aHR, 1.6), and 2.0 (aHR, 1.8); for both, *P* for trend < .001.

Conclusion In this general population cohort, elevated nonfasting triglyceride levels were associated with increased risk of MI, IHD, and death in men and women.

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dominant role.¹⁰⁻¹² If this is true, increased levels of nonfasting triglycerides, reflecting increased levels of rem-

nant lipoproteins, may predict risk of myocardial infarction (MI), ischemic heart disease (IHD), and death.

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We tested the hypothesis that nonfasting triglycerides predict risk of MI, IHD, and death in the general population. We studied 7587 women and 6394 men from the Copenhagen City Heart Study cohort who were followed up for a mean of 26 years (maximum follow-up, 28 years).

METHODS

Participants

The Copenhagen City Heart Study is a prospective cardiovascular study of the Danish general population initiated in 1976.¹³ We invited 19 329 white women and men of Danish descent stratified into 5-year age groups from 20 years to 80 years or older, and drawn randomly from the Copenhagen Central Person Register. Of those participants invited, 14 223 (74%) attended and 13 981 (72%) had nonfasting triglyceride levels determined on fresh plasma samples. Participants were followed up using their unique Central Person Register number from baseline at the 1976-1978 examination until the beginning of 2004. Follow-up was 100% complete.

Diagnoses of MI and IHD (*International Classification of Diseases, Eighth Revision* codes 410 and 410-414; and *International Classification of Diseases, Tenth Revision* codes I21-I22 and I20-I25) were collected and verified by reviewing hospital admissions and diagnoses entered in the Danish National Patient Register, causes of death entered in the Danish National Register of Causes of Death, and medical records from hospitals and general practitioners. Ischemic heart disease was determined on the basis of a previous MI or characteristic symptoms of stable or unstable angina pectoris¹⁴; time to IHD was determined from the date of study entry until the first date of a diagnosis of either MI or angina pectoris. A diagnosis of MI required the presence of at least 2 of the following criteria: characteristic chest pain, increased cardiac enzymes, or electrocardiographic changes indicative of MI. Information on death was obtained from the Danish National Central Person Register.

Hypertension was defined as use of antihypertensive medication, a systolic blood pressure of more than 140 mm Hg, or a diastolic blood pressure of more than 90 mm Hg. Diabetes mellitus was defined as self-reported disease, use of insulin or oral hypoglycemic agents, or nonfasting plasma glucose levels of more than 198.2 mg/dL (>11 mmol/L). Smokers were defined as active smokers. Heavy drinkers consumed alcohol at least twice weekly, while light drinkers consumed alcohol less often. Physical inactivity was defined as leisure time activity less than 4 hours weekly. Women reported menopausal status and use of hormone therapy. We did not have information on food consumed during the 8 hours before blood testing.

A fat tolerance test was performed on 66 healthy participants from the Copenhagen City Heart Study aged 46 to 88 years.¹⁵ In another study population of 10 284 participants aged 20 to 90 years, the Copenhagen General Population Study ascertained like the Copenhagen City Heart Study, but in 2003 through 2005, we also measured nonfasting triglyceride levels. We measured 1 triglyceride value in each participant and noted the amount of time that had elapsed since their last meal. Data from this study have never previously been published.

The studies were approved by Herlev University Hospital and a Danish ethical committee (100.2039/91 and 01-144/01, Copenhagen and Frederiksberg committee) and conducted according to the Declaration of Helsinki. Participants gave written informed consent.

Analyses

Enzymatic methods (Boehringer Mannheim, Mannheim, Germany) were used on fresh samples to measure plasma levels of nonfasting triglycerides, total cholesterol, and high-density lipoprotein (HDL) cholesterol, the latter after precipitation of apolipoprotein B-containing lipoproteins. The coefficient of variation for measurement of triglycerides at the lev-

els of 1.0 and 3.2 mmol/L (88.5 and 283.2 mg/dL) were 5% and 2%, respectively. Remnant lipoprotein cholesterol was total cholesterol minus cholesterol in HDLs and low-density lipoproteins (LDLs). Low-density lipoprotein was calculated using the Friedewald formula if triglycerides were less than 4 mmol/L (<354.0 mg/dL), and measured directly at higher triglyceride levels (Thermo, Helsinki, Finland).

Statistical Analysis

Statistical analyses were stratified by sex. *t* Test or Pearson χ^2 test was used in 2-group comparisons; plasma triglycerides were logarithmically transformed to approach normal distribution. Baseline nonfasting triglyceride levels were stratified into 6 categories (<1 mmol/L [<88.5 mg/dL], 1-1.99 mmol/L [88.5-176.1 mg/dL], 2-2.99 mmol/L [177.0-264.6 mg/dL], 3-3.99 mmol/L [265.5-353.1 mg/dL], 4-4.99 mmol/L [354.0-441.6 mg/dL], and ≥ 5 mmol/L [≥ 442.5 mg/dL]). To examine the effect of very high levels of nonfasting triglycerides vs low levels, we preplanned stratification cutoffs at each increase in 1 mmol/L (88.5 mg/dL) until the top group became too small for statistically meaningful comparison with the bottom group (<1 mmol/L [<88.5 mg/dL]).

Cumulative incidences were plotted using Kaplan-Meier curves and differences between strata of nonfasting triglyceride levels determined using log-rank tests. Cox proportional hazards regression models estimated hazard ratios (HRs) for MI, IHD, and death. Proportionality of hazards over time for nonfasting triglyceride levels was assessed by plotting $-\ln[-\ln(\text{survival})]$ vs $\ln(\text{analysis time})$. Suspicion of nonparallel lines was further tested using Schoenfeld residuals. No major violations of the proportional hazard assumption were detected. For triglyceride levels between 2 and 2.99 mmol/L (177.0 and 264.6 mg/dL) and between 3 and 3.99 mmol/L (265.5 and 353.1 mg/dL) and total mortality in women, the proportional hazards assumption

was not fulfilled; however, the assumption was fulfilled for the other triglyceride categories in this model. For all survival statistics, age was the time scale using left truncation (or delayed entry), which implies that age is automatically adjusted for.

Hazard ratios were adjusted for age alone (age-adjusted), or for age and other cardiovascular risk factors (multifactorially adjusted for age, total cholesterol, body mass index, hypertension, diabetes, smoking, alcohol consumption, physical inactivity, lipid-lowering therapy, and in women also for postmenopausal status and hormone therapy). Information on baseline covariates was more than 99% complete; individuals with incomplete information on covariates were excluded from multifactorial analysis. Data from the 1976-1978, 1981-1983, 1991-1994, and 2001-2003 examinations were used as time-dependent covariates for multifactorial adjustments. This implies that initially baseline covariate values are used for the following years until that person is examined again, after which the new

value is used in the analyses. If only baseline values were available, these were used for adjustment during the entire follow-up period.

Hazard ratios were corrected for regression dilution bias using a nonparametric method.¹⁶ For this correction, we used nonfasting triglyceride values from 6709 individuals without lipid-lowering therapy attending both the baseline 1976-1978 examination and the 1991-1994 examination (available from authors upon request); however, the main analyses were conducted on 13 981 individuals. These 2 measurements were 15 years apart, equivalent to halfway through the observational period, the ideal time difference for this correction.¹⁶ A regression dilution ratio of 0.57 was computed for women and a regression dilution ratio of 0.60 was computed for men.

Due to the complete Danish registers, we had no losses to follow-up among responders or nonresponders. Data were analyzed using Stata version 9.2 (StataCorp LP, College Station, Texas). Two-sided $P < .05$ was considered significant.

RESULTS

Baseline characteristics of individuals from the general population by quartiles of nonfasting triglyceride levels are shown in TABLE 1. At the 1976-1978 (baseline), 1981-1983, 1991-1994, and 2001-2003 examinations, 0%, 0%, 1%, and 2%, respectively, of the participants took lipid-lowering drugs. The study included 13 981 individuals (7587 women and 6394 men) aged 20 to 93 years, with mean 26 years of follow-up. A total of 1793 (691 women and 1102 men) developed MI, 3479 (1567 women and 1912 men) developed IHD, and 7818 (3731 women and 4087 men) died.

Nonfasting Triglycerides and Remnant Lipoprotein Cholesterol

In a cross-sectional sample of the Danish general population of 10 284 adults from the Copenhagen General Population Study, the plasma triglyceride levels were noted to be increased among participants who had eaten their most recent meal from 1 to 7 hours previously (FIGURE 1). The measured levels of nonfasting triglycerides after nor-

Table 1. Baseline Characteristics of Individuals From the General Population by Quartiles of Triglyceride Levels^a

	Quartile of Triglycerides, Mean (95% CI), mmol/L							
	Men				Women			
	1	2	3	4	1	2	3	4
	0.96 (0.81-1.08)	1.43 (1.32-1.55)	2.03 (1.84-2.24)	3.37 (2.84-4.33)	0.78 (0.67-0.87)	1.10 (1.02-1.19)	1.48 (1.37-1.61)	2.28 (1.98-2.84)
No. of observations	1612	1590	1605	1587	1901	1934	1858	1894
Age, median (IQR), y	52 (41-61)	54 (44-62) ^b	55 (46-62) ^b	54 (45-60) ^b	48 (39-56)	53 (44-59) ^b	55 (48-62) ^b	57 (51-64) ^b
Total cholesterol, median (IQR), mmol/L	5.4 (4.8-6.1)	5.7 (5.1-6.4) ^b	6.0 (5.3-6.7) ^b	6.4 (5.7-7.2) ^b	5.6 (4.9-6.3)	6.0 (5.3-6.8) ^b	6.3 (5.6-7.2) ^b	6.7 (6.0-7.6) ^b
BMI, median (IQR)	24 (22-26)	25 (23-27) ^b	26 (24-28) ^b	27 (25-30) ^b	23 (21-25)	23 (21-26) ^b	24 (22-27) ^b	26 (23-29) ^b
Hypertension	747 (47)	817 (52) ^c	892 (56) ^b	1038 (66) ^b	545 (29)	765 (40) ^b	855 (47) ^b	1074 (58) ^b
Diabetes mellitus	34 (2)	62 (4) ^c	58 (4) ^c	121 (8) ^b	16 (1)	18 (1)	35 (2) ^c	77 (4) ^b
Smoker	1072 (67)	1103 (69)	1129 (70) ^c	1162 (73) ^b	1020 (54)	1109 (57) ^c	1129 (61) ^b	1139 (60) ^b
Heavy alcohol drinker	461 (29)	523 (33) ^c	455 (29)	420 (27)	1176 (62)	1265 (66) ^c	1188 (64)	1277 (68) ^b
Physical inactivity	1044 (65)	1103 (70) ^c	1122 (70) ^c	1133 (71) ^b	1393 (73)	1504 (78) ^c	1498 (81) ^b	1547 (82) ^b
Postmenopausal	NA	NA	NA	NA	868 (48)	1153 (64) ^b	1295 (74) ^b	1458 (82) ^b
Postmenopausal with HT	NA	NA	NA	NA	278 (15)	352 (18) ^c	326 (18) ^c	368 (19) ^b

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; HT, hormone therapy; IQR, interquartile range. SI conversion factors: To convert triglycerides to mg/dL, divide values by 0.0113; and cholesterol to mg/dL, divide values by 0.0259.

^aData are presented as number (percentage) unless otherwise specified. Hypertension was defined as use of anti-hypertensive medication, a systolic blood pressure of more than 140 mm Hg, or a diastolic blood pressure of more than 90 mm Hg. Diabetes mellitus was defined as self-reported disease, use of insulin or oral hypoglycemic agents, or nonfasting plasma glucose levels of more than 198.2 mg/dL (>11 mmol/L). Smoker was defined as active smoker. Heavy alcohol drinkers consumed alcohol at least twice weekly.

^bPhysical inactivity was defined as leisure time activity of less than 4 hours weekly. Women reported menopausal status and use of HT.

^c $P < .001$.

^d $P < .05$ by t test or Pearson χ^2 test comparing individuals with those in the 1st quartile of triglycerides.

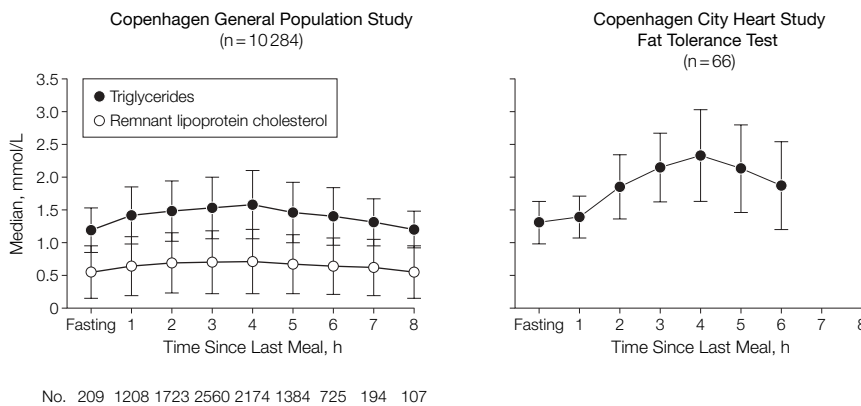
mal food intake marked increased levels of cholesterol in remnant lipoproteins. During a fat tolerance test, plasma triglyceride levels reached a mean peak level of 2.3 mmol/L (203.5 mg/dL) 4 hours after fat intake, whereas in individuals from the general population the mean peak level was 1.6 mmol/L (61.8

mg/dL) 4 hours after normal food intake. Triglyceride levels normally return to baseline fasting levels at 10 hours after the fat meal¹⁷; however, we only had data for 6 hours after the fat meal.

With increasing levels of nonfasting triglycerides, levels of remnant

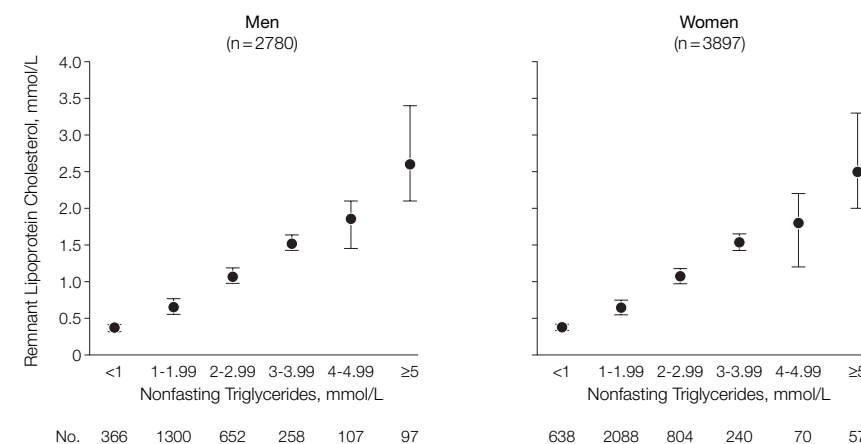
lipoprotein cholesterol increased (FIGURE 2). These levels were measured in 6677 of the original participants from the Copenhagen City Heart Study, who also had nonfasting triglycerides and remnant lipoprotein cholesterol measured at the 1991-1994 examination.

Figure 1. Triglyceride Levels and Levels of Remnant Lipoprotein Cholesterol as a Function of Time Since the Last Meal



Values are median and interquartile range (error bars). To convert triglycerides to mg/dL, divide values by 0.0113; and remnant lipoprotein cholesterol to mg/dL, divide values by 0.0259. For both plots, we compared the various nonfasting values (at 1-8 hours after the last meal) vs fasting levels. For triglycerides and remnant lipoprotein cholesterol in the Copenhagen General Population Study, 1, 2, 3, 4, and 5 hours since last meal, $P < .001$ by unpaired t test without correction for multiple comparisons; for 6 hours since last meal, $P < .01$; and for 7 hours since last meal, $P < .05$. For triglycerides in the Copenhagen City Heart Study, 2, 3, 4, 5, and 6 hours since last meal, $P < .001$ by paired t test without correction for multiple comparisons.

Figure 2. Levels of Remnant Lipoprotein Cholesterol as a Function of Levels of Nonfasting Triglycerides



Values are median and interquartile range (error bars). To convert triglycerides to mg/dL, divide values by 0.0113; and remnant lipoprotein cholesterol to mg/dL, divide values by 0.0259. These levels were measured in 6677 of the original participants from the Copenhagen City Heart Study. These participants also had nonfasting triglycerides and remnant lipoprotein cholesterol levels measured at the 1991-1994 examination. For each increase in nonfasting triglyceride levels of 1 mmol/L (88.5 mg/dL) for both men and women, $P < .001$ by unpaired t test vs individuals with less than 1 mmol/L (<88.5 mg/dL) in nonfasting triglyceride levels.

MI, IHD, and Total Death

In men and women, the cumulative incidence of MI, IHD, and death increased with increasing levels of nonfasting triglyceride levels (all log-rank trend tests, $P < .001$) (FIGURE 3).

For MI, the incidence rates in women in events per 10 000 person-years were 21 (95% confidence interval [CI], 18-26; 109 events) for nonfasting triglyceride level categories of less than 1 mmol/L (<88.5 mg/dL), 46 (95% CI, 42-51; 382 events) for 1 to 1.99 mmol/L (88.5-176.1 mg/dL), 77 (95% CI, 65-91; 141 events) for 2 to 2.99 mmol/L (177.0-264.6 mg/dL), 71 (95% CI, 49-101; 30 events) for 3 to 3.99 mmol/L (265.5-353.0 mg/dL), 77 (95% CI, 46-130; 14 events) for 4 to 4.99 mmol/L (354.0-441.6 mg/dL), and 152 (95% CI, 92-252; 15 events) for 5 mmol/L or more (≥ 442.5 mg/dL). The corresponding incidence rates in men in events per 10 000 person-years were 60 (95% CI, 49-73; 104 events), 90 (95% CI, 82-98; 477 events), 114 (95% CI, 101-128; 270 events), 143 (95% CI, 120-169; 133 events), 137 (95% CI, 105-178; 54 events), and 150 (95% CI, 117-192; 64 events), respectively.

For MI, women with increased nonfasting triglyceride levels had age-adjusted HRs of 2.2 (95% CI, 1.6-3.2) for triglyceride levels of 1 to 1.99 mmol/L (88.5-176.1 mg/dL), 4.4 (95% CI, 2.9-6.8) for 2 to 2.99 mmol/L (177.0-264.6 mg/dL), 3.9 (95% CI, 2.0-7.7) for 3 to 3.99 mmol/L (265.5-353.0 mg/dL), 5.1 (95% CI, 2.0-12.9) for 4 to 4.99 mmol/L (354.0-441.6 mg/dL), and 16.8 (95% CI, 6.8-41.6) for 5 mmol/L or more (≥ 442.5 mg/dL) vs women with nonfasting triglyceride levels of less than 1 mmol/L (<88.5 mg/dL) (FIGURE 4). The corresponding values for men were 1.6

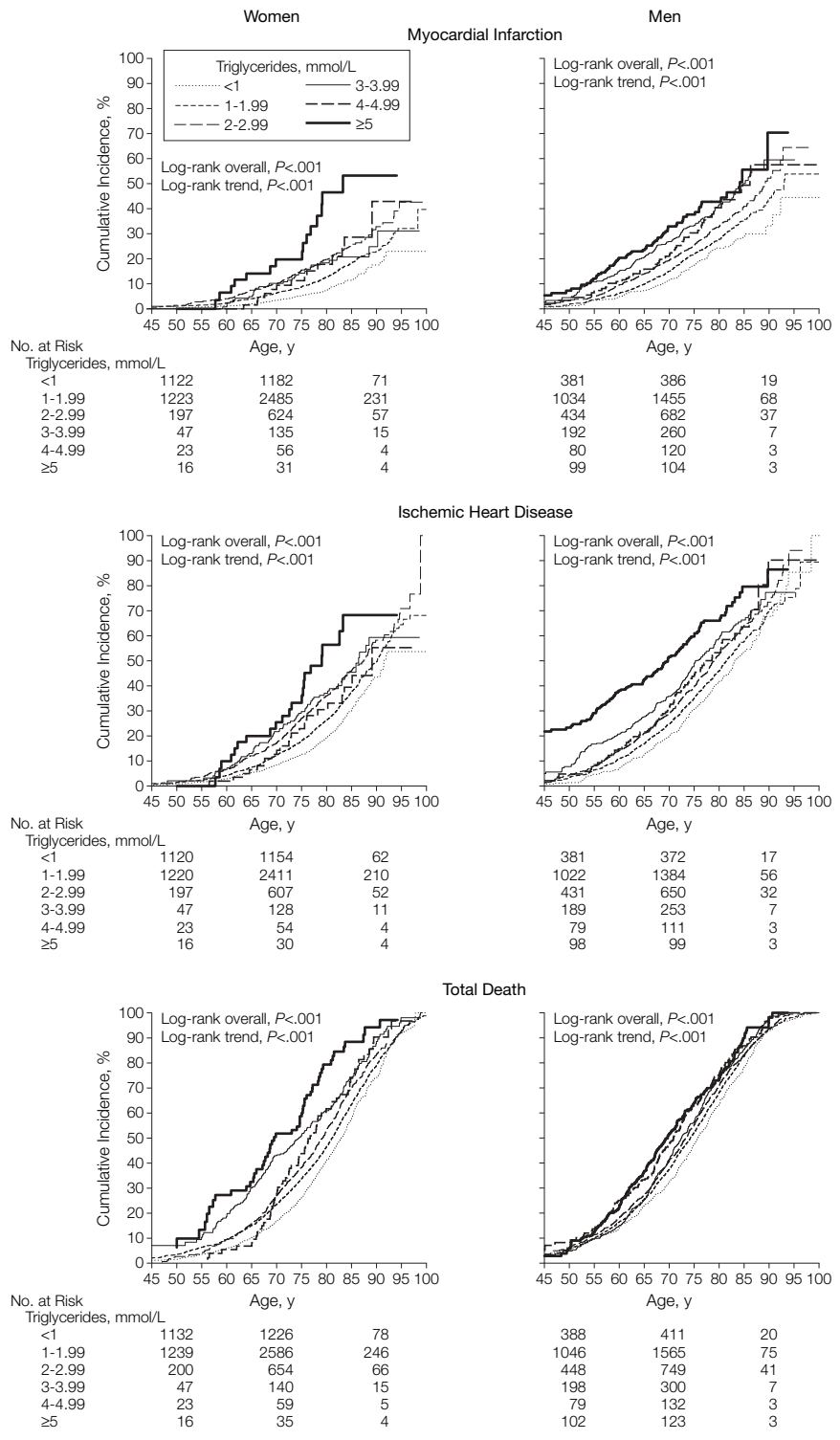
(95% CI, 1.1-2.3), 2.3 (95% CI, 1.5-3.4), 3.6 (95% CI, 2.3-5.7), 3.3 (95% CI, 1.9-5.9), and 4.6 (95% CI, 2.7-8.0), respectively.

For IHD, the incidence rates in women in events per 10 000 person-years were 58 (95% CI, 51-65; 290 events), 109 (95% CI, 102-117; 878 events), 163 (95% CI, 145-183; 289 events), 164 (95% CI, 129-209; 66 events), 130 (95% CI, 86-195; 23 events), and 223 (95% CI, 146-342; 21 events), respectively, for the 6 nonfasting triglyceride level categories. The corresponding incidence rates in men in events per 10 000 person-years were 126 (95% CI, 110-144; 214 events), 167 (95% CI, 156-178; 853 events), 205 (95% CI, 188-225; 469 events), 220 (95% CI, 191-252; 198 events), 211 (95% CI, 170-263; 80 events), and 238 (95% CI, 195-290; 98 events), respectively.

For IHD, women with increased nonfasting triglyceride levels had age-adjusted HRs of 1.7 (95% CI, 1.4-2.1), 2.8 (95% CI, 2.1-3.6), 3.0 (95% CI, 1.9-4.7), 2.1 (95% CI, 1.0-4.3), and 5.9 (95% CI, 2.8-12.4), respectively, for the 5 nonfasting triglyceride level categories vs women with nonfasting triglyceride levels of less than 1 mmol/L (<88.5 mg/dL) (Figure 4). The corresponding values in men were 1.3 (95% CI, 1.0-1.7), 1.7 (95% CI, 1.3-2.3), 2.1 (95% CI, 1.5-3.0), 2.0 (95% CI, 1.2-3.1), and 2.9 (95% CI, 1.9-4.5), respectively.

For total death, the incidence rates in women in events per 10 000 person-years were 145 (95% CI, 135-156; 754 events), 245 (95% CI, 235-256; 2076 events), 325 (95% CI, 300-351; 623 events), 373 (95% CI, 320-435; 164 events), 345 (95% CI, 270-441; 64 events), and 469 (95% CI, 356-619; 50 events), respectively, for the 6 nonfasting triglyceride level categories. The corresponding incidence rates in men in events per 10 000 person-years were 260 (95% CI, 238-285; 470 events), 345 (95% CI, 330-360; 1920 events), 380 (95% CI, 356-405; 959 events), 384 (95% CI, 348-424; 386 events), 412

Figure 3. Cumulative Incidences of Myocardial Infarction, Ischemic Heart Disease, and Total Death by Levels of Nonfasting Triglycerides



Cumulative incidence values are from the Copenhagen City Heart Study, with mean 26 years of follow-up. *P* values for overall log-rank tests examine whether the 6 different Kaplan-Meier curves differ. *P* values for log-rank trend tests examine whether increased levels of triglycerides associate with increased cumulative incidence.

(95% CI, 355-477; 176 events), and 377 (95% CI, 325-436; 176 events), respectively.

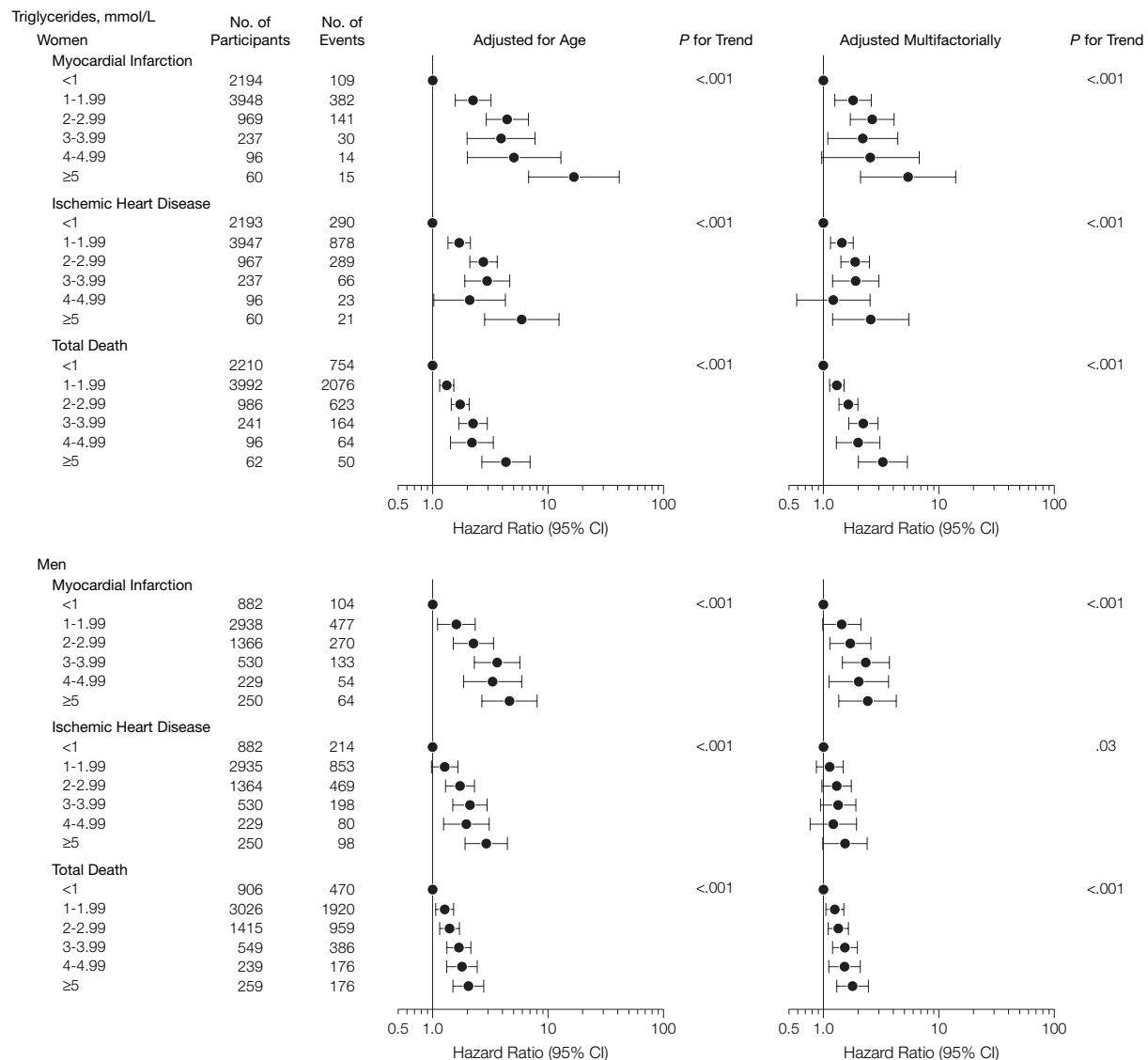
For total death, women with increased nonfasting triglyceride levels had age-adjusted HRs of 1.3 (95% CI, 1.2-1.5), 1.7 (95% CI, 1.5-2.1), 2.2 (95% CI, 1.7-3.0), 2.2 (95% CI, 1.4-3.4), and 4.3 (95% CI, 2.7-7.0), respectively, for the 5 nonfasting triglyceride level categories vs women with

nonfasting triglyceride levels of less than 1 mmol/L (<88.5 mg/dL) (Figure 4). The corresponding values in men were 1.3 (95% CI, 1.1-1.5), 1.4 (95% CI, 1.2-1.7), 1.7 (95% CI, 1.3-2.1), 1.8 (95% CI, 1.3-2.4), and 2.0 (95% CI, 1.5-2.8), respectively.

Hazard ratios for risk of MI, IHD, and death were attenuated after multifactorial adjustment (Figure 4). For MI in women, the multifactorially adjusted

HRs were 1.7 (95% CI, 1.2-2.5), 2.5 (95% CI, 1.6-3.9), 2.1 (95% CI, 1.0-4.3), 2.4 (95% CI, 0.9-6.2), and 5.4 (95% CI, 2.1-13.9), respectively, for the 5 nonfasting triglyceride level categories vs triglyceride levels of less than 1 mmol/L (<88.5 mg/dL). The corresponding values in men were 1.4 (95% CI, 1.0-2.1), 1.6 (95% CI, 1.1-2.4), 2.3 (95% CI, 1.4-3.7), 1.9 (95% CI, 1.0-3.4), and 2.4 (95% CI, 1.3-4.2), respec-

Figure 4. Hazard Ratios for Myocardial Infarction, Ischemic Heart Disease, and Total Death by Increasing Levels of Nonfasting Triglycerides



Hazard ratios and 95% confidence intervals (CIs) are from the Copenhagen City Heart Study, with mean 26 years of follow-up. Multifactorial adjustment was for age, total cholesterol, body mass index, hypertension, diabetes, smoking, alcohol consumption, physical inactivity, lipid-lowering therapy, and in women also for postmenopausal status and hormone therapy. P values for trend tests examined whether increased levels of triglycerides associate with increased hazard ratios (triglyceride categories were coded 0, 1, 2, 3, 4, and 5 for increasing triglyceride levels). To convert triglycerides to mg/dL, divide values by 0.0113.

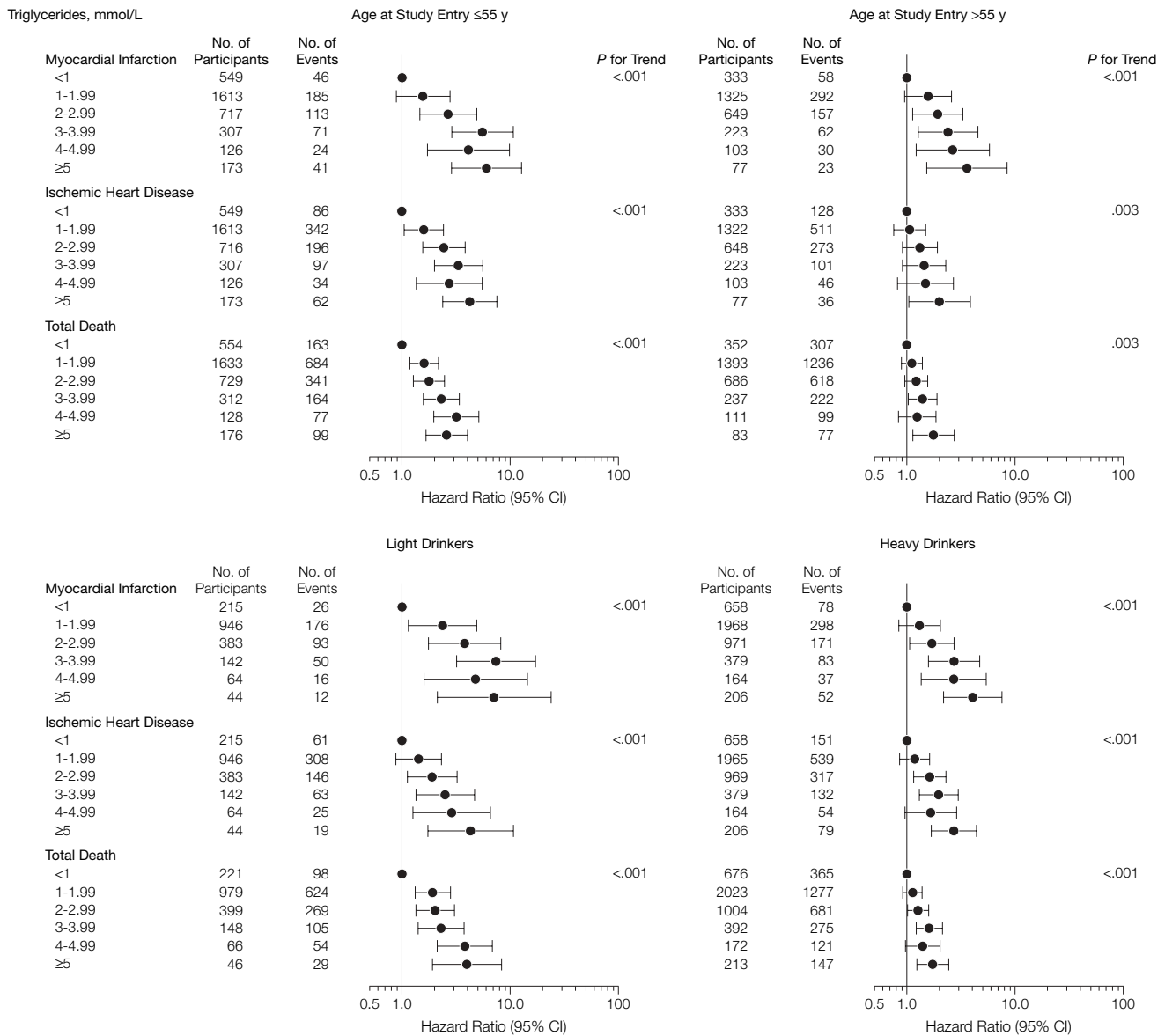
tively. For IHD in women, the multifactorially adjusted HRs were 1.4 (95% CI, 1.1-1.8), 1.8 (95% CI, 1.4-2.5), 1.8 (95% CI, 1.2-2.9), 1.2 (95% CI, 0.6-2.5), and 2.6 (95% CI, 1.2-5.5), respectively, for the 5 nonfasting triglyceride level categories vs triglyceride levels of less than 1 mmol/L (<88.5 mg/dL). The corresponding values in men were

1.1 (95% CI, 0.8-1.4), 1.3 (95% CI, 0.9-1.7), 1.3 (95% CI, 0.9-1.9), 1.2 (95% CI, 0.7-1.9), and 1.5 (95% CI, 1.0-2.4), respectively. For death in women, the multifactorially adjusted HRs were 1.3 (95% CI, 1.1-1.5), 1.6 (95% CI, 1.4-2.0), 2.2 (95% CI, 1.7-3.0), 1.9 (95% CI, 1.2-3.0), and 3.3 (95% CI, 2.0-5.4), respectively, for the 5 nonfasting

triglyceride level categories vs triglyceride levels of less than 1 mmol/L (<88.5 mg/dL). The corresponding values in men were 1.2 (95% CI, 1.0-1.5), 1.4 (95% CI, 1.1-1.7), 1.5 (95% CI, 1.2-2.0), 1.6 (95% CI, 1.1-2.1), and 1.8 (95% CI, 1.3-2.5), respectively.

In post hoc analyses in men, age-adjusted HRs were more pronounced

Figure 5. Age-adjusted Hazard Ratios for Myocardial Infarction, Ischemic Heart Disease, and Total Death for Increasing Levels of Nonfasting Triglycerides in Men Stratified for Alcohol Consumption and Age at Entry



Hazard ratios and 95% confidence intervals (CIs) are from the Copenhagen City Heart Study, with mean 26 years of follow-up. P values for trend tests examine whether increased levels of triglycerides associate with increased hazard ratios (triglyceride categories were coded 0, 1, 2, 3, 4, and 5 for increasing triglyceride levels). To convert triglycerides to mg/dL, divide values by 0.0113.

Table 2. Risk of Myocardial Infarction, Ischemic Heart Disease, and Total Death by a 1-mmol/L Increase in Nonfasting Triglyceride Levels

	Hazard Ratio (95% Confidence Interval) ^a		
	Age-Adjusted	Adjusted for Age and HDL Cholesterol ^b	Adjusted Multifactorially ^c
Women			
Myocardial infarction	1.46 (1.34-1.59)	1.41 (1.26-1.57)	1.20 (1.05-1.37)
Ischemic heart disease	1.30 (1.22-1.40)	1.25 (1.14-1.37)	1.10 (0.99-1.21)
Total death	1.26 (1.20-1.32)	1.18 (1.11-1.26)	1.18 (1.10-1.27)
Men			
Myocardial infarction	1.18 (1.13-1.23)	1.16 (1.10-1.22)	1.04 (0.98-1.11)
Ischemic heart disease	1.14 (1.10-1.19)	1.12 (1.07-1.18)	1.00 (0.95-1.06)
Total death	1.10 (1.06-1.13)	1.10 (1.06-1.15)	1.08 (1.03-1.13)

Abbreviation: HDL, high-density lipoprotein.

^aBased on nonfasting triglycerides on a continuous scale.

^bHDL measured at the 1981-1983, 1991-1994, and 2001-2003 examinations; HDL cholesterol was not measured at the 1976-1978 examination.

^cAdjusted multifactorially for age, total cholesterol, body mass index, hypertension, diabetes, smoking, alcohol consumption, physical inactivity, lipid-lowering therapy, and in women also for postmenopausal status and hormone therapy.

in those individuals with entry age of 55 years or younger vs older than 55 years, and in light vs heavy alcohol drinkers (FIGURE 5).

Nonfasting Triglyceride Levels on a Continuous Scale

When considered as a continuous variable, nonfasting triglyceride levels were independently predictive of MI and death in women and of death in men (TABLE 2).

COMMENT

We found that elevated nonfasting triglyceride levels, which indicate the presence of remnant lipoproteins, were associated with increased risk of MI, IHD, and total death in men and women in the general population. Because most previous studies¹⁸⁻²⁰ have focused on fasting levels of triglycerides that exclude remnant lipoproteins, and studied mainly tertiles or quartiles of triglycerides rather than very high levels, the demonstrated predictive ability of nonfasting triglyceride levels of 5 mmol/L or more (≥ 442.5 mg/dL) has previously gone unnoticed. In our data, there even appears in some cases to be a “jump” in HRs between triglyceride levels of less than 5 mmol/L and triglyceride levels of 5 mmol/L or more. It is not triglycerides per se that cause athero-

sclerosis but rather the cholesterol content of remnant lipoproteins. This finding is apparent from comparing the age-adjusted HRs with the multifactorially adjusted HRs; multifactorial adjustment masks the effect of triglycerides by adjusting for factors like overweight and diabetes, which are known to lead to elevated levels of triglycerides and remnant lipoproteins.

Increased levels of nonfasting triglycerides may indicate the presence of increased levels of atherogenic remnant lipoproteins.¹⁰ Because all human cells can degrade triglycerides but not cholesterol, and because remnant lipoproteins like LDL carry large amounts of cholesterol, it is the cholesterol content of remnant particles that upon entrance into the arterial intima can cause atherosclerosis.^{10,12} Like LDLs, remnant lipoproteins can enter into the arterial intima⁷ and may even be trapped preferentially within the arterial wall.⁸ Patients with genetic disorders leading to large amounts of plasma remnant lipoproteins develop premature atherosclerosis² and patients with familial hypertriglyceridemia have increased risk of cardiovascular death.¹ Also, heterozygosity for genetic defects in lipoprotein lipase, the plasma enzyme degrading triglycerides, associates with increased triglyceride levels as well as increased risk of

IHD.^{4,21,22} Furthermore, patients with the familial chylomicronemia syndrome who during part of their life due to lipid-lowering treatment have triglyceride levels of 3 to 7 mmol/L (265.5-619.5 mg/dL) also develop premature atherosclerosis.²³ Finally, subanalyses of 3 randomized double-blind trials suggest that among patients with increased triglyceride levels, a 20% to 40% reduction in triglyceride levels associates with a 30% to 40% reduction in risk of IHD.²⁴⁻²⁶

Our cross-sectional data (Figure 1) suggest that most people eat less fat during normal food intake than during a fat tolerance test, simply because individuals in the general population have less plasma triglycerides in response to normal food intake than during a fat tolerance test of 1-gram dairy cream per kilogram of body weight. The only modest increase in triglyceride levels during normal food intake together with our demonstration of high predictive ability of nonfasting triglycerides for risk of MI, IHD, and death opens the possibility that nonfasting rather than fasting triglyceride levels should be used for risk prediction. If implemented, this would simplify blood sampling for lipid measurements.

Increased triglyceride levels associate with reduced levels of HDL cholesterol, a strong risk factor for IHD.²⁷ However, increased triglyceride levels is a risk factor for cardiovascular disease independent of HDL cholesterol levels.¹⁸ Because genetically reduced levels of HDL associate with decreased rather than increased risk of IHD,²⁸ and vice versa for genetically increased levels of HDL cholesterol,²⁹⁻³¹ HDL cholesterol levels per se may not directly influence development of atherosclerosis and IHD. Increased levels of triglycerides also associate with increased levels of small, dense LDLs, both of which associate with atherosclerosis.³² This association with atherosclerosis possibly can be explained by increased levels of remnant lipoproteins present in the nonfasting state rather than by small, dense LDL per se.³³

Most previous studies on triglycerides have focused on fasting levels that exclude remnant lipoproteins, and most have only compared moderately increased vs low levels.¹⁸⁻²⁰ Therefore, most previous studies cannot be compared directly with the results of our study. However, in accordance with our results, a Norwegian study found that nonfasting triglyceride levels of 3.5 mmol/L or more (≥ 309.7 mg/dL) vs less than 1.5 mmol/L (< 132.7 mg/dL) was associated with a 5-fold risk of death from coronary heart disease and a 2-fold risk of total death in women.³⁴ A recent meta-analysis found similar predictive ability for fasting and nonfasting upper vs lower tertiles of triglyceride levels on risk of coronary heart disease.²⁰

In women, we observed better predictive ability of nonfasting triglyceride levels than in men, in accordance with similar findings for fasting triglyceride levels in some^{18,19} but not all previous meta-analyses.²⁰ Our stratified analyses suggest that the predictive ability of nonfasting triglyceride levels for risk of MI, IHD, and death in young men who only consume small amounts of alcohol is similar to that in women. Therefore, because large alcohol intake often leads to increased triglyceride levels, and because these triglyceride-rich lipoproteins may differ from most remnant lipoproteins present in nonfasting plasma (type V vs type IIb hyperlipidemia), it is likely that high alcohol intake may have confounded the association between triglyceride levels and risk of MI, IHD, and death in men in this and former studies.

Our study limitations include that we only studied white participants, and therefore our results may not necessarily apply to other racial groups. Furthermore, the relatively small sample sizes and wide CIs in groups with the highest triglyceride levels are of concern. A few participants took lipid-lowering drugs late in the follow-up period, which could have confounded the results slightly; however, at the 1991-1994 and 2001-2003 examinations af-

ter the first 15 and 25 years of follow-up, only 1% and 2% of the participants took lipid-lowering drugs. When the analyses were adjusted for lipid-lowering drugs, the results changed only minimally. Nonfasting triglyceride level is dependent on the duration of fasting; however, since information on timing since the last meal was not available for participants of the Copenhagen City Heart Study examined in 1976-1978, this could not be taken into account in our analyses. Therefore, if triglyceride levels were measured at a fixed time point after a normal meal or even after a fat tolerance test, the predictive ability of nonfasting or postprandial triglyceride levels may be even better than that observed in our study for random nonfasting triglycerides.

Low participation rates may limit the ability to extend the results obtained to the population at large. However, we invited people at random to represent the general population, had a participation rate of 74%, and found incidences of MI and IHD, but not of total death, to be similar between responders and nonresponders. In addition, regression dilution bias may influence results,¹⁶ although we corrected for this bias. Furthermore, population admixture may bias results; however, 100% of our participants were white of Danish descent. Thus, our study strengths include an ethnically homogeneous large sample from a white general population with a very high participation rate, 26 years of 100% complete follow-up, and correction for regression dilution bias.

In this population, with 10 baseline dichotomized risk factors, smoking, hypertension, nonfasting hypercholesterolemia, obesity, physical inactivity, and diabetes in both sexes, nonfasting hypertriglyceridemia in women and no daily alcohol intake in men independently predicted increased risk of IHD.¹³ As levels of HDLs and LDLs were first measured at the 1991-1994 examination, these risk factors could not be evaluated during the entire period of follow-up; however, both these lipoproteins measured in the nonfasting

state also predicted increased risk of IHD in the Copenhagen City Heart Study.^{35,36}

We found that nonfasting triglyceride levels independently predict MI, IHD, and death, particularly in women. These findings may reflect the effects of remnant lipoproteins and therefore may be of considerable interest when designing future trials of agents aimed at reducing triglyceride levels or attenuating atherogenic metabolic abnormalities. If our findings are confirmed, clinical care might be simplified by using nonfasting lipid profiles for atherosclerosis risk prediction.

Author Contributions: Drs Nordestgaard and Benn 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.

Study concept and design: Nordestgaard, Benn, Schnohr.

Acquisition of data: Nordestgaard, Benn, Schnohr.

Analysis and interpretation of data: Nordestgaard, Benn, Tybjaerg-Hansen.

Drafting of the manuscript: Nordestgaard, Benn.

Critical revision of the manuscript for important intellectual content: Nordestgaard, Benn, Schnohr, Tybjaerg-Hansen.

Statistical analysis: Nordestgaard, Benn, Tybjaerg-Hansen.

Obtained funding: Nordestgaard, Schnohr, Tybjaerg-Hansen.

Administrative, technical, or material support: Nordestgaard, Schnohr.

Study supervision: Nordestgaard, Benn.

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