Fasting Serum Triglycerides Predict New Onset Diabetes in Healthy Middle-Aged Men

A 35-year follow-up of a Norwegian cohort

Running title: Triglycerides Predict New Onset Diabetes

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Abstract

Objective: We tested the hypothesis that fasting serum triglycerides (TG) predict new onset diabetes (NOD) in apparently healthy men, and that physical fitness (PF) modifies this association. Secondly, we aimed to compare the predictive ability of TG with TG/HDL-cholesterol (TG/HDL) ratio for NOD.

Research Design and Methods: TG was measured 1972-1975 in 1962 healthy men aged 40-59 years with fasting blood glucose (FBG) levels (< 6.1mmol/l). Data from an almost identical follow-up, performed in 1979-1982, including HDL measurements, were used to compare the predictive impact of TG with TG/HDL ratio. PF was measured using a cycle ergometer exercise test, and defined as total work divided by body weight (kJ/kg). Survival models were analyzed in TG tertiles, and relative risks were adjusted for age, BMI, FBG, family history of maternal diabetes mellitus, and PF.

Results: Incidence of NOD was 202 cases (10.3%) during 35 years follow-up. The highest TG tertile was associated with increased risk of NOD compared to the lowest tertile (hazard ratio [HR] 1.90, [95% CI] 1.32-2.79) and 1.73 [1.20-2.54]) without and with adjustments for PF, respectively. HR for risk of NOD (up to 28 years follow-up) per SD increase in log (TG) and log (TG/HDL ratio) were 1.43 (1.18-1.73) and 1.49 (1.23-1.81), respectively.

Conclusions: Fasting serum TG is a strong long-term predictor of incident NOD among apparently healthy men, even after adjustments for physical fitness. The triglyceride/HDL ratio may be slightly better than TG alone to predict NOD.

Key Words: Epidemiology, lipids, diabetes, prediction, fitness.
Early identification of individuals at high risk of new onset diabetes (NOD) is important to facilitate preventive intervention. There is some evidence that high levels of fasting serum triglycerides (TG) predict NOD among both women and men (1-4). These studies have, however, used different inclusion criteria and methods for assessing TG-associated risk of NOD. Perry et al studied risk factors of NOD in a general population of middle-aged men, and Tirosh et al studied the TG-NOD association in young men (2, 5). The long-term prognostic ability of TG for NOD in healthy middle aged men has not been reported earlier.

*Physical fitness* (PF) and *physical activity* (PA) are only modestly correlated, but both high PF and high PA are associated with reduced risk of NOD (1, 6-9). Previous studies have only adjusted for self-reported PA when assessing the association between TG levels and the risk of NOD (1, 2, 5). High density lipoprotein cholesterol (HDL) levels are inversely associated with TG levels and directly associated with PF. HDL might therefore modify the TG-NOD risk association. To our knowledge, no study has evaluated the combined prognostic impact of TG, HDL and PF.

The aims of the present study were to test whether TG levels predict NOD in healthy middle-aged men and to assess whether PF modifies any association. Finally we also compared the predictive power of TG with the TG/HDL ratio.

**Research Design and Methods**

**Study population**

All apparently healthy men aged 40–59 years, working in five governmental agencies in Oslo, Norway, were invited to participate in a cardiovascular survey in 1972, and 2014 (86%) of 2341 eligible men agreed to participate and gave their informed consent. Employees with known diabetes, fasting blood glucose (FBG) levels > 7.8 mmol/l, cardiovascular- or other
chronic diseases, malignancy during the last five years and any chronic drug regimen were primarily excluded. The baseline examination was conducted from 1972 to 1975. Details about the selection and inclusion criteria have been reported elsewhere (10, 11).

In 1979-82; 1756 (91.5%) of all men had an almost identical examination on average 7.3 (range 4.5-9.5) years later except that FBG was not measured and HDL measured in most men (see below).

**Baseline examinations**

All participants answered an extensive questionnaire including queries on physical activity during working and leisure hours and on alcohol intake on the last two days prior to examination.

The examinations took place in the morning (between 07.00 AM and 11.00 AM). All had been requested to fast for at least twelve hours and abstain from smoking for eight hours. All followed the same examination program (10-12). TG was measured using a fluorimetric method and FBG by an enzymatic method (11-13). The disappearance rate of glucose ($k$-value) was measured in 1970 men (97.8%) performing intravenous glucose tolerance test (IVGGT) (12). After blood sampling, the participants went through a symptom limited cycle ergometer exercise test (10). PF was defined as exercise capacity in kcal divided by body weight (kg). HDL was measured (heparin-$Mn^{2+}$ (46 mmol/l) precipitation) in 1678 (95.6%) men. Incomplete measurement of HDL in 78 men was due to logistical reasons e.g. technical problems.

**Follow-up**

Morbidity data have been obtained after permission from all relevant Norwegian authorities and registered from the following sources: 1) data obtained during the 7.3 year follow-up, 2) a detailed postal questionnaire, asking for possible diseases and use of drugs, sent to earlier participants in 1987 (answered by 99% of men alive), 3) a third survey conducted in 1989-90,
4) a fourth survey in 1994-95 and 5) from two nationwide searches in the hospital files in all Norwegian hospitals of all men, applying their Norwegian social security number when searching in the hospital files. Thus all hospital records in all Norwegian hospitals were manually scrutinized on site, and relevant data were obtained from all sections of the files including outpatient records and letters from general practitioners. Cause-specific mortality data until Dec 31st 2007 have been obtained from Statistics Norway.

The diagnosis of NOD was based on data from clinical examinations and hospital records (see above). The time of diagnosis was defined as when a patient was registered with diabetes supported by FBG measurements in the diabetic range (> 7.8 mmol/l) and/or glucosuria or when he was started on blood glucose lowering drugs. Available clinical information including drugs, risk profiles of men who developed NOD and age at onset indicate that most cases were diabetes type 2.

Of the 2014 men who constitute the cohort, 52 were excluded in the present study of the following reasons: Eleven where date of NOD diagnosis remained unidentified, twenty-five with FBG > 6.1 mmol/l and sixteen who lacked FBG measurement because of technical problems. The men with FBG > 6.1 mmol/l were excluded because of possible impaired glucose tolerance at baseline (thirteen later developed NOD). The present study therefore includes 1962 men, 1936 (98.7%) of whom had an IVVGT.

**Statistical analyses**

Differences in baseline data between groups were tested by Student’s t-test or Pearson’s chi-square test according to data type. Kendal rank test was used to assess correlation (trend) between tertiles of triglycerides and baseline data. The risk of NOD in different tertiles of TG was estimated by Kaplan Meier plots and tested with log rank tests.

Cox proportional hazard analyses were performed to study the risk association between TG and NOD. Diagnostic plots of log S (t) versus log (t) indicated that the proportional hazard
assumption of the Cox model was acceptably fulfilled. Hazard ratios (HR, [95% CI]) were calculated between TG tertiles and/or for one standard deviation (SD) section increase in a variable (see results). Variables with skewed distribution were logarithmic transformed. Significant variables in univariate analyses (p<0.05) were entered into multivariate analysis and a final model reached by stepwise backward variable selection (Table 2). The main final model included adjustment for age, BMI, FBG and family history of maternal diabetes mellitus. All relative risks referred to are multiple adjusted unless otherwise stated.

Data from the 7.3 year follow-up on men who were still apparently healthy were used to compare the predictive ability of TG versus the TG/HDL-ratio according to baseline criteria (n = 1328). When entering log TG and log HDL simultaneously into Cox regression (multiple adjusted), log TG was significant (p=0.01) while log HDL was borderline significant (p<0.1). The regression coefficients were about equal in magnitude and of opposite sign, suggesting that log TG/HDL is a natural way of integrating the information from TG and HDL. FBG from the first examination was carried forward to the 7.3 year follow-up. All statistical analyses were performed using the JMP 9 (SAS Institute Inc., Cary, NC, USA).

**Results**

**Baseline characteristics**

Mean fasting serum TG for all 1962 men was 1.31 mmol/l (range 0.2-11.6) and 98 men had TG above 2.5 mmol/l. Men examined on Mondays (n=397) as compared to other weekdays had a higher mean TG (1.38 mmol/l versus 1.30 mmol/l (p<0.05) respectively) and also reported a more frequent intake of alcohol during the 2 days prior to examination (42.5% versus 17.6% (p<0.05) respectively).

Median follow-up until diagnosis of diabetes or end of observation was 28.5 years (range 0.3-34.3).
The proportion of current smokers, total cholesterol, systolic and diastolic blood pressure, FBG, BMI, resting heart rate and erythrocyte sedimentation were all associated with increasing TG levels, whereas PF and TG were inversely associated. Age and maximal heart rate at exercise were similar across TG tertiles (Table 1). The proportion of men who had a family history of mother with diabetes was numerically highest in the highest TG tertile.

**Predictors of NOD**

The incidence of NOD was 202 cases (10.3%) in total, 41 (6.0%), 50 (7.9%), and 111 (16.9%) in tertiles 1, 2 and 3, respectively.

Men in the highest TG tertile had the highest risk of NOD. (Figure 1). Further, the incidence of NOD among the 98 men with TG > 2.50 mmol/l was 27/98 cases = (27.6%). As outlined in Table 2, FBG and BMI were the strongest predictors of NOD, but also TG and PF were strong and significant predictors. TG and PF appeared to have similar predictive impact in multivariate analysis. The low number of men who had a mother with diabetes made the direct comparison of this variable to other NOD predictors difficult (Table 1 and 2). Age was a significant predictor in multivariate analysis without PF, but not when including PF. When included in the multivariate model in addition to predictors outlined in the multivariate section of table, an increase of 1 SD in log k-value was associated with a HR of NOD of 0.61 (0.52-0.73) with a chi square of 30.7 and p-value < 0.0001.

In multivariate analysis, relative risk of NOD was higher in the highest TG tertile compared to the lowest, and the association was only modestly weakened adding PF to the adjustments (Table 3). Additional adjustment for k-value still revealed increased risk of NOD in the highest TG tertile (Table 3). Tertile two was not associated with increased risk of diabetes compared to the lowest tertile. Neither adjustment for alcohol intake nor weekday of examination changed risk associations (data not shown). Self reported physical activity was a significant predictor of NOD in multivariate analysis not including PF, but non-significant
when PF was included. Self reported PA modified the TG-NOD risk association less than PF did (data not shown).

**Interaction between triglycerides and physical fitness**

When introducing the product of TG and PF in the Cox model in addition to TG and PF, no interaction was detected. Furthermore, HRs for NOD between the highest versus the lowest TG tertile were similar for men with age-adjusted PF above and below median (data not shown).

**TG/HDL- cholesterol ratio**

The incidence of NOD was 120 cases among the 1328 men who remained apparently healthy at 7.3 years follow-up. Median follow-up was 23.7 years (range 0.3-27.8) until death or end of observation when using the 7.3 years follow-up study (1979-1982) as baseline. Mean HDL was 1.55 mmol/l, TG 1.40 mmol/l, TG/HDL ratio 0.99 and mean BMI 24.6 kg/m². The risk of NOD increased with a HR of 1.48 (1.23-1.78) and 1.54 (1.27-1.86) per SD increase in log (TG) and log (TG/HDL-ratio), respectively. Further adjustments for PF had similar impact on the predictive ability of TG and TG/HDL-ratio.

**Conclusions**

We prospectively investigated the long-term prognostic impact on TG for the risk of NOD, and the modifying effect of PF on the risk association, among initially healthy middle-aged Caucasian men, followed up to 35 years. Our findings support the notion that TG is a powerful independent long-term predictor of NOD. Adjustment for PF modified this association only modestly, and we found no interaction between TG and PF for prediction of NOD. Alcohol intake during the last days prior to examination did not modify these associations. Our results also indicate that the TG/HDL- ratio has a somewhat stronger predictive impact on the risk of NOD than TG alone.
Differences in the incidence of NOD in different studies are mainly associated with varying participant characteristics, such as age, BMI, gender, physical activity and duration of follow-up (1, 4, 5). There is substantial evidence that a high proportion of cases of diabetes in the general population are undiagnosed (14, 15). Since our criteria for the diagnosis of diabetes are rather conservative it is likely that the incidence observed in our study is lower compared to what might have been detected through e.g. repeated measurements of FBG, oral glucose tolerance test and urinalyses.

Mean TG (1.31 mmol/l) at baseline in the present cohort was similar to TG levels in men without diabetes in the DESIR study (4), but was substantially lower than levels found in the study by Perry et al where randomly selected men from the general population were studied (2). This difference may be partially explained by the strict selection of healthy men in our cohort. Direct comparisons of the association between TG and NOD between our study and studies of other cohorts are inferential because of differences in baseline characteristics. Tirosh et al followed 13 953 men for 10.5 years (5). This population had similar TG levels as found in our cohort but lower mean age at inclusion (32.4 years) which may explain the lower incidence of NOD as compared to the present study. Their main finding was, however, similar to ours with a HR of 2.01 (1.20-4.38) for risk of NOD in the highest TG tertile versus the lowest tertile adjusted for age, BMI, total cholesterol/HDL-ratio, family history of diabetes, blood pressure, FBG, physical activity and smoking status (5). Dotevall et al (6) found a stronger association between future development of NOD and TG levels among Swedish women aged 39-65 years at inclusion followed for up to 18 years. This association was, however, not adjusted for baseline FBG values. Women with TG above 2.0 mmol/l had a HR of 4.49 (2.01 - 10.03) for the development of NOD as compared to women with baseline TG below 1.0 mmol/l (1). Consistent with findings from these studies, FBG and BMI were the strongest predictors of NOD in our study (2, 4, 16, 17).
Physical fitness

All methods of measuring PF have limitations because physical fitness is an integrated measure of aerobic performance dependent of functions of several organs, and how physical fitness is defined. The method used to measure PF in this cohort has, however, been shown to be a strong predictor of cardiovascular risk and highly correlated with maximal oxygen uptake which is the most widely accepted measurement of PF (18-20). Measured PF modified risk association between TG and NOD substantially more than self reported physical activity did.

Are raised TG levels a risk factor or surrogate marker for the development of NOD?

Whether raised TG plays a causal role in the development of NOD, or is secondary to undiagnosed abnormalities in glucose metabolism/insulin signaling cannot be deducted from epidemiological studies. Fasting TG levels appear to be a sensitive marker of lifestyle risk factors for NOD (5), and one might claim that the predictive ability of TG for NOD reflects this. Several clues indicate, however, that TG may be involved in the pathogenesis of impaired glucose tolerance and diabetes. Hypertriglyceridemia is associated with higher plasma concentrations of free fatty acids (FFA) and reduced insulin sensitivity (21, 22). Increased TG levels may increase FFA levels which reduces insulin sensitivity and stimulates hepatic glucose production and thus induce higher FBG levels (23, 24). Furthermore, increased FFA and insulin levels stimulate hepatic esterification of FFA to TG that may in turn further increase serum TG levels (25). Elevated serum TG levels may therefore be part of a "vicious metabolic circle" increasing the risk of diabetes.

Strengths and limitations

The present study is prospective in design, all data sets are virtually complete and the findings refer to an initially apparently healthy population of middle-aged men followed for up to 35 years. We have no work-up bias, and all event data are based on cause-specific death records
and complete hospital records. Since the study group has not interfered with patient care, bias is minimized. The study demonstrates the natural consequences of various levels of triglycerides since no men have been treated with triglyceride modifiers.

Our cohort consists of middle-aged Caucasian men who were healthy and employed at baseline. Our findings cannot therefore be generalized to individuals of other ethnicity, age, gender or individuals with morbidity. Since only seventeen men reported participating in competitive sports, the findings can therefore not be generalized to athletes. However, the association between TG and risk of NOD among women appears to be at least as strong for women as for men (4), and inferentially, our findings might therefore to some degree also be valid for women.

In summary, fasting serum triglycerides is a strong long-term predictor of NOD among healthy middle-aged men. Adjustment for physical fitness only modestly modifies this association, and we did not find any interaction between triglycerides and physical fitness in prediction of NOD. The ratio of TG/HDL may be slightly better than triglycerides alone for estimating the risk of NOD.

Acknowledgments

Author contribution paragraph:

All authors have contributed to analysis, interpretation of data and manuscript revision and have given their final approval of the manuscript submitted.
Jan Eriksson initiated and designed the study. Gunnar Eriksson has contributed to clinical follow-ups and data collection. Johan Bodegard was responsible for, and performed, the fifth follow up of the cohort in the years 2005-2008 collecting data from patient files of all the men in the cohort.
Disclosures

The corresponding author has no disclosures.

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J Bodegard also holds a full time position as epidemiologist in AstraZeneca

The other authors have no disclosures.

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Figure legends

Legend figure 1

Kaplan Meier curves showing survival (% of men) free new onset diabetes mellitus among 1962 initially healthy middle aged men according to fasting triglyceride tertiles (T1-T3) during 35 years follow-up.
References


Table 1 Baseline data according to fasting serum triglyceride tertiles (T1-T3)

<table>
<thead>
<tr>
<th></th>
<th>T1 (0.23-1.00 mmol/l)</th>
<th>T2 (1.01-1.35 mmol/l)</th>
<th>T3 (1.36-11.57 mmol/l)</th>
<th>p-value (trend)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) ± SD</td>
<td>49.6 ± 5.5</td>
<td>50.0 ± 5.5</td>
<td>49.8 ± 5.5</td>
<td>ns</td>
</tr>
<tr>
<td>Current smoker (n, %)</td>
<td>255, 37.7</td>
<td>286, 45.4</td>
<td>315, 48.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>Total serum cholesterol (mmol/l) ± SD</td>
<td>6.09 ± 1.01</td>
<td>6.73 ± 1.05</td>
<td>7.15 ± 1.23</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Systolic BP (mmHg) ± SD</td>
<td>126.5 ± 16.8</td>
<td>129.9 ± 17.3</td>
<td>133.5 ± 17.8</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Diastolic BP (mmHg) ± SD</td>
<td>85.0 ± 10.2</td>
<td>86.8 ± 10.0</td>
<td>89.3 ± 10.3</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Fasting serum triglycerides (mmol/l) ± SD</td>
<td>0.78 ± 0.14</td>
<td>1.17 ± 0.12</td>
<td>2.00 ± 0.80</td>
<td>na</td>
</tr>
<tr>
<td>Physical fitness (kcal/kg) ± SD</td>
<td>0.52 ± 0.21</td>
<td>0.46 ± 0.18</td>
<td>0.41 ± 0.15</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Fasting blood glucose (mmol/l) ± SD</td>
<td>4.35 ± 0.46</td>
<td>4.43 ± 0.49</td>
<td>4.49 ± 0.51</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>BMI (kg/m²) ± SD</td>
<td>23.6 ± 2.4</td>
<td>24.5 ± 2.5</td>
<td>25.6 ± 2.9</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Resting heart rate (beats per minute) ± SD</td>
<td>60.6 ± 9.7</td>
<td>60.5 ± 9.1</td>
<td>62.9 ± 9.8</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Maximal heart rate (beats per minute) ± SD</td>
<td>163.8 ± 13.2</td>
<td>161.9 ± 14.3</td>
<td>162.9 ± 13.1</td>
<td>ns</td>
</tr>
<tr>
<td>SBP 100W (mmHg) ± SD</td>
<td>176.8 ± 24.1</td>
<td>180.8 ± 23.3</td>
<td>186.2 ± 23.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ESR (millimeter per/hour) ± SD</td>
<td>6.8 ± 7.0</td>
<td>7.5 ± 6.6</td>
<td>7.8 ± 6.3</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Mother with diabetes (n, %)</td>
<td>42, 6.2</td>
<td>42, 6.7</td>
<td>57, 8.7</td>
<td>ns</td>
</tr>
<tr>
<td>k-value determined by IVGTT, (n=1936)*</td>
<td>1.99 ± 0.9</td>
<td>1.96 ± 0.93</td>
<td>1.84 ± 0.82</td>
<td>0.0016</td>
</tr>
</tbody>
</table>

All data are mean values except number of smokers and number of men who had mother with diabetes, BP=blood pressure, bpm=beats per minute, ESR= erythrocyte sedimentation rate n=number of men in each tertile/number of men in each tertile who had IVGTT performed, na=not applicable, ns=not significant, p=p value for correlation (trend) across tertiles with Kendall’s rank test, SD=standard deviation, maximal heart rate=maximal heart rate achieved during exercise test, SBP 100W= systolic BP at 100 Watt workload on exercise test, IVGTT = intravenous glucose tolerance test. * k-value is given in mg/dl/100 minutes.
Table 2 Predictors of new onset diabetes during 35 years observation ranked according to Chi square in multivariate analysis.

<table>
<thead>
<tr>
<th></th>
<th>Univariate analysis</th>
<th></th>
<th>Multivariate analysis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95 % CI</td>
<td>p-value</td>
<td>Chi</td>
</tr>
<tr>
<td>Fasting blood glucose (mmol/l), 1 SD</td>
<td>2.47</td>
<td>2.13-2.87</td>
<td>&lt;0.0001</td>
<td>130.4</td>
</tr>
<tr>
<td>BMI (kg/m²), 1 SD</td>
<td>1.97</td>
<td>1.75-2.21</td>
<td>&lt;0.0001</td>
<td>106.0</td>
</tr>
<tr>
<td>Mother with diabetes (yes/no)</td>
<td>2.83</td>
<td>1.91-4.07</td>
<td>&lt;0.0001</td>
<td>22.9</td>
</tr>
<tr>
<td>Physical fitness (kcal/kg), 1SD</td>
<td>0.45</td>
<td>0.37-0.54</td>
<td>&lt;0.0001</td>
<td>82.2</td>
</tr>
<tr>
<td>Log serum triglycerides, 1SD</td>
<td>1.61</td>
<td>1.43-1.81</td>
<td>&lt;0.0001</td>
<td>27.1</td>
</tr>
<tr>
<td>Age (years), 1 SD*</td>
<td>1.25</td>
<td>1.09-1.44</td>
<td>0.0017</td>
<td>9.8</td>
</tr>
<tr>
<td>SBP 100W (mmHg), 1 SD†</td>
<td>1.44</td>
<td>1.26-1.64</td>
<td>&lt;0.0001</td>
<td>27.5</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg), 1 SD†</td>
<td>1.44</td>
<td>1.26-1.64</td>
<td>&lt;0.0001</td>
<td>27.1</td>
</tr>
<tr>
<td>Maximal heart rate (beats per minute), 1 SD†</td>
<td>0.77</td>
<td>0.68-0.89</td>
<td>0.0003</td>
<td>13.0</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l), 1 SD†</td>
<td>1.20</td>
<td>1.04-1.37</td>
<td>0.0101</td>
<td>6.6</td>
</tr>
<tr>
<td>Current smoker (yes/no)</td>
<td>1.29</td>
<td>0.97-1.70</td>
<td>&lt;0.0746</td>
<td>3.2</td>
</tr>
</tbody>
</table>

HR=hazard ratio per SD increase in variable except smoking status and mother with diabetes where HR is given for yes versus no, SD=standard deviation, maximal heart rate=maximal heart rate achieved during exercise test, SBP 100W= systolic BP at 100 Watt workload on exercise test.

*significant without physical fitness in multivariate analysis, †not significant in multivariate analysis
Table 3 Relative risks of new onset diabetes mellitus during 35 years observation in fasting serum triglyceride tertiles (T1-T3) compared to the lowest tertile.

<table>
<thead>
<tr>
<th></th>
<th>T1 (0.23-1.00mmol/l)</th>
<th>T2 (1.01-1.35mmol/l)</th>
<th>T3 (1.36-11.57mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=677/673</td>
<td>n=630/619</td>
<td>n=655/644</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.00</td>
<td>1.44 (0.95-2.19)</td>
<td>3.27 (2.30-4.73)</td>
</tr>
<tr>
<td>Multiple adjusted* without physical fitness</td>
<td>1.00</td>
<td>1.17 (0.78-1.78)</td>
<td>1.90 (1.32-2.79)</td>
</tr>
<tr>
<td>Multiple adjusted* with physical fitness</td>
<td>1.00</td>
<td>1.12 (0.74-1.70)</td>
<td>1.73 (1.20-2.54)</td>
</tr>
<tr>
<td>Multiple adjusted* with physical fitness and log k-value (n=1936)</td>
<td>1.00</td>
<td>1.06 (0.69-1.61)</td>
<td>1.65 (1.14-2.43)</td>
</tr>
</tbody>
</table>

Relative risks are given in hazard ratios with 95% confidence interval in parentheses, n=number of men in each tertile/ number of men in each tertile who had IVGGT performed.

*Adjusted for age, BMI, fasting blood glucose and family history of mother with diabetes.

Log k=log glucose fall coefficient determined by 60 minutes IVGGT (intravenous glucose tolerance test)