Changes in triglyceride levels over time and risk of type 2 diabetes in young men

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Objective: The association between changes in triglycerides (TG) over time and diabetes is unknown. We determined whether two TG determinations obtained 5 years apart can predict incident type 2 diabetes.

Research Design and Methods: Baseline TG (Time1) and 5 years later (Time2), followed by subsequent follow-up of 5.5 years were measured among 13,953 apparently healthy men (age 26-45) with TG<300mg/dL(3.39mmol/L).

Results: During 76,742 person-years, 322 diabetes cases occurred. A multivariate model adjusted for age, body mass index (BMI), total cholesterol:HDL-cholesterol ratio, family history of diabetes, fasting glucose, blood pressure, physical activity, and smoking status, revealed a continuous independent rise in incident diabetes with increasing Time1 TG levels, (P trend<0.001). Men in the lowest tertile of Time1 TG who progressed to the highest tertile over follow-up (Low-High), exhibited hazard ratio (HR) of 12.62(95%CI;3.52–31.34) compared to those remaining in the lowest tertile at both time points (reference group: Low-Low). While men who were at the top TG tertile throughout follow-up (High-High) had a HR for diabetes of 7.08(95%CI;2.52–14.45), those whose TG decreased to the lowest tertile (High-Low) exhibited HR of 1.97(95%CI;0.67–6.13). Alterations in TG during follow-up were associated with changes in BMI, physical activity, and breakfast-eating habit (P<0.05), but remained an independent modifier of diabetes risk even after adjustment for such changes.

Conclusions: Two measurements of fasting TG obtained 5 years apart can assist in identifying apparently healthy young men at increased risk for diabetes, independent of traditional risk factors and of associated changes in BMI and life-style parameters.
Elevated triglycerides (TG) is a common dyslipidemic feature accompanying type 2 diabetes and pre-diabetic states (1). Fasting TG of 150mg/dL (1.70mmol/L) or more is one of five accepted criteria for defining persons at high risk for cardiovascular disease and type 2 diabetes, arguably termed the "metabolic syndrome" (2-4). Some evidence suggests that fasting TG can aid in predicting future type 2 diabetes (5, 6). Yet, this was mainly shown when TG was combined with additional clinical parameters such as body mass index (BMI), blood pressure (7), and other classical risk factors for cardiovascular disease (8, 9), or with "high-normal" fasting plasma glucose levels (10).

The level of circulating TG is highly influenced by the fed-fasted state and insulin sensitivity, and by life-style factors such as diet and physical activity (1, 11, 12). These render TG a highly sensitive life-style biomarker at a given time point, but suggest that a TG determination at a single time-point may inaccurately reflect long-term triglyceridemia, particularly if life-style modification occurred during follow-up. Whether assessing TG at more than one time-point could improve the association between TG and diabetes is largely unknown. Recently we reported in a large cohort of young (age 26-45) men that significant changes between two fasting TG measurements obtained 5 years apart corresponded to alterations in life-style parameters (13). Furthermore, such changes modified the risk for heart disease attributed to elevated TG levels (13).

Most studies assessing the risk factors for type 2 diabetes have overlooked the parameters specifically relevant for the apparently healthy, young adult population. Although the incidence rate of diabetes in this group is relatively low, recent studies suggest a surge in type 2 diabetes in young adults (14). Identifying persons at high risk of developing diabetes in this group is therefore challenging, but with a potentially significant benefit if preventive measures are employed. Here, we utilized the cohort of young, apparently healthy men (10, 13) to assess whether baseline TG measurements as well as life-style-associated changes in TG over time can predict the risk of diabetes.

**METHODS**

The **MELANY cohort**: The MEtabolic, Life-style, And Nutritional assessment in Young adults (MELANY) study is based on a computerized database established in 1992, which includes all medical records of Israel Defense Forces (IDF) career service personnel, as detailed previously (10, 13). More than 95% of the population are Caucasians. Every visit to the staff periodic examination center (SPEC) participants complete a detailed questionnaire assessing demographic, nutritional, lifestyle, and medical parameters. Height, weight, and blood pressure are recorded by trained medics, venous blood samples are obtained after 14 h fasting, and a complete physical examination is performed by physicians. Between visits, primary care for IDF personnel is obtained at designated military clinics, and all medical information is recorded on the same central database.

The IDF Medical Corps Institutional Review Board approved this study, which was exempt from the requirement for written informed consent based on maintaining participants' anonymity. IDF authorities did not censor or limit any aspect of the study design, analyses, and reporting.

**Criteria for inclusion, exclusion, and outcome:** Women were not included, as the database includes an insufficient number of incident cases of diabetes to facilitate meaningful analyses.

Included are apparently healthy men 26–45-years-of-age, with fasting triglycerides less than 300mg/dL (3.40mmol/L) at their initial visit. Of 15,165 men who had at least
two visits, the following were excluded: 227 with diabetes and 17 with coronary heart disease at baseline; 686 with triglycerides of 300mg/dL (3.40mmol/L) or more, since they were referred to nutritional/pharmacological intervention. An additional 282 men were excluded since they received chronic medications.

Two analyses are presented: Analysis-1 determines the association between TG values at enrollment (Time1) and incident diabetes during 10-years of follow-up. Analysis-2 evaluates the effect of change in fasting TG between two measurements: 'Time1' at enrollment and 'Time2' obtained 5 years later. In this analysis, Time2 value became the 'baseline measurement' (Time1 turning into a 'historical', pre-baseline determination), and incident diabetes was assessed in the subsequent 5.2 years of follow-up. For analysis-1 13,953 men were included, and the predictive value of Time1 TG measurement for incident diabetes was assessed. For analysis-2 additional 413 men were excluded: 363 did not have TG results at Time2; 38 and 12 men were diagnosed with diabetes or coronary heart disease, respectively between Time1 and Time2. Therefore analysis-2 included 13,540 men.

Diagnosis of type 2 diabetes was defined as the primary study end-point. All cases of diabetes were diagnosed according to the American Diabetes Association Expert Committee criteria(15). The diagnosis of all 322 incident cases of diabetes was based on two fasting plasma glucose levels of 126mg/dL (7.00mmol/L) or greater. Endpoint determination was made at each sequential SPEC visit by measuring fasting glucose levels. Between visits, diabetes was diagnosed by the IDF primary care physician(15), and was reviewed by a military physicians' committee.

Laboratory Methods: Fresh blood samples were analyzed in a core laboratory facility. The laboratory is authorized according to international quality standard ISO-9002 and is subject to periodic quality control assessment (by the British National External Quality Assessment Service). For venous fasting plasma glucose determinations, blood samples were collected in sodium fluoride-containing tubes. All biochemical parameter measurements were performed using a BM/Hitachi917-automated analyzer (Boehringer Mannheim GmbH).

Statistical Analysis: A general linear model was used to assess the age-adjusted means and proportions of the population's characteristics across quintiles of TG, and to fit the median of the quintiles as a continuous variable to estimate the trend of variables across quintiles. For analysis-1 we conducted a Cox proportional-hazards analysis during each interval of follow-up to estimate the hazard ratios and 95 percent confidence intervals(CI) for the development of diabetes according to TG levels of Time1 (first measurement). In step-wise models values for body mass index (BMI), fasting plasma glucose, and family history of diabetes were added separately into the age-adjusted model, to evaluate the potential role of each as a confounder. In the final multivariate model, we controlled for age, BMI, total cholesterol:HDL-c, family history of diabetes, fasting plasma glucose, mean arterial blood pressure, physical activity, and smoking status.

For analysis-2 TG levels at both Time1 and Time2 were cross-classified by tertiles. In parallel, we determined changes in BMI, smoking status, physical activity, and pattern of eating breakfast between Time2 and Time1. Next, we evaluated the joint risk attributed to TG levels at Time1 and Time2, categorized according to Low, Intermediate, and High tertiles, and used the group of men in the Low-Low TG levels as a reference group (HR=1). To evaluate the direct association of TG changes, we further adjusted for the changes between Time2 and
Time1 in BMI, physical activity, smoking, and eating breakfast pattern in a final multivariate model. In this analysis we added the calculated differences (deltas) of BMI, and for categorical variables we created 4 groups, describing the positive or negative states at Time1/Time2 of smoking, physical activity, and eating breakfast pattern (yes/yes, yes/no, no/yes, no/no). All statistical analyses were performed using SAS statistical software, version 9.1.

RESULTS

We analyzed data from 13,953 apparently healthy men (mean age, 32.4 years; range 26 to 45) with TG levels less than 300 mg/dL (3.40mmol/L) at enrollment (Time1). Age-adjusted values for BMI, LDL-c, and fasting plasma glucose levels, were more likely to increase across TG quintiles, as well as the proportion of men with a family history of diabetes and percent of current smokers (Table 1). Concomitantly, levels of HDL-c, the proportion of men who were physically active or who reported eating breakfast regularly, were more likely to decrease across quintiles of TG.

Analysis-1: During nearly 77,000 person-years (mean follow-up, 10.5 years) there were 322 documented incident cases of type 2 diabetes. Age-adjusted hazard ratios (HR) for diabetes increased across quintiles of TG (Table 2), reaching 4.77 (95%CI: 3.22–7.06) for the top quintile compared to the bottom quintile (P trend <0.001). Further adjustment for BMI attenuated the risk values to 2.61 for the top quintile (95%CI; 3.22–7.06) for the top quintile compared with the bottom quintile (P trend <0.001). Further adjustment for BMI attenuated the risk values to 2.61 for the top quintile (95%CI; 3.22–7.06) for the top quintile compared with the bottom quintile (P trend <0.001). Further adjustment for BMI attenuated the risk values to 2.61 for the top quintile (95%CI; 3.22–7.06) for the top quintile compared with the bottom quintile (P trend <0.001).

Analysis-2: We next evaluated the association between changes in TG and diabetes risk. We analyzed data from 13,540 men as detailed in the Methods section. TG at Time1 and Time2 was divided into tertiles (Low, Intermediate, and High), and diabetes risk was assessed using the multivariate model described above during subsequent mean 5.2 years after Time2. Consistent with analysis-1 (Table 2), the risk of incident diabetes was 2.01-fold higher (95%CI:1.20–4.38) in the High tertile of Time1 TG compared to the Low tertile (P trend <0.001). Adding Time2 TG resulted in nine groups cross-classified according to TG at both time points, for which the HR for diabetes was calculated and expressed using persons with low tertile TG at both time points (Low-Low) as reference group (Figure 1A). In this group the incidence rate of diabetes during follow-up was 52.2 cases per 10,000 persons (16 cases out of 3066). In the multivariate model, which now also controlled for the time interval between Time1 and Time2, the HR for diabetes was 3.17 (95%CI;1.09-8.67) and 7.08 (95%CI; 2.52–14.45) in persons with TG levels at both time points in the Intermediate or High tertile levels, respectively. By contrast, persons who had low Time1 TG, but whose TG level increased to Intermediate or
High tertiles in Time2, were 4.47 (95%CI; 1.37–9.48)- and 12.62 (95%CI; 3.52–31.34)-times more likely to develop diabetes compared to those remaining with low TG at Time2 (Low-Low). Importantly, Time2 TG values also modified diabetes risk in those with TG in the High tertile at Time1: HR for diabetes was 7.08 in the High-High compared to the Low-Low group, but decreased to 4.28 (95%CI; 1.42–9.69) and 1.97 (95%CI; 0.67–6.13) in persons whose Time2 TG decreased to Intermediate or Low tertile levels, respectively.

In a recent paper (13), we characterized the Low-Low and High-High, as well as Low-High and High-Low groups, representing persons with stable or dynamic TG levels during follow-up, respectively. Men in the Low-Low TG group were more likely to retain a lower BMI, maintain high physical activity parameters, and continue a high percent of reported habit of eating breakfast. Importantly, men in the High-Low group, i.e., whose TG decreased between Time1 and Time2 from the high to the low tertile without lipid-lowering medication, were the only group of the four whose BMI decreased. Furthermore, they were the group who exhibited the highest increase in physical activity and percentage of persons reporting eating breakfast regularly.

To assess whether changes in TG had a risk-modifying effect beyond changes in BMI, physical activity, smoking, and eating breakfast habit, HR for diabetes were further adjusted for the change in these parameters. In this model, dynamic changes in TG remained a significant modifying factor of the risk of incident diabetes: Persons whose TG levels progressed from the Low to the High tertile had an HR for diabetes of 7.32 (95%CI; 2.62–20.70) compared to those remaining at the Low TG tertile at both time points. Conversely, in those whose TG levels decreased from the High to the Low tertile, the HR for diabetes was 1.56 (95%CI; 0.33–7.40), hence, not significantly different from those who retained low TG levels at both time points. The comparison to the association between changes in TG and heart disease in a model controlling also for the change in BMI and lifestyle factors in the same population (13) is described in Figure 1B. Stable high TG level (High-High group) increased the risk of heart disease 8-fold compared to the stable low TG group, and to diabetes by 4-fold. However, young men with an initial high TG level followed by lifestyle-associated decrease in TG level to the low level at Time2 (High-Low group), had a 4.9 HR for heart disease, representing a lower risk than observed in the High-High group, but still significantly elevated compared to the Low-Low group. In contrast, risk of diabetes among the High-Low group was statistically indistinguishable compared to men with stable low-tertile TG.

CONCLUSIONS

Three major observations emerge from this study on TG as an independent risk predictor for future type 2 diabetes in young men. First, baseline TG level was found in our large-scale cohort of young men to be an independent risk factor for diabetes during over 10 years of follow-up. Second, two TG measurements 5 years apart reveal that in persons whose TG changed diabetes risk was correspondingly modified: diabetes risk increased over 12-fold if TG level increased between Time1 and Time2 from the Lowest to the top tertile. Conversely, in persons with TG at the High tertile in the first determination, diabetes risk changed from HR of 7 to less than 2 if the second TG measurement was in the Low tertile range (compared to the Low-Low group). Importantly, such TG changes were not related to initiation of lipid lowering therapy, but instead, were associated with measurable changes in lifestyle parameters (13). This seemingly tight association between dynamic
TG level and diabetes risk not only strengthens the role of TG in determining diabetes risk, but also signifies TG as a sensitive biomarker for life-style habits related to the risk of developing diabetes. Thirdly, fasting TG predicts incident diabetes in a more "acute" manner than it associates with heart disease. This is reflected by i. the fact that people with initial low but subsequent high TG have higher HR even than those with stable high levels at both time points. ii. In the High-Low group, who exhibited positive lifestyle changes, a HR statistically indistinguishable from those with stable low TG levels was observed. Both phenomena are not present in the association between changes in TG and heart disease in the same population (Figure 1B). Thus, although type 2 diabetes and heart disease share multiple common risk factors, a shorter "metabolic memory" of TG levels may underlie the pathogenesis of diabetes versus heart disease, at least in the young apparently healthy male population.

The strengths and weaknesses of this cohort have been discussed in detail in previous publications (10, 13). Worth mentioning here, is that baseline measurements are highly similar to other published cohorts of young adults(16, 17), possibly excluding the "healthy worker bias" in our cohort. Secondly, although we could not draw conclusions regarding the relation between TG and diabetes in women, a previous study assessing a cohort of 39–65-year-old Swedish women also reported TG as an independent diabetes risk factor (5). Thirdly, although laboratory parameters do not include advanced measurements such as circulating insulin levels, they constitute a set of routine tests typically available to the practicing physician, but which are not routinely screened in young adults. Finally, the large size of the cohort enabled us to define sub-groups with a relatively high risk for developing type 2 diabetes in a population otherwise characterized by a low background incidence rate of the disease.

Baseline TG were found to be an independent risk factor for diabetes in our cohort of young men, even after adjustment for metabolic parameters, clinical variables, and life-style indices. Many of these factors are known to be tightly correlated with TG (11, 12). Consistently, controlling for these parameters in the step-wise multivariate model demonstrated a marked attenuation of the diabetes risk associated with higher quintiles of TG. Nevertheless, a significantly elevated HR was observed in the multivariate model for persons with TG at the fourth and fifth quintiles, [i.e., already at TG levels above 120mg/dL (1.36mmol/L)] compared to those at the bottom quintile [TG of 66mg/dL (0.75mmol/L) or lower]. The notion that TG constitutes an independent diabetes risk factor was proposed by several studies on cohorts of older persons or of women (5, 6, 8, 9). Here we also show the relevance of TG measurements for diabetes risk assessment in the young adult, apparently healthy male population.

The modifying effect of changes in TG on diabetes risk provides potential new insights on diabetes prevention strategies and mode of action of life-style modification. Compared with pharmacological intervention with metformin, life-style modification showed superior efficacy in preventing diabetes (18). The close association observed between changes in TG and alterations in BMI, physical activity, and eating habits (13), suggests TG as a sensitive life-style biomarker that is relevant to diabetes risk assessment. Intriguingly, dynamics in TG levels remained a significant determinant of diabetes risk even after adjusting for the accompanying changes in BMI, smoking, physical activity, and eating breakfast (Figure 1B). This may suggest an effect of TG on diabetes risk that is independent of life-style factors altogether and, indeed, conditions such
as familial hypertriglyceridemia suggest that genetic factors can determine TG levels. Alternatively, life-style factors that were unaccounted for in this study may mediate the change in TG and/or the associated modification of diabetes risk.

Circulating TG levels represent a balance between TG synthesis and utilization (1). These are greatly affected by life-style factors (nutritional habits, exercise), and by insulin sensitivity. Consistently, increasing TG, particularly when accompanied by low HDL, was shown to be a surrogate marker of insulin resistance (19), a strong predisposing condition for type 2 diabetes. Furthermore, high free fatty acids potentially derived from TG may further deteriorate insulin sensitivity (20), creating a vicious cycle between TG and insulin resistance. Such a process may have operated to acutely increase diabetes risk when TG levels progress during follow-up from the lowest to the highest tertile, potentially surpassing the excessive risk associated with persistently elevated TG levels. Finally, improving insulin sensitivity and glucose tolerance by pharmacological means, decreased circulating free fatty acids or TG (21-23). Thus, although our observational study falls short in unraveling cause–effect relationships, it is tempting to speculate that lowering TG levels, either pharmacologically or through life-style modification, may constitute a viable means to attenuate diabetes risk in apparently healthy young men.

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Table 1: Baseline Characteristics of 13,953 Young Adult Men Across Quintiles of Triglycerides (Time1)*

| Quintile | Quintile2 | Quintile3 | Quintile4 | Quintile5 | P value for trend | Total (mean) |
|----------|-----------|-----------|-----------|-----------|------------------|--------------|
| Quintile1 (N=2844) | Quintile2 (N=2739) | Quintile3 (N=2789) | Quintile4 (N=2795) | Quintile5 (N=2786) | | (N=13,953) |
| Triglyceride level (mg/dL) | | | | | | 116.9 |
| Mean | 52±9.6 | 78.1±6.9 | 104±8.4 | 139±12.6 | 212±35.7 | |
| Median [25th; 75th] | 53 [45;60] | 78 [72;84] | 104 [97;111] | 138 [128;150] | 204 [182;236] | |
| Range | 30-66 | 67-90 | 91-119 | 120-163 | 164-299 | |
| Age | 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 (yr) | 10.4 | 10.3 | 10.1 | 10.6 | 10.7 | 0.58 |
| Age adjusted: | | | | | | |
| Family history of Type 2 diabetes† (% | 16.0 | 16.7 | 16.7 | 21.0 | 23.2 | <0.001 |
| Body-mass index (kg/m2) | 24±3.1 | 24.7±3.4 | 25.5±3.5 | 26.3±3.5 | 27.3±3.6 | <0.001 |
| Blood pressure (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±9.1 | 78.9±9.7 | <0.001 |
| Mean 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 | 22.0 | 27.7 | 29.7 | 32.9 | 37.0 | <0.001 |
| Former | 20.0 | 18.5 | 22.0 | 19.8 | 20.5 | 0.81 |
| Physical activity | | | | | | |
| >60 min/week (%) | 13.0 | 11.8 | 9.0 | 9.3 | 6.6 | <0.001 |
| min/week (mean) | 91 | 89 | 88 | 81 | 83 | 0.057 |
| Eating breakfast # (%) | 22 | 19.3 | 17.7 | 17.9 | 16.4 | 0.002 |
| Biomarkers | | | | | | |
| HDL cholesterol (mg/dL) | 54±11.2 | 48.2±10.5 | 47.1±9.8 | 44.3±9.8 | 40.8±9.6 | <0.001 |
| TC:HDL ratio | 3.70±0.9 | 4.28±1.1 | 4.80±1.3 | 5.34±1.5 | 6.03±1.6 | <0.001 |
| FPG (mg/dL) | 89.0±9.7 | 90.3±9.6 | 91.4±9.8 | 92.0±10.1 | 93.3±10.3 | 0.005 |

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* The first, out of two repeated measurements of triglycerides within a 5 years interval. Plus-minus values are means ± SD. To convert the values for triglycerides to millimoles per liter, multiply by 0.0113. To convert the values for glucose to millimoles per liter, multiply by 0.0555. To convert the values for cholesterol to millimoles per liter, multiply by 0.0259.
† A family history for type 2 diabetes indicates the presence of type 2 diabetes in a first-degree relative.
# Eating breakfast denotes the % of persons reporting eating breakfast regularly.
### Table 2: Hazard Ratios for Type 2 Diabetes among 13,953 Young Adult Men Across Quintiles of triglycerides levels

|                  | Quintile 1 | Quintile 2 | Quintile 3 | Quintile 4 | Quintile 5 | P Value for trend |
|------------------|------------|------------|------------|------------|------------|------------------|
| Triglyceride (mg/dL) | 30-66      | 67-90      | 91-119     | 120-163    | 164-299    |                  |
| Person years of follow-up | 15,941     | 15,115     | 15,340     | 15,428     | 15,100     |                  |
| No. of incident cases of type 2 diabetes | 22         | 41         | 43         | 79         | 137        | <0.001           |
| Adjusted risk ratio (95%CI)* |           |            |            |            |            |                  |
| Age               | 1          | 1.49       | 1.72       | 2.88       | 4.77       | <0.001           |
|                   | (0.94-2.35)| (1.10-2.68)| (1.90-4.36)| (3.22-7.06)|           |                  |
| Age and BMI       | 1          | 1.21       | 1.34       | 1.89       | 2.61       | <0.001           |
|                   | (0.77-1.93)| (0.86-2.08)| (1.24-2.87)| (1.75-3.91)|           |                  |
| Age, BMI and FPG  | 1          | 1.16       | 1.23       | 1.69       | 2.13       | <0.001           |
|                   | (0.73-1.83)| (0.79-1.92)| (1.11-2.57)| (1.42-3.19)|           |                  |
| Age, BMI, FPG and family history of diabetes# | 1          | 1.18       | 1.25       | 1.72       | 2.10       | <0.001           |
|                   | (0.75-1.87)| (0.80-1.95)| (1.13-2.61)| (1.40-3.14)|           |                  |
| Multivariate†     | 1          | 1.15       | 1.24       | 1.72       | 2.11       | <0.001           |
|                   | (0.73-1.82)| (0.78-1.94)| (1.12-2.64)| (1.38-3.22)|           |                  |

*CI denotes confidence interval.

# family history of diabetes is a reported first-degree relative with type 2 diabetes

† The multivariate Cox regression model was adjusted for age, BMI, TC:HDL-c ratio, fasting plasma glucose, 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, non-current smoker, or missing information).

To convert the values for triglycerides to millimoles per liter, multiply by 0.0113.
**Figure Legend**

**Figure 1: Association between changes in triglycerides and future morbidity (analysis-2)**

A. *Multivariate model showing the association between fasting serum triglyceride levels obtained at 2 measurements 5 years apart* and incidence of type 2 diabetes. The multivariate Cox regression model was adjusted for age, body-mass index, TC:HDL-c ratio, fasting plasma glucose, time lapse between Time1 and Time2 determinations, and mean arterial blood pressure as continuous variables. Physical activity (yes, no, or missing information), family history of diabetes (positive, negative, or missing information), and smoking status (current, non-current smoker, or missing information). To convert the values for triglycerides to millimoles per liter, multiply by 0.0113.  

B. *Multivariate model comparing Hazard Ratios for Diabetes or Heart Disease associated with fasting triglycerides in 2 measurements 5 years apart*. The model was adjusted, as in A, 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). In addition, the model was adjusted also for the 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). The results regarding Heart Disease have been published in (13).

* Time 1 is determination at enrollment; Time 2 is determination obtained 5 years after Time 1 determination. In this analysis (analysis-2) follow-up begins from Time 2, as detailed in the Methods section.
Figure 1

A

Time 1 triglyceride levels, tertiles (mg/dL)

| HR (mg/dL) | Low | Intermediate | High |
|------------|-----|--------------|------|
| 1          | 4.47| 3.12         | 1.97 |
| 2.20       | 7.00| 7.06         |

B

| Diabetes  | Low Time 2 | High Time 2 | Heart Disease | Low Time 2 | High Time 2 |
|-----------|------------|-------------|---------------|------------|-------------|
| Low Time 1| 1          | 7.32        | 1             | 6.76       |
|           | (2.62-25.70)|             |               | (1.34-33.52)|             |
| High Time 1| 1.96     | 4.10        | 4.99          | 8.23       |
|           | (0.55-7.4) | (1.93-8.73) | (1.61-24.55) | (2.50-27.13)|             |