

Gamma-glutamyltransferase activity and development of the metabolic syndrome (IDF definition), in middle-aged men and women: the D.E.S.I.R. cohort

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OBJECTIVE--Among hepatic enzymes, gamma-glutamyltransferase (GGT) is the main predictor of type 2 diabetes incidence, although it has not been shown that GGT predicts pre-diabetic states. Our aim was to study the association of GGT with the development of the metabolic syndrome (MetS).

RESEARCH DESIGN AND METHODS--We analysed the 3-year data from the D.E.S.I.R. prospective cohort of 1656 men and 1889 women without baseline MetS, according to the International Diabetes Federation definition.

RESULTS--Over the 3-years, 309 participants developed the MetS. After adjustment for age, alcohol intake, physical activity, smoking habits and alanine-aminotransferase (ALT), the odds ratios (OR) for incident MetS increased across baseline GGT quartiles: 1, 1.96, 2.25, 3.81 in men ($P<0.03$); and 1, 1.23, 1.80, 1.58 in women ($P<0.05$). After additional adjustment for insulin resistance markers (fasting insulin or HOMA-IR index) the association was attenuated and the linear relation was no longer significant in both sexes ($P=0,08$, $P=0,16$). However, men in the highest in comparison to the lowest quartile of GGT retained a significant risk for incident MetS. In women there was no longer a significant risk. GGT was significantly associated with the 3-year incidence of individual components of the MetS. The incidence of the MetS also increased with ALT, but after adjustment on GGT, this association remained significant only in women.

CONCLUSIONS--GGT, a predictor of type 2 diabetes, was associated with a risk of incident MetS. This association was mainly related with insulin resistance but was independent of other confounding factors.

Abbreviations: ALT, alanine-aminotransferase; AST, aspartate-aminotransferase; GGT, gamma-glutamyltransferase; FPG, fasting plasma glucose; HOMA-IR, homeostasis model insulin resistance assessment index; IDF, International Diabetes Federation; MetS, metabolic syndrome; NCEP, National Cholesterol Education Program, OR, odds ratio

Prospective data (1-10) show that gamma-glutamyltransferase (GGT) is a predictor of incident type 2 diabetes, independently of factors associated with GGT such as excessive alcohol consumption and liver diseases (2-10). Other hepatic enzymes alanine-aminotransferase (ALT), aspartate-aminotransferase (AST) and alkaline phosphatase, have also been identified as being associated with type 2 diabetes incidence (1-5,7-9,11-13), but when they were tested along with GGT, only the latter remained associated with type 2 diabetes (5,8).

However, it is not clear whether increased GGT is a cause or a consequence of the hyperglycaemia, which precedes overt diabetes. To clarify this question it is of interest to investigate whether GGT is associated with states preceding diabetes: the metabolic syndrome (MetS) and abnormal glycaemia (14). Some cross-sectional data have shown that GGT is associated with insulin resistance (15), insulin resistance markers (16) and the MetS (17) in large non-diabetic populations. This suggests that the increased GGT level could be related with insulin resistance, one of the physiopathological causes of diabetes. A study of Japanese men has shown an association between GGT and incident MetS, defined by an adapted NCEP definition (5).

Our aim was to examine in men and women, separately, as they have different relations between GGT and confounding factors (1,8):

- 1- GGT activity and incident MetS, as defined by the International Diabetes Federation (IDF) (18);

- 2- whether this association was independent of confounding factors associated with GGT (19) and of reported risk markers of the MetS such as insulin resistance markers (20-21), ALT (22) and physical activity (23);

- 3- GGT activity and the incidence of impaired fasting glucose (IFG); fasting plasma glucose (FPG) ≥ 5.6 mmol/l (18).

Research Design and Methods

Study population

Data is from the inclusion and three-year follow-up examination of the prospective cohort D.E.S.I.R. (Data from Epidemiological Study on the Insulin Resistance syndrome) (24). Between September 1994 and February 1996, 2576 men and 2636 non-pregnant women from the centre-west of France, aged 30-65 years, gave informed consent to participate in the study when they volunteered for a free periodical health check-up in one of the ten health examination centres. All were insured by the French Social Security System. The protocol was approved by the ethics committee of Kremlin-Bicêtre hospital.

Of the 5212 participants included at baseline, 4549 (87%) were re-examined at three years. Among these, 819 (18%) had the MetS at baseline, by the IDF definition (18), and 185 had some data missing at baseline or at the 3-year visit. This analysis is of the remaining 3545 participants. The 185 participants with missing data were older (43 ± 9 versus 46 ± 10 years, respectively) but they were not different for other baseline variables used in the analysis excepting triglycerides (1.29 ± 1.28 versus 0.86 ± 0.43 mmol/l), after adjusting on age. The 663 participants not re-examined at three years, were younger with higher GGT, ALT, AST, triglycerides, fasting insulin, systolic and diastolic blood pressure but they did not differ on FPG, body mass index (BMI), waist circumference or alcohol consumption.

Data collection

Data collection has been more precisely described elsewhere and was identical

at baseline and three-years (8,24). Trained medical personnel measured blood pressure and anthropometry: weight, height, and waist circumferences; self-administered questionnaires included tobacco smoking, alcohol intake, physical activity; a medical interview documented the use of medication, personal and family history of chronic diseases such as diabetes, hypertension, and cardiovascular diseases.

Blood was drawn after 12 hours of fasting. Serum insulin concentrations were centrally measured by a micro-enzyme immunoassay. All other biochemical measurements were made in one of four health centre laboratories (IRSA, Blois, Chartres or Orléans) which maintained an inter-laboratory quality control. Insulin resistance was estimated from the homeostasis model assessment (HOMA): $\text{HOMA-IR} = \text{fasting insulin } (\mu\text{U/ml}) \times \text{fasting glucose } (\text{mmol/l}) / 22.5$ (25).

We used the International Diabetes Federation (IDF) definition of the MetS (18):

- central obesity: waist circumference $\geq 94/80$ cm for men/women

plus any of two of the following four factors:

- raised triglycerides: ≥ 150 mg/dl (1.7 mmol/l) or specific treatment for this lipid abnormality .

- reduced HDL-cholesterol: < 40 mg/dl (1.03 mmol/l) men and < 50 mg/dl (1.29 mmol/l) women or specific treatment for this lipid abnormality

- raised blood pressure: systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg, or treatment of previously diagnosed hypertension

- raised FPG ≥ 100 mg/dl (5.6 mmol/l) or previously diagnosed type 2 diabetes (treated by anti-diabetic drugs and/or FPG $> 7,0$ mmol/l).

Statistical analysis

Data are described by mean \pm SD. Differences between men and women were assessed by t-tests. Spearman correlation coefficients quantified relations between baseline GGT and anthropometric and metabolic variables.

The three-year risk of the MetS and baseline GGT (in quartiles) were analyzed by logistic regression, separately for men and women because of their different baseline characteristics and MetS prevalence. The sex-specific quartiles of GGT were: 19.7, 26.6, 41.2 IU/l in men (normal range < 30 IU/l) and 12.6, 16.4, 23.0 IU/l in women (normal range < 24 IU/l). Linear trends for the risk of incident MetS were also evaluated over the continuous values of GGT (log transformed).

Covariates were: baseline age (years), ALT (in quartiles), smoking habits (never, former, current), physical activity (low, moderate, high, intensive), alcohol intake (gram/day), waist circumference (cm), fasting insulin ($\mu\text{U/ml}$) and HOMA-IR (continuous variable). For each covariate, interactions with GGT were tested by likelihood ratio tests comparing models with and without the interaction terms. To avoid any over or under estimate of the associations, syndrome components such as waist circumference, triglycerides, FPG, have not been included in the multivariate analyses. Potential effects of ALT and alcohol consumption on the association between GGT and MetS incidence were studied: baseline ALT was analyzed by logistic regression with ALT divided by sex-specific quartiles: 19.5, 25.4, 33.4 IU/l in men (normal range ≤ 40 IU/l) and 13.5, 17.2, 21.3 IU/l in women (normal range ≤ 35 IU/l) and then it was used as covariate, linear trends were evaluated over the continuous values of ALT (log transformed). Further, the association between GGT and MetS incidence was tested in participants with normal

baseline values of ALT and separately in non-alcohol drinkers.

Relations between GGT and the three-year incidence of each individual component of the MetS were analysed separately in men and women, using logistic regression analysis, in the population free of this component abnormality at baseline and the linear trends for the risk of incident component were evaluated over the continuous values of GGT (log transformed).

The SAS statistical program, version 8.0, was used in all analyses; quoted *P* values are two-sided.

Results

Characteristics of participants at baseline

Men had higher mean values than women for most tested variables (Table 1): liver enzymes, alcohol consumption, BMI, HOMA-IR and components of the MetS (waist circumference, blood pressure, fasting glucose, triglycerides concentrations). Age and fasting insulin did not differ between men and women and HDL-cholesterol was significantly lower in men.

Correlations with GGT

Spearman correlation coefficients between GGT and the covariates were similar but generally, slightly stronger in men than in women. Significant correlations ($P < 0.0001$) were observed in men and women for GGT with age (0.12/0.17), ALT (0.51/0.44), AST (0.30/0.25), alcohol consumption (0.24/0.11), BMI (0.26/0.19). GGT was also correlated with insulin resistance markers, fasting insulin (0.21/0.16) and HOMA-IR (0.21/0.16) and components of the MetS: waist circumference (0.29/0.20), triglycerides (0.29/0.20), FPG (0.14/0.06), systolic (0.13/0.16) and diastolic blood pressure (0.14/0.13). Two variables not correlated with GGT

were bilirubin (0.02/0.01) and HDL-cholesterol (0.04/-0.01).

GGT and incidence of the metabolic syndrome

Over three years, 309 participants developed the MetS: 9.2% of men, 8.2% of women (Table 2) and the risk increased across quartiles of baseline GGT, for both sexes. Compared to the first quartile group, the age-adjusted odds ratio (OR) of incident MetS increased from 2.06 (95%CI: 1.09-3.88) for quartile 2 to 4.14 (2.32-7.49) for quartile 4 in men and from 1.33 (0.73-2.40) to 2.33 (1.34-4.03) in women. This relation between GGT and incident MetS was linear in both sexes. Adjustment on baseline confounders (alcohol intake, physical activity, smoking habits, ALT), attenuated the association, but it remained significant in both sexes. In men after further adjustment on fasting plasma insulin or the HOMA-IR, the ORs for the MetS increased across GGT quartile groups, and the highest quartile group had a significantly higher OR compared to the first quartile group, although the linear trend was no longer significant. After adjusting on fasting plasma insulin or HOMA-IR, women were no longer at risk of developing the MetS with increasing baseline GGT.

This prospective association remained significant with similar ORs with other MetS definitions or after excluding participants exposed to drugs that modify GGT level (oral contraceptive, carbamazepine...) or those exposed to hypolipidemic drugs that decrease triglycerides (data not shown).

Impact of ALT activity on the GGT-metabolic syndrome association

The risk of developing the MetS increased across quartiles of baseline ALT (Table 2). Compared to subjects in the first quartile, the ORs of incident MetS increased from 1.46 (0.85-2.49)

for the second quartile group to 2.16 (1.29-3.61) for the highest quartile group in men and from 1.30 (0.71-2.38) to 2.87 (1.68-4.90), in women, after adjusting for age. This relation was linear in both sexes. After further adjustment on GGT level, the association was no longer significant in men but it remained significant in women.

In participants with a normal baseline ALT (<40 IU/L in men and <35 IU/L in women), the 3-year ORs to develop the MetS increased across quartiles of GGT activity: 1, 2.08 (1.09-3.92), 2.22 (1.18-4.18) to 3.92 (2.04-7.09) in men (*P* for linear trend <0.0004) and 1, 1.30 (0.72-2.35), 1.94 (1.11-3.40) to 2.25 (1.28-3.96) in women (*P* for linear trend <0.02).

Impact of alcohol on the GGT-metabolic syndrome association

In non-alcohol drinkers, the ORs to develop the MetS increased across quartiles of GGT: 1, 2.93 (0.69-12.46), 1.82 (0.35-9.61), 5.68 (1.37-23.46) in men (*P* for trend <0.05) and 1, 1.65 (0.70-3.88), 1.79 (0.75-4.28), 1.67 (0.70-3.92) in women (*P* for trend <0.11).

GGT and the incidence of individual components of the metabolic syndrome (IDF definition)

After adjustment for age, the 3-year incidences of individual components of the MetS were associated with increasing baseline GGT, for four of the five components, in both sexes (Table 3): central obesity, high triglycerides, high arterial blood pressure and impaired fasting glycaemia. These associations were linear and at least the fourth quartile group had a significantly higher three-year risk of developing an individual component of the MetS than the first quartile group. In participants free of IFG at baseline, 487 developed an IFG including 68 diabetes and the ORs to develop IFG at 3 years increased across GGT quartiles from

1.32 (0.89-1.98) in quartile 2 to 1.80 (1.22-2.65) in quartile 4 in men and from 0.93 (0.57-1.53) to 1.97 (1.26-3.09) in women.

Conclusions

In men and women free of the MetS at baseline, GGT was significantly correlated with markers of insulin resistance (fasting insulin, HOMA-IR) and overall adiposity (BMI), as well as four of the five components of the MetS: waist circumference, triglycerides, blood pressure and FPG – HDL-cholesterol was not associated with GGT. Baseline GGT was associated with the three-year risk of developing the MetS, after adjustment for age. After additional adjustment for alcohol consumption, physical activity, smoking habits and ALT, the association remained significant, with a linear trend in both sexes. However, after further adjustment for fasting insulin or the HOMA-IR, the association differed between sexes. In men, while MetS incidence still increased across quartiles, the association was no longer significantly linear but men with the highest values of GGT (quartile 4) had an OR significantly higher than 1. The majority of these men had GGT levels above the upper limit of the normal range (>30IU/l).

In women, the risk of developing the MetS no longer increased across quartiles, the ORs were not significantly different from 1 and the relation was no longer linear. Moreover, ALT was also associated with an incident MetS, but in men ALT was no longer associated with the MetS when GGT was introduced into the model, but it remained associated in women. GGT was significantly associated with the three-year incidence of individual components of the MetS, excepting a low HDL-cholesterol.

Triglycerides and waist circumference, both components of the MetS (21), physical activity (23), adiponectin (26) and C-reactive protein (27) have all been shown to be associated with an incident MetS. The first study to evaluate hepatic enzymes: GGT, ALT, AST and alkaline phosphatase was in Japanese men (5). Only GGT and alkaline phosphatase were significantly associated with the seven-year risk to develop the MetS, independently of potential confounding factors such as alcohol consumption, other hepatic enzymes, BMI. These results, using an adapted NCEP definition with BMI replacing waist circumference, agree with our results in men. A recent analysis from the IRAS study, that assessed ALT, AST, alkaline phosphatase and bilirubin but not GGT, showed that ALT and alkaline phosphatase were significantly associated with MetS incidence as defined by the NCEP (22). Men and women were combined in this analysis and these results con cord with our study for the crude association, in each sex. In our study, while the association remained significant in women after adjustment on GGT, ALT was no longer significant in men, as in the Japanese men (5). Indeed, GGT seems to be a better risk marker for the incidence of the MetS and type 2 diabetes than ALT activity (5,8).

Our results support the hypothesis that GGT is a risk marker for the development of type 2 diabetes, rather than a consequence of diabetes. GGT is associated with the IFG incidence, in subjects with normal FPG at baseline (3), in agreement with our results for IFG (8). Further, GGT is associated with MetS incidence which is a risk marker for Type 2 diabetes (14).

GGT could be a marker of insulin resistance in the general population, as it is associated with insulin resistance markers at baseline in cross-sectional

analyses, in agreement with other studies (7,15-17). It is associated with diabetes and MetS incidence (1-13), both of which are associated with a worsening insulin resistance. In our study, GGT is associated with incident MetS and also the incidence of each component of the syndrome, excepting a low HDL-cholesterol. When insulin resistance was taken into account, there was no longer a graded linear relation between GGT and MetS incidence, in either sex.

Currently, the mechanisms underlying the association of GGT with insulin resistance, the MetS and diabetes incidence have not been elucidated, but there are at least two potential mechanisms:

- GGT as marker of hepatic steatosis or visceral obesity (19,28,29);
- GGT as a marker of oxidative status, especially of glutathione homeostasis (19,30,31).

Our results are compatible with these two potential mechanisms. Both could be involved in the pathogenesis of insulin resistance, of which GGT could be a marker. Previous published results, as well as our own results support the hypothesis that GGT is a marker of insulin resistance, whatever the aetiology, and that ALT is a specific marker of *hepatic* insulin resistance. ALT is an epidemiological marker of Non Alcoholic Fatty Liver Disease (NAFLD), thus MetS and type 2 diabetes incidences could be related, specifically, to hepatic insulin resistance, due to the hepatic steatosis of NAFLD, independently of alcohol intake and other classical hepatic diseases (22). This hypothesis is supported by the IRAS study which showed that the association between ALT and MetS incidence was not modified by adjustment on markers of general insulin resistance (22). Further, in patients with steatosis of different aetiologies, GGT was shown to be

associated with insulin resistance evaluated by HOMA-IR (32), a marker of general insulin resistance. GGT and ALT are both markers of hepatic insulin resistance. GGT was strongly correlated with triglycerides and central obesity, as defined by IDF, reflecting hepatic exposure to high concentrations of free fatty acids, however GGT is also associated with incident central obesity and hyper-triglyceridaemia in participants without central obesity or hypertriglyceridemia at baseline.

GGT is expressed in several organs and tissues with a central role for intracellular glutathione homeostasis (19) and it has recently been proposed as a sensitive and reliable marker of oxidative stress (30). The association between GGT and both MetS and type 2 diabetes incidence could reflect non-specific insulin resistance, associated with the oxidative stress process, whatever the organ localisation, including hepatic insulin resistance. This hypothesis is compatible with our results that the association between GGT and MetS incidence is independent of the ALT level but the association between ALT and MetS incidence is dependent on the GGT level, as previously showed for type 2 diabetes (5,8). The association between GGT and MetS incidence is very sensitive to any adjustment for markers of insulin resistance in our study, in contrast to the association between ALT and MetS incidence (22). These results are supportive of GGT as a clinical marker of overall insulin resistance and not only of hepatic insulin resistance, in contrast to ALT. To estimate insulin resistance, GGT is easier to use in epidemiological studies or in clinical practice than currently available markers. This ability of GGT to reflect insulin resistance could also be related to the fact that GGT could be a marker of oxidative stress as suggested by previous studies

(19,30,31). This hypothesis needs further investigation with data on oxidative stress status or a direct evaluation of insulin resistance.

Our study has a number of limitations. Participants in the D.E.S.I.R. cohort were volunteers and certainly not representative of the general population, with an under-representation of chronic disease. Further, the 87% of the baseline cohort who could be studied were more healthy than participants who dropped-out, with lower baseline fasting insulin, GGT and ALT, but similar fasting glucose, BMI and alcohol consumption. The lack of complete data on the detection of sub-clinical hepatic diseases such as viral hepatitis is a limitation; however the relationship remained significant in participants with ALT in the normal range.

In conclusion, our results, in a middle aged French cohort, are the first to show in both men and women, that GGT, which predicted type 2 diabetes incidence, is also associated with incident MetS but this association appears to be mainly related to the association of GGT with insulin resistance. It is independent of other confounding factors: in men, only GGT and not ALT was associated with incident MetS, while in women both GGT and ALT were associated with incident MetS.

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TABLE 1--Characteristics of men and women at baseline: The D.E.S.I.R. study

	Men n=1656	Women n=1889	P value
Age (years)	46.2 ±10.0	46.4 ±9.9	0.59
GGT (IU/l)	37.1 ±34.5	20.9 ±16.9	0.0001
ALT (IU/l)	28.9 ±16.7	19.4 ±13.3	0.0001
AST (IU/l)	22.4 ±10.1	17.8 ±8.3	0.0001
Bilirubin (mg/ml)	7.4 ±3.6	6.1 ±3.4	0.0001
Alcohol intake (gram/day)	23 ±23	7 ±11	0.0001
BMI (kg/m ²)	24.4 ±2.5	23.3 ±3.5	0.0001
Waist circumference (cm)	86.4 ±7.3	74.9 ±8.5	0.0001
Waist hip ratio	0.90 ±0.05	0.78 ±0.06	0.0001
Fasting Insulin (μU/ml)	5.60 ±3.04	5.60 ±2.75	0.73
HOMA-IR*	1.39 ±0.85	1.26 ±0.67	0.0001
Fasting Plasma Glucose (mmol/l)	5.44 ±0.50	5.05 ±0.50	0.0001
Triglycerides (mmol/l)	0.98 ±0.48	0.76 ±0.35	0.0001
HDL-cholesterol (mmol/l)	0.59 ±0.15	0.71 ±0.16	0.0001
Systolic Blood Pressure (mm Hg)	132 ±13	126 ±15	0.0001
Diastolic Blood Pressure (mm Hg)	81 ±9	77 ±9	0.0001

Data are means ±SD

*HOMA-IR for homeostasis model insulin resistance assessment

TABLE 2--Odds ratios (95% confidence intervals) of 3-year incident metabolic syndrome (IDF definition) with GGT & ALT level at baseline, adjusted on baseline covariates. The D.E.S.I.R. study

Men					
	Q1	Q2	Q3	Q4	<i>P</i> for trend
GGT (IU/L)	<19.7	≥19.7-<26.6	≥26.6-<41.2	≥41.2	
cases/persons at risk	15/402	33/421	39/412	66/421	
Model 1	1	2.06 (1.09-3.88)	2.44 (1.31-5.52)	4.14 (2.32-7.49)	0.0002
Model 2	1	1.96 (1.03-3.72)	2.25 (1.19-4.25)	3.81 (1.99-7.28)	0.03
Model 3	1	1.66 (0.87-3.15)	1.84 (0.97-3.50)	3.19 (1.66-6.11)	0.08
Model 4	1	1.75 (0.92-3.34)	1.98 (1.04-3.76)	3.29 (1.72-6.31)	0.16
ALT (IU/L)					
	Q1	Q2	Q3	Q4	<i>P</i> for trend
cases/persons at risk	25/408	36/410	45/417	47/421	
OR adjusted on age	1	1.46 (0.85-2.49)	1.92 (1.14-3.21)	2.16 (1.29-3.61)	0.002
OR adjusted on age and GGT	1	1.31 (0.76-2.27)	1.42 (0.83-2.44)	1.25 (0.70-2.21)	0.17
Women					
	Q1	Q2	Q3	Q4	<i>P</i> for trend
GGT (IU/L)	<12.6	≥12.6-<16.4	≥16.4-<23.0	≥23.0	
cases/persons at risk	19/427	31/492	51/497	55/473	
Model 1	1	1.33 (0.73-2.40)	2.06 (1.19-3.59)	2.33 (1.34-4.03)	0.0001
Model 2	1	1.23 (0.68-2.24)	1.80 (1.02-3.15)	1.58 (0.88-2.85)	0.05
Model 3	1	1.12 (0.61-2.05)	1.27 (0.71-2.28)	1.19 (0.65-2.19)	0.35
Model 4	1	1.17 (0.64-2.13)	1.31 (0.73-2.35)	1.27 (0.69-2.33)	0.34
ALT (IU/L)					
	Q1	Q2	Q3	Q4	<i>P</i> for trend
cases/persons at risk	19/458	28/463	38/444	71/453	
OR adjusted on age	1	1.30 (0.71-2.38)	1.87 (1.05-3.31)	2.87 (1.68-4.90)	0.0001
OR adjusted on age and GGT	1	1.21 (0.66-2.23)	1.70 (0.95-3.04)	2.87 (1.40-4.43)	0.0001

Model 1: adjusted for age

Model 2: adjusted for age, alcohol intake, physical activity, smoking habits, ALT

Model 3: model 2 + fasting insulin

Model 4: model 2 + HOMA-IR

TABLE 3--Age adjusted odds ratios (OR, 95% confidence intervals) for the 3-year incidence of each metabolic syndrome components (IDF definition) according to quintiles of GGT at baseline. The D.E.S.I.R. study

Men	Q1	Q2	Q3	Q4	P for trend
GGT (IU/L)	<19.7	≥19.7-<26.6	≥26.6-<41.2	≥41.2	
Central obesity					
cases/persons at risk	22/378	33/377	36/343	52/336	
OR	1	1.50 (0.86-2.63)	1.77 (1.02-3.09)	2.72 (1.61-4.61)	0.002
Low HDL					
cases/persons at risk	24/407	38/460	37/496	39/597	
OR	1	1.43 (0.84-2.43)	1.27 (0.75-2.17)	1.10 (0.65-1.87)	0.91
High TG					
cases/persons at risk	31/403	61/425	69/425	100/436	
OR	1	2.01 (1.28-3.18)	2.34 (1.49-3.67)	3.59 (2.33-5.53)	0.0001
High Blood Pressure					
cases/persons at risk	42/191	42/155	47/151	46/135	
OR	1	1.36 (0.82-2.26)	1.59 (0.97-2.62)	1.76 (1.06-2.92)	0.04
High Fasting Glucose					
cases/persons at risk	57/296	67/276	75/277	88/280	
OR	1	1.32 (0.89-1.98)	1.47 (0.99-2.18)	1.80 (1.22-2.65)	0.0002
Women	Q1	Q2	Q3	Q4	P for trend
GGT (IU/L)	<12.6	≥12.6-<16.4	≥16.4-<23.0	≥23.0	
Central obesity					
cases/persons at risk	48/367	44/388	54/369	64/316	
OR	1	0.80 (0.52-1.24)	1.04 (0.68-1.59)	1.49 (0.98-2.26)	0.02
Low HDL					
cases/persons at risk	38/423	49/498	44/507	61/544	
OR	1	1.15 (0.74-1.80)	1.04 (0.66-1.63)	1.42 (0.92-2.20)	0.08
High TG					
cases/persons at risk	18/439	32/507	34/508	59/540	
OR	1	1.51 (0.89-2.74)	1.51 (0.83-2.73)	2.60 (1.49-4.50)	0.0001
High Blood Pressure					
cases/persons at risk	40/302	44/292	63/280	58/270	
OR	1	0.99 (0.61-1.61)	1.57 (0.99-2.48)	1.38 (0.87-2.20)	0.008
High Fasting Glucose					
cases/persons at risk	32/387	36/458	62/453	70/449	
OR	1	0.93 (0.57-1.53)	1.71 (1.08-2.69)	1.97 (1.26-3.09)	0.0001