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Changes in Triglyceride Levels and Risk for Coronary Heart Disease in Young Men

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Background: Current triglyceride levels might be only a weak predictor of risk for coronary heart disease (CHD).

Objective: To assess the association between changes over time in fasting triglyceride levels and CHD risk in young adults.

Design: Follow-up study over 5.5 years after 2 measurements of fasting triglycerides 5 years apart.

Setting: The Staff Periodic Examination Center of the Israel Defense Forces, Zrifin, Israel.

Patients: 13 953 apparently healthy, untreated, young men (age 26 to 45 years) with triglyceride levels less than 3.39 mmol/L (<300 mg/dL).

Measurements: Two triglyceride measurements (at enrollment [time 1] and 5 years later [time 2]), lifestyle variables, and incident cases of angiography-proven CHD.

Results: Within 5.5 years, 158 new cases of CHD were identified. The multivariate model was adjusted for age; family history; fasting glucose; high-density lipoprotein cholesterol; blood pressure; body mass index; and changes between time 1 and time 2 in body mass index, physical activity, smoking status, and habit of eating breakfast. Investigators categorized triglyceride levels according to low, intermediate, and high tertiles (as measured at time 1 and time 2 [expressed as tertile at time 1/tertile at time 2]). The risk for CHD in men with high-tertile triglyceride levels at time 1 changed depending on the tertile at time 2 (hazard ratios, 8.23 [95% CI, 2.50 to 27.13] for high/high, 6.84 [CI, 1.95 to 23.98] for high/intermediate, and 4.90 [CI, 1.01 to 24.55] for high/low, compared with the stable low/low group). The risk for CHD in men with low-tertile levels at time 1 also changed depending on the tertile at time 2 (hazard ratios, 3.81 [CI, 0.96 to 15.31] for low/intermediate and 6.76 [CI, 1.34 to 33.92] for low/high, compared with the stable low/low group).

Limitations: Participants were healthy and had a low incidence rate of CHD. The study was observational.

Conclusions: Two triglyceride measurements obtained 5 years apart may assist in assessing CHD risk in young men. A decrease in initially elevated triglyceride levels is associated with a decrease in CHD risk compared with stable high triglyceride levels. However, this risk remains higher than in those with persistently low triglyceride levels.

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A recent meta-analysis (1) and most published papers suggest a moderate association between fasting triglyceride levels and coronary heart disease (CHD) (2–11). Of the lipid fractions, the triglyceride-rich very-low-density lipoprotein particle is probably the most sensitive to lifestyle modification (8). For example, estimates from meta-analyses suggest that for every 4.5 kg (approximately 10 lb) of stable weight reduction, triglyceride levels decrease by at least 0.068 mmol/L (≥6 mg/dL) (12). Accordingly, a considerable increase in the proportion of hypertriglyceridemic patients accompanies the obesity epidemic (6, 9). In addition, aerobic exercise, independent of weight loss, has been shown to modestly reduce triglyceride levels in a dose-dependent fashion (13). Hence, when assessing the risk associated with triglyceride levels, triglyceride measurement at a single time point (typically at enrollment) may not be a reliable indicator of a person's long-term triglyceridemia during follow-up. Whether changes in triglyceride levels over time can improve cardiovascular risk assessment is largely unknown, particularly in young adults, in whom information on the association between triglycerides and CHD is not available (1).

For 13 953 apparently healthy young adult men (mean age, 32 years; range, 26 to 45 years) from the MELANY (Metabolic, Lifestyle, and Nutrition Assessment in Young Adults) study (14), we obtained 2 measurements of fasting serum triglycerides and lifestyle variables 5 years apart and followed for incident cases of angiography-proven CHD. Here, we estimate the effect of baseline triglyceride levels (time 1) and changes (between time 1 and time 2) in triglyceride levels on CHD risk.

METHODS

The MELANY Study

The MELANY study, which was designed to investigate risk factors for common diseases in young adults, is being conducted at the Israel Defense Forces Staff Periodic Examination Center (SPEC), Zrifin, Israel. All career service personnel are evaluated every 5 years between 25 and

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Context

Whether the serum triglyceride level is an independent risk factor for coronary heart disease (CHD) is not clear.

Contribution

The authors measured triglyceride levels and performed stress electrocardiographies 5 years apart on 13 593 young Israeli male career soldiers and did coronary angiography if the stress test was abnormal. Triglycerides and change in triglyceride levels strongly predicted incident CHD after adjustment for known CHD risk factors and lifestyle. Decreases in triglyceride levels were associated with adoption of a healthier lifestyle and lower CHD risk. The lowest CHD risk occurred when triglyceride levels remained low.

Caution

The participants were healthy male soldiers.

Implication

In healthy young men, triglycerides and changes in triglyceride levels are an independent CHD risk factor.

—The Editors

35 years of age and every 3 years thereafter until they are discharged from service. A computerized database established in 1992 is the source of data for the MELANY study. At each SPEC visit, participants complete a detailed questionnaire that assesses demographic, nutritional, lifestyle, and medical factors. Thereafter, blood samples are drawn after a 14-hour fast and analyzed. A trained medical technician measures height, weight, and blood pressure (by mercury sphygmomanometers), and a physician at the center performs a complete physical examination.

Inclusion and Exclusion Criteria

We included apparently healthy men 26 to 45 years of age who had fasting triglyceride levels less than 3.39 mmol/L (<300 mg/dL) at their initial SPEC visit. We used the cutoff value of 3.39 mmol/L (300 mg/dL) because SPEC persons with greater triglyceride values are subjected to additional interventions—nutritional, pharmacologic, or both. Of 15 155 men age 26 to 45 years, 1202 were excluded because they had diabetes (type 1 or 2) ($n = 227$) or CHD ($n = 17$) at baseline; had fasting triglyceride levels of 3.39 mmol/L or greater (≥300 mg/dL) ($n = 676$); or were receiving long-term medications ($n = 282$), including lipid-lowering medications. Therefore, for analysis of the association between baseline triglyceride levels and incident CHD, we included 13 953 men. In studying the effect of changes in triglyceride levels on CHD, we excluded an additional 413 men who did not have a triglyceride measurement from the second SPEC visit ($n = 363$) or had received a diagnosis of diabetes ($n = 38$) or CHD ($n = 12$) between the first and second SPEC visit or during the second visit. Women were not included because the number of new cases of CHD in women was too small to facilitate meaningful analysis.

Outcome Definition

The outcome definition of the study was clinically significant CHD (angiography-proven stenosis >50% in at least 1 coronary artery) or fatal or nonfatal myocardial infarction (MI). At each sequential SPEC visit, all Israel Defense Forces military personnel older than 35 years of age who were participating in the current analysis had a treadmill exercise test (Bruce protocol [15]) in the presence of a board-certified cardiologist. End points for the exercise test were clinically significant ST-segment depression (>2 mm in 2 contiguous leads, measured 80 ms after the J point), intolerable symptoms of angina and exhaustion, or achievement of the target heart rate. All cases with a pathologic stress test were referred for coronary angiography. In participants with a borderline stress test, or when participants reported angina symptoms without diagnostic electrocardiographic changes, stress perfusion imaging with thallium-201 was performed. Those with a pathologic thallium-201 cardiac scan underwent coronary angiography. All Israel Defense Forces personnel obtain primary care between scheduled SPEC visits at designated military clinics, and all medical records are stored in the same central database, thereby facilitating ongoing, tight, and uniform follow-up. Individuals presenting with symptoms of angina, MI, or both between SPEC visits were also referred for coronary angiography after consultation with a board-certified cardiologist.

Laboratory Methods

Investigators performed biochemical analyses of fresh blood samples in an adjacent core laboratory facility that handles 1.2 million samples per year. The laboratory is authorized to perform tests according to the International Organization for Standardization standard 9002. The United Kingdom National External Quality Assessment Service, Sheffield, United Kingdom, performed periodic assessment of quality control on a regular basis. All lipid levels were directly measured, except for low-density lipoprotein (LDL) levels, which were calculated. Investigators measured all biochemical markers by using a BM/Hitachi 917 automated analyzer (Boehringer, Mannheim, Germany).

Statistical Analysis

For the primary analysis, we included 13 953 untreated, apparently healthy young men with triglyceride levels lower than 3.39 mmol/L (<300 mg/dL). We used a general linear model to assess the age-adjusted means and proportions of the population's characteristics across quintiles of triglycerides and to fit the median of the quintiles as a continuous variable to estimate the trend of variables across quintiles (**Table 1**). We conducted Cox proportional hazards analysis during the 10.5-year follow-up to estimate the hazard ratios and 95% CIs for the development of

Table 1. **Baseline (Time 1) Characteristics, by Quintile of Triglyceride Level***

Characteristic	Quintile 1 (*n* = 2844)	Quintile 2 (*n* = 2739)	Quintile 3 (*n* = 2789)	Quintile 4 (*n* = 2795)	Quintile 5 (*n* = 2786)	*P* Value for Trend
Triglyceride level						–
Mean (SD)						
mmol/L	0.59 (0.11)	0.88 (0.08)	1.17 (0.09)	1.57 (0.14)	2.39 (0.40)	
mg/dL	52 (9.6)	78 (6.9)	104 (8.4)	139 (12.6)	212 (35.7)	
Median (25th, 75th percentiles)						
mmol/L	0.60 (0.51, 0.68)	0.88 (0.81, 0.95)	1.17 (1.10, 1.25)	1.56 (1.45, 1.69)	2.30 (2.05, 2.66)	
mg/dL	53 (45, 60)	78 (72, 84)	104 (97, 111)	138 (128, 150)	204 (182, 236)	
Range						
mmol/L	0.34–0.75	0.76–1.02	1.03–1.34	1.35–1.84	1.85–3.38	
mg/dL	30–66	67–90	91–119	120–163	164–299	
Mean age (SD), *y*	31.0 (4.8)	31.7 (5.1)	32.3 (5.3)	33.0 (5.4)	33.9 (5.2)	<0.001
Mean follow-up, *y*	10.4	10.3	10.1	10.6	10.7	0.58
Age-adjusted variables						
Family history of CHD, %†	16.1	15.3	16.7	15.9	18.8	0.33
Mean BMI (SD), kg/m^2	24 (3.1)	24.7 (3.4)	25.5 (3.5)	26.3 (3.5)	27.3 (3.6)	<0.001
Mean blood pressure (SD), *mm Hg*						
Systolic	117 (11.4)	119 (11.6)	120 (12.2)	121 (12.3)	122 (12.6)	<0.001
Diastolic	75 (8.4)	76.3 (8.6)	77.1 (9.1)	77.8 (9.0)	78.9 (9.7)	<0.001
Arterial pressure	88.4 (8.6)	89.2 (8.7)	90.5 (9.4)	91.2 (9.3)	92.3 (9.8)	<0.001
Smoking status, %						
Current	22	27.7	29.7	32.9	37	<0.001
Former	20	18.5	22	19.8	20.5	0.81
Physical activity, % *(min/wk)*‡	38 (91)	35.4 (89)	32.2 (88)	29.9 (81)	24.6 (83)	<0.001 (0.057)
Habit of eating breakfast, %	22	19.3	17.7	17.9	16.4	0.002
Age-adjusted biomarkers						
Mean HDL cholesterol level (SD)						<0.001
mmol/L	1.40 (0.29)	1.25 (0.27)	1.22 (0.25)	1.15 (0.25)	1.06 (0.25)	
mg/dL	54 (11.2)	48.2 (10.5)	47.1 (9.8)	44.3 (9.8)	40.8 (9.6)	
Mean LDL cholesterol level (SD)						<0.001
mmol/L	3.08 (0.72)	3.39 (0.88)	3.65 (0.89)	3.83 (0.93)	3.78 (0.95)	
mg/dL	119 (27.7)	131 (33.9)	141 (34.5)	148 (36.1)	146 (36.8)	
TC–HDL ratio (SD)	3.7 (0.9)	4.28 (1.1)	4.8 (1.3)	5.34 (1.5)	6.03 (1.6)	<0.001
Mean fasting plasma glucose level (SD)						0.005
mmol/L	4.94 (0.54)	5.02 (0.53)	5.08 (0.54)	5.11 (0.56)	5.18 (0.57)	
mg/dL	89 (9.7)	90.3 (9.6)	91.4 (9.8)	92 (10.1)	93.3 (10.3)	

* "Time 1" is the first of 2 measurements of triglycerides obtained 5 years apart. BMI = body mass index; CHD = coronary heart disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TC = total cholesterol.
† A family history of CHD includes the presence of heart disease in a first-degree relative before age 65 y (women) or 55 y (men).
‡ Defined as engagement in physical activity for a minimum of 20 minutes, 3 times per week.

CHD (the dependent variable) according to triglyceride levels at time 1 (first measurement). In stepwise models (**Table 2**), we added the values for body mass index (BMI), high-density lipoprotein (HDL) cholesterol, and family history of CHD separately to the age-adjusted model to evaluate their potential role as confounders. In the final multivariate model, we controlled for age, BMI, HDL cholesterol, family history of CHD, fasting plasma glucose, mean arterial blood pressure, physical activity, and smoking status. Because the total cholesterol–HDL cholesterol ratio is a predictor of CHD (8), we performed a secondary analysis that included this ratio instead of HDL cholesterol in the multivariate model.

To assess the risk associated with *changes* in triglyceride levels, we analyzed data from 13 540 men who had 2 triglyceride measurements (obtained at time 1 and time 2, 5 years apart) that were available before the end of follow-up or before being censored after a diagnosis of CHD or diabetes. In the model, time 2 was considered the baseline of 5.2 years of subsequent follow-up, whereas time 1 was considered prebaseline. We cross-classified triglyceride levels at each time point by tertiles: median levels of 0.68, 1.18, and 2.08 mmol/L (60, 104, and 184 mg/dL) at time 1 and 0.79, 1.33, and 2.49 mmol/L (70, 118, and 220 mg/dL) at time 2. In parallel, we determined changes in BMI, smoking status, physical activity, and habit of eating breakfast between time 2 and time 1 (**Figure 1**). Next, we evaluated the joint risk attributed to triglyceride levels at time 1 and time 2, categorized according to low (bottom), intermediate, and high (top) tertiles, and we used men with triglyceride levels in the low tertile at both time 1 and time 2 as a reference group (low/low group; hazard ratio,

Table 2. **Hazard Ratios for Coronary Heart Disease, by Quintile of Time-1 Triglyceride Level***

Variable	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P* Value for Trend
Range of triglyceride level						–
mmol/L	0.34–0.75	0.76–1.02	1.03–1.34	1.35–1.84	1.85–3.38	
mg/dL	30–66	67–90	91–119	120–163	164–299	
Follow-up, *person-years*	29 578	28 212	28 169	29 627	29 810	
Incident cases of CHD, *n*	8	13	37	42	70	<0.001
Adjusted risk ratio (95% CI)						
Age	1.00 (reference)	1.43 (0.70–2.94)	4.48 (1.97–8.85)	5.10 (2.19–10.63)	7.06 (3.72–14.81)	<0.001
Age and BMI	1.00 (reference)	1.26 (0.63–2.78)	4.17 (1.90–8.11)	4.03 (2.02–9.41)	6.22 (3.19–12.68)	<0.001
Age, BMI, and HDL cholesterol level	1.00 (reference)	1.12 (0.59–2.34)	3.70 (1.81–7.57)	3.84 (1.86–8.29)	5.15 (2.84–10.02)	<0.001
Age, BMI, HDL cholesterol level, and family history of CHD	1.00 (reference)	1.13 (0.62–2.41)	3.78 (1.96–7.60)	3.96 (1.91–8.35)	5.29 (2.93–10.17)	<0.001
Multivariate†	1.00 (reference)	1.04 (0.56–2.30)	2.92 (1.65–6.39)	3.18 (1.72–7.24)	4.05 (2.68–8.61)	<0.001

* BMI = body mass index; CHD = coronary heart disease; HDL = high-density lipoprotein.
† The multivariate Cox regression time-dependent model was adjusted for age, BMI, HDL cholesterol level, fasting plasma glucose level, mean arterial blood pressure (continuous variables), family history of CHD (positive, negative, or missing information), physical activity (yes, no, or missing information), and smoking status (current, noncurrent, or missing information).

1.0). To evaluate the direct association of changes in triglyceride levels (**Figure 2**), we used a multivariate model to further adjust for the interval between the 2 measurements and for the changes between time 2 and time 1 in BMI and lifestyle variables (physical activity, smoking, and habit of eating breakfast). We included these variables by calculating differences (Δ) in BMI and creating 3 groups of each categorical variable (smoking, physical activity, and habit of eating breakfast) based on their status at time 1 and time 2 (yes/yes, yes/no, no/yes, or no/no).

For the analysis of the association between cardiovascular risk and baseline triglyceride measurement (**Table 2**), follow-up consists of the interval between time 1 and the end of follow-up (or diagnosis)—that is, 10.5 years—and includes the cases that occurred between time 1 and time 2 ($n = 12$). For the analysis of the association between cardiovascular risk and different directionality of changes in triglycerides (**Figure 2**), follow-up was from the second triglyceride determination (time 2) to the end of follow-up (or diagnosis)—that is, 5.2 years—effectively converting the value at time 1 into a prebaseline variable. We used SAS statistical software, version 9.1 (SAS Institute, Cary, North Carolina), for all statistical analyses.

Role of the Funding Source

The Ben-Gurion University of the Negev, Beer-Sheva, Israel, and funds from the Israel Defense Forces National Budget provided support for the study. The funding sources had no role in the conduct of the study or in the decision to submit the manuscript for publication. The Israel Defense Forces had a role in the design of the cohort and in performing the follow-up and outcome measurements. Dr. Tirosh and Ms. Shochat 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.

RESULTS

We analyzed the data of 13 953 untreated, apparently healthy men (26 to 45 years of age) with fasting serum triglyceride levels lower than 3.39 mmol/L (<300 mg/dL). At time 1, age-adjusted LDL cholesterol and fasting plasma glucose levels, BMI, blood pressure, and proportion of current smokers were more likely to increase across quintiles of triglycerides, whereas HDL cholesterol levels and the proportion of men who were physically active and who reported eating breakfast regularly were more likely to decrease (**Table 1**).

A total of 170 incident cases of angiography-proven CHD occurred during 145 396 person-years of follow-up (mean follow-up, 10.5 years): 163 cases were diagnosed by coronary angiography, and 7 men had nonfatal MI as their presenting symptom before their scheduled SPEC visit. No cases of fatal MI were documented during follow-up. Age-adjusted hazard ratios for CHD increased across quintiles of triglyceride level, reaching 7.06 (95% CI, 3.72 to 14.81) for the top quintile (median, 2.30 mmol/L [204 mg/dL]) versus the bottom quintile (median, 0.60 mmol/L [53 mg/dL]) ($P < 0.001$ for trend) (**Table 2**). Further adjustment for BMI attenuated the risk value to 6.22 (CI, 3.19 to 12.68) for the top quintile. Predictably, this association was additionally attenuated after adjustment for HDL cholesterol (hazard ratio, 5.15 [CI, 2.84 to 10.02] for the top quintile) but did not change after further adjustment for family history of CHD. In a multivariate model adjusted for age, BMI, HDL cholesterol level, family history of CHD, fasting plasma glucose level, mean arterial blood pressure, physical activity, and smoking status, the association between triglyceride level and CHD remained independent from the third quintile (median, 1.17 mmol/L [104 mg/dL]), reaching a hazard ratio of 4.05 (CI, 2.68 to 8.61) for the top quintile versus the bottom quintile ($P < 0.001$ for trend). This association remained unchanged in

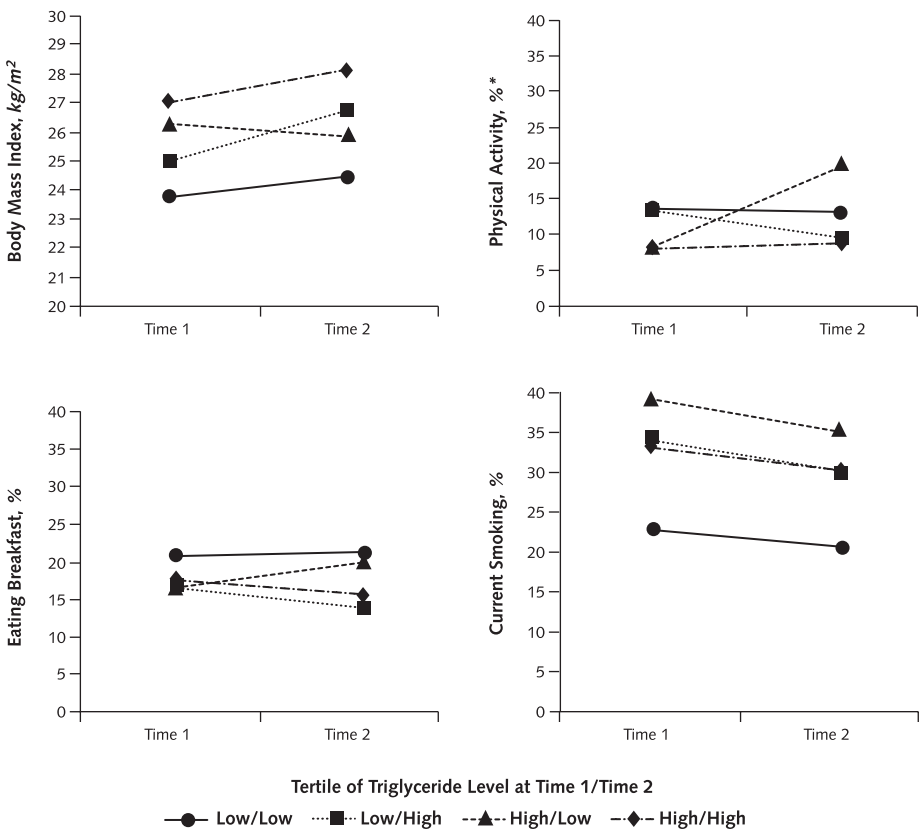
a secondary analysis that included the total cholesterol–HDL cholesterol ratio, instead of HDL cholesterol level, in the multivariate model. To exclude the possibility that elevated triglyceride levels already reflected clinically unrecognized CHD at baseline, we confirmed these clinically significant findings in a secondary analysis that excluded 5 persons with CHD that was diagnosed within the first 2 years of follow-up (data not shown).

We next analyzed data from 13 540 men for whom we had triglyceride measurements at 2 time points (time 1 and time 2) 5 years apart before being censored because of a diagnosis of CHD. Within this group (**Figure 1**), we characterized the men whose triglyceride levels were in the low (bottom) or high (top) tertile at time 1 and either remained stable in time 2 (that is, low/low [$n = 2846$] or high/high [$n = 2840$], respectively) or had a marked change in their time-2 measurement (that is, low/high [$n = 388$] or high/low [$n = 402$], respectively). These changes in triglycerides were associated with significant alterations in BMI, physical activity, and habit of eating breakfast between the 2 time points ($P < 0.05$). An increase in triglyceride levels between time 1 and time 2 (that is, low/high) was associated with increased BMI, decreased levels of physical activity, and a decrease in the proportion of men who ate breakfast. Conversely, young men in the high/low group (that is, whose triglyceride levels decreased without antidyslipidemic therapy) had a decrease in mean BMI and increase in physical activity and in the proportion of eating breakfast, consistent with the sensitivity of triglycerides to lifestyle factors. Retaining low triglyceride levels (that is, low/low) was associated with stable physical activity levels and habit of eating breakfast and the lowest BMI and proportion of current smoking.

Consistent with the findings presented in **Table 2**, a multivariate model to show the relationship of triglyceride values defined in tertiles at enrollment (time 1) revealed that the risk for incident CHD was 3.59-fold (CI, 1.89 to 7.69) and 4.66-fold (CI, 2.50 to 9.86) higher ($P < 0.001$ for trend) in the intermediate and high tertiles of triglyceride levels, respectively, compared with the low tertile.

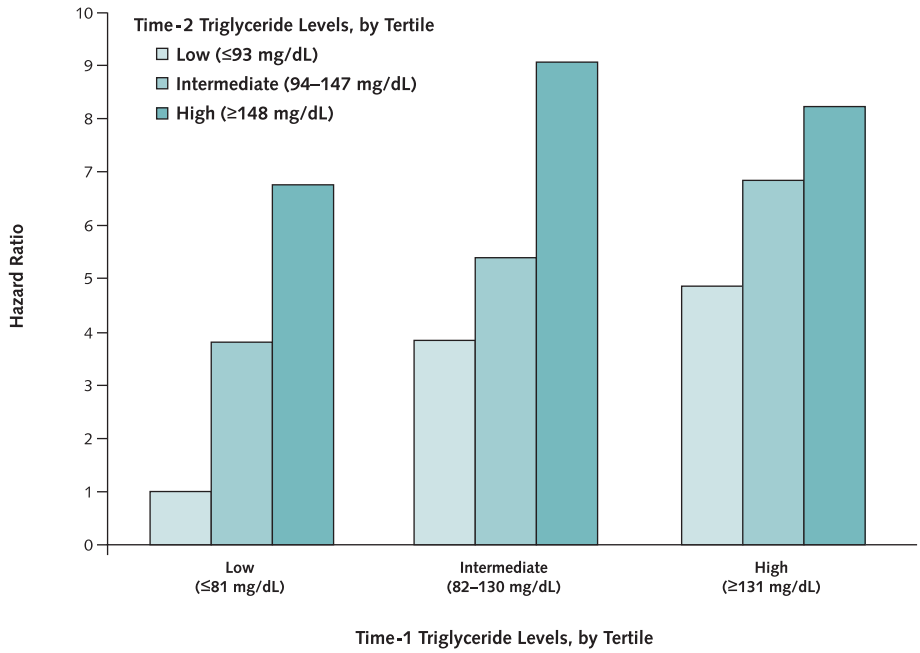
We further evaluated the risk for CHD according to changes of triglyceride levels over time (**Figure 2** and **Table 3**)

Figure 1. **Changes in selected lifestyle variables associated with 5-year changes, without medications, in triglyceride levels between time 1 and time 2.**



Tertiles were defined as low, the bottom tertile of triglyceride level (median at time 1, 0.68 mmol/L [60 mg/dL]; median at time 2, 0.79 mmol/L [70 mg/dL]), or high, the top tertile of triglyceride level (median at time 1, 2.08 mmol/L [184 mg/dL]; median at time 2, 2.48 mmol/L [220 mg/dL]). *Engagement in physical activity for a minimum of 20 minutes, 3 times per week.

Figure 2. **Multivariate model showing the association between fasting serum triglyceride levels obtained at 2 measurements 5 years apart and incidence of coronary heart disease.**



The model was adjusted for age, family history of coronary heart disease (positive, negative, or missing information), interval between time 1 and time 2, time-1 levels of fasting plasma high-density lipoprotein cholesterol, glucose, mean arterial blood pressure, and body mass index (as continuous variables), and for changes between time 1 and time 2 in BMI, physical activity (nonactive/nonactive, nonactive/active, active/nonactive, active/active), smoking status (current/current, current/noncurrent, noncurrent/current, noncurrent/noncurrent), and habit of eating breakfast (no/no, no/yes, yes/no, yes/yes). To convert triglyceride values to mmol/L, multiply by 0.0113. Incidence rates and hazard ratios (with 95% CIs) are given in Table 3.

by using a multivariate model that was further adjusted for the changes in BMI and lifestyle variables (physical activity, smoking, and habit of eating breakfast). Young men who had low triglyceride levels at time 1 had a 3.81-fold (CI, 0.96 to 15.31) or 6.76-fold (CI, 1.34 to 33.92) greater risk for CHD within the 5.5-year follow-up if their second triglyceride measurement (at time 2) increased to intermediate or high levels, respectively, compared with the low/low group. The risk for CHD for men with low levels of triglycerides at time 2 was modified by their time-1 values, being 3.88-fold (CI, 1.04 to 22.50) and 4.90-fold (CI, 1.01 to 24.55) higher if previous triglyceride (time 1) levels were intermediate or high, respectively, compared with the low/low group. The risk for CHD in men with initially high triglyceride levels (at time 1) changed if triglyceride levels subsequently decreased to intermediate or low levels at time 2 (6.84-fold [CI, 1.95 to 23.98] or 4.90-fold [CI, 1.01 to 24.55], respectively) or remained high (8.23-fold [CI, 2.50 to 27.13]), compared with the low/low group. These hazard ratios were independent of the *changes* in BMI and the other lifestyle variables (smoking status, physical activity, and habit of eating breakfast).

Table 3. **Incidence Rates and Hazard Ratios of Coronary Heart Disease, by Tertile of Triglyceride Level and Time of Measurement***

Variable	Low: Time 1				Intermediate: Time 1				High: Time 1			
	Population at Risk, *n*	Events, *n*	Incidence Rate per 10 000 Persons	HR (95% CI)	Population at Risk, *n*	Events, *n*	Incidence Rate per 10 000 Persons	HR (95% CI)	Population at Risk, *n*	Events, *n*	Incidence Rate per 10 000 Persons	HR (95% CI)
Low: Time 2	2846	4	14.1	1	1230	8	65	3.88 (1.04–22.50)	402	5	124.4	4.90 (1.01–24.55)
Intermediate: Time 2	1266	7	55.3	3.81 (0.96–15.31)	1992	23	115.5	5.40 (1.57–18.63)	1271	20	157.4	6.84 (1.95–23.98)
High: Time 2	388	6	154.6	6.76 (1.34–33.92)	1305	29	222.2	9.06 (2.65–30.90)	2840	56	197.2	8.23 (2.50–27.13)

* Multivariate model, as described in the legend of Figure 1, was also adjusted for changes in lifestyle variables. HR = hazard ratio.

DISCUSSION

In our follow-up study of more than 13 000 young men, we estimate the association of baseline values and changes in triglyceride levels with CHD. The results suggest that information on triglyceride levels at 2 time points 5 years apart are clinically relevant for assessing the risk for CHD. Among young men with triglyceride levels lower than 3.39 mmol/L (<300 mg/dL) who were not receiving lipid-lowering therapy, changes in triglyceride levels were statistically significantly associated with alterations in BMI, physical activity, and the habit of eating breakfast. These findings corroborate triglycerides as a sensitive marker of lifestyle changes. However, a substantial proportion of the CHD risk remained attributable to changes in triglyceride levels during the subsequent 5.5 years of follow-up, independent of the associated alterations in BMI and lifestyle habits, suggesting an independent cumulative effect. Collectively, these findings highlight the predictive value of follow-up triglyceride measurements for CHD risk assessment in apparently healthy young men and may assist in estimating the potential value of lifestyle interventions for the primary prevention of CHD.

The strengths of the MELANY study include its prospective design; detailed, uniform, and systematic follow-up assisted by a centralized, computerized database; the use of a well-defined "hard" clinical end point (angiography-proven CHD); the follow-up measurements of blood and lifestyle variables by using a standard questionnaire in a single center and laboratory; and the direct measurement of BMI (rather than self-reported weight and height).

Several limitations of the study warrant consideration. First, assessment of triglyceride levels at each time point was based on single measurements. Given the high level of intraindividual variability in triglyceride measurements (16, 17), the observed associations between triglycerides and CHD might underestimate the true strength of the association. Yet, the relatively large cohort may alleviate this limitation, and the association between changes in triglyceride levels and clinical variables (**Figure 1**) suggest that assigning persons to different triglyceride groups could not be a mere consequence of measurement error. Second, the MELANY cohort of career military personnel is a selected group of healthy young men. However, the characteristics of the population are remarkably similar to those of young men from various industrialized countries (18–22), and the relatively homogeneous environment to which participants in our study were exposed might reduce the effects of unknown confounders. Third, although changes in lifestyle variables were associated with changes in triglyceride levels, we still cannot claim a causal link between change in triglyceride level and CHD risk given the observational nature of the study. Finally, in assessing the contribution of changes in triglyceride levels to the CHD risk, we could control only for associated changes in those few lifestyle variables that were available, which may limit the validity of concluding that change in triglyceride levels affects CHD risk independent of lifestyle factors.

Our results suggest a stronger association between triglycerides and CHD among men in their 40s compared with older-age cohorts. A recent meta-analysis of studies (mean participant age at entry, 56.6 years; mean follow-up, 12.1 years) yielded an adjusted odds ratio of 1.72 for the extreme tertiles of triglyceride levels (1). A meta-analysis of prospective studies conducted in the Asia-Pacific region (6) indicated that participants grouped in the highest fifth of triglyceride levels had a 1.8-fold greater risk for CHD. In the Framingham study (3), a 2-fold increase in CHD risk was reported in patients with triglyceride levels ranging from 2.8 to 4.5 mmol/L (250 to 400 mg/dL), compared with patients with triglyceride levels ranging from 0.6 to 1.1 mmol/L (50 to 100 mg/dL). In the Copenhagen Male Study (5), middle-aged (age >54 years) white men with fasting triglyceride levels of 1.6 mmol/L or greater (≥142 mg/dL) had a statistically significant adjusted risk ratio for CHD of 2.2. In the Lipid Research Clinics Follow-up Study (23), triglyceride levels showed no independent association with coronary death, but a stronger association has been noted in a subgroup of younger participants. The apparently stronger association reported in our study (adjusted hazard ratio, 4.05 when comparing men with triglyceride levels >1.9 mmol/L [>164 mg/dL] with those with triglyceride levels <0.7 mmol/L [<66 mg/dL] [**Table 2**]) could be explained by the younger age of the cohort, which means that the reference group was a particularly low-risk group, and by the proactive approach (angiography-proven CHD) used to screen for and diagnose CHD.

A unique element of our study is the follow-up triglyceride measurements 5 years after enrollment. This may be used as follows. If a previous triglyceride measurement is available, current values can be looked at as the time-2 determination. In this case, current high triglyceride levels are associated with a 6.8- to 9.1-fold increase in CHD risk, compared with the stable low levels. However, if current levels are intermediate or low, the past triglyceride level modifies the risk associated with current measurements: A current low triglyceride level may still indicate a 4.9-fold elevated risk for CHD if past levels were high. We used the first available triglyceride measurement as the time-1 determination. Future changes in triglyceride levels modify CHD risk at any level of the time-1 value. For example, a presently low triglyceride level would still be associated with a 3.8- or 6.8-fold increased risk for CHD if a future triglyceride level would place the patient in the low/intermediate or low/high subgroup, respectively. Furthermore, a present triglyceride value within the high tertile can be associated with a 8.23-, 6.84-, or 4.90-fold risk for CHD if a second measurement 5 years later would place an individual in the high/high, high/intermediate, or high/low subgroups, respectively, compared with those with stable low-tertile levels. Finally, a 5.4-fold increase in CHD risk

was observed already in men with median triglyceride levels of 1.2 mmol/L (104 mg/dL) and 1.3 mmol/L (118 mg/dL) at time 1 and time 2, respectively, compared with men with low triglyceride levels at both time points. This result highlights the association between moderately high triglyceride levels within the normal range and the development of CHD, further suggesting a cumulative effect of exposure to high triglyceride levels.

Atherosclerosis begins in childhood and progresses gradually throughout adulthood. Data from the Pathobiological Determinants of Atherosclerosis in Youth study (24) suggest that increased fatty streaks occur in the right coronary arteries of approximately 30% of apparently healthy individuals 30 to 34 years of age who died of noncardiovascular causes. Increased triglyceride levels are directly associated with atherogenic chylomicron and very-low-density lipoprotein remnants and more dense atherogenic LDL particles (25). The difference in CHD risk between the high/high and the high/low groups may suggest that decreasing triglyceride levels dramatically affects CHD risk within a relatively short period given the slow progression of CHD. As explained earlier, in this young age group, high triglyceride levels may identify those exhibiting accelerated atherosclerosis, resulting in clinically significant CHD by the mid-40s. A decrease in the rate of atherosclerosis per se, as well as other related processes with more short-term effects (such as the known interaction of triglycerides with the fibrinolytic–coagulation system [26]), may be involved. In previous randomized clinical intervention trials, the intervention affected several lipid components and lipoproteins classes simultaneously (27) rather than merely lowering triglyceride levels—this is why the isolated contribution of plasma triglyceride levels to the pathogenesis of CHD is still difficult to decipher.

Within 5 years, the median levels of triglycerides in the 3 tertiles have increased in our cohort from 0.68, 1.17, and 2.08 mmol/L (60, 104, and 184 mg/dL) to 0.79, 1.33, and 2.48 mmol/L (70, 118, and 220 mg/dL), respectively, suggesting a cohort effect. Analyses of data from the National Health and Nutrition Examination Survey (28) showed a similar increase in mean age-adjusted triglyceride levels in the U.S. population between 1988 to 1994 and 1999 to 2002, which may be attributed to increased prevalence of obesity in the U.S. population (29). Against this background, the subgroup that has experienced a medication-independent reduction in triglyceride levels during follow-up is a unique group for study. In this group, the decrease in triglyceride levels between time 1 and time 2 (the high/low group) was associated with reduced BMI, a diminished proportion of smoking, and an increase in physical activity and eating breakfast, all of which are related to adopting a healthier lifestyle (30). Thus, triglycerides might be a valuable biomarker of lifestyle (and/or weight) changes. However, the association of triglycerides with CHD risk remained statistically significant even after controlling for changes in BMI, smoking status, eating breakfast, and physical activity—suggesting that triglycerides also exert a lifestyle-independent effect on atherosclerosis.

One clinical implication of our study is in highlighting the value of integrating both previous and current values of triglycerides: Changes in triglyceride levels over time beyond those expected (that is, change represented herein by the cohort effect) modify the strength of the association of triglycerides with incident CHD, suggesting a cumulative effect. Furthermore, our study provides compelling evidence for the potential value of targeting triglyceride levels when trying to reduce CHD risk in young men. Targeted intervention trials are needed to prove that lowering triglyceride levels reduces CHD risk in young adult men.

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