γ-Glutamyltransferase Activity and Development of the Metabolic Syndrome (International Diabetes Federation Definition) in Middle-Aged Men and Women

Data From the Epidemiological Study on the Insulin Resistance Syndrome (DESIR) cohort

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

RESEARCH DESIGN AND METHODS — We analyzed the 3-year data from the Data from Epidemiological Study on the Insulin Resistance Syndrome prospective cohort of 1,656 men and 1,889 women without MetS at baseline, according to the International Diabetes Federation definition.

RESULTS — Over 3 years, 309 participants developed the MetS. After adjustment for age, alcohol intake, physical activity, smoking habits, and alanine aminotransferase (ALT), the odds ratios for incident MetS increased across baseline GGT quartiles (1, 1.96, 2.25, and 3.81 in men, $P < 0.03$; and 1, 1.23, 1.80, and 1.58 in women, $P < 0.05$). After additional adjustment for insulin resistance markers (fasting insulin or homeostasis model assessment of insulin resistance index), the association was attenuated and the linear relation 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.

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Prospective data (1–10) show that γ-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, such as 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 hyperglycemia, 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 glycemia (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 nondiabetic populations. This suggests that the increased GGT level could be related with insulin resistance, one of the physiopathological causes of diabetes. A study (5) of Japanese men has shown an association between GGT and incident MetS, defined by an adapted National Cholesterol Education Program definition.

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

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

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Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DESIR, Data From Epidemiological Study on the Insulin Resistance Syndrome; FPG, fasting plasma glucose; GGT, γ-glutamyltransferase; IDF, International Diabetes Federation; IFG, impaired fasting glucose; HOMA-IR, homeostasis model assessment of insulin resistance; MetS, metabolic syndrome.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

markers (20,21), ALT (22), and physical activity (23); and
3. GGT activity and the incidence of impaired fasting glucose (IFG): fasting plasma glucose (FPG) ≥5.6 mmol/l (18).

RESEARCH DESIGN AND METHODS

— Data are from the inclusion and 3-year follow-up examination of the Data from the Epidemiological Study on the Insulin Resistance Syndrome (DESIR) prospective cohort (24). Between September 1994 and February 1996, 2,576 men and 2,636 nonpregnant women from the center-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 1 of the 10 health examination centers. All were insured by the French Social Security System. The protocol was approved by the ethics committee of Kremlin-Bicêtre hospital.

Of 5,212 participants included at baseline, 4,549 (87%) were reexamined at 3 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 3,545 participants. The 185 participants with missing data were older (43 ± 9 vs. 46 ± 10 years, respectively), but they were not different with regard to other baseline variables used in the analysis, except triglycerides (1.29 ± 1.28 vs. 0.86 ± 0.43 mmol/l, respectively), after adjusting for age. The 663 participants not reexamined at 3 years were younger with higher GGT, ALT, AST, triglycerides, fasting insulin, and systolic and diastolic blood pressure, but they did not differ on FPG, BMI, waist circumference, or alcohol consumption.

Data collection

Data collection has been more precisely described elsewhere and was identical at baseline and 3 years (8,24). Trained medical personnel measured blood pressure and anthropometry (weight, height, and waist circumferences). Self-administered questionnaires included questions regarding tobacco smoking, alcohol intake, and physical activity. A medical interview documented the use of medication and personal and family history of chronic conditions such as diabetes, hypertension, and cardiovascular diseases.

Blood was drawn after 12 h of fasting. Serum insulin concentrations were centrally measured by a microenzyme immunoassay. All other biochemical measurements were made in one of four health center laboratories (Institut Inter Régional pour la Santé, Blois, Chartres, or Orléans), which maintained an interlaboratory quality control. Insulin resistance was estimated from the homeostasis model assessment of insulin resistance (HOMA-IR): HOMA-IR = fasting insulin (μU/ml) × fasting glucose (mmol/l)/22.5 (25).

We used the IDF definition of the MetS (18) for central obesity, defined as waist circumference ≥94/80 cm for men/women plus any two of the following four factors: *1*) Raised triglycerides: ≥150 mg/dl (1.7 mmol/l) or specific treatment for this lipid abnormality. *2*) Reduced HDL cholesterol: <40 mg/dl (1.03 mmol/l) for men and <50 mg/dl (1.29 mmol/l) for women or specific treatment for this lipid abnormality. *3*) Raised blood pressure: systolic blood pressure ≥130 or diastolic blood pressure ≥85 mmHg or treatment of previously diagnosed hypertension. *4*) Raised FPG ≥100 mg/dl (5.6 mmol/l) or previously diagnosed type 2 diabetes (treated by antidiabetes drugs and/or FPG >7.0 mmol/l).

Statistical analysis

Data are described by means ± 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 3-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, and 41.2 IU/l in men (normal range <30 IU/l) and 12.6, 16.4, and 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, or current), physical activity (low, moderate, high, or intensive), alcohol intake (grams per day), waist circumference (in centimeters), fasting insulin (in microunits per milliliter), 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 underestimate of the associations, syndrome components, such as waist circumference, triglycerides, and 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, and 33.4 IU/l in men [normal range ≤40 IU/l] and 13.5, 17.2, and 21.3 IU/l in women [normal range ≤35 IU/l]), and then it was used as a 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 those who do not drink alcohol.

The relationship between GGT and the 3-year incidence of each individual component of the MetS were analyzed 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, and 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), such as liver enzymes, alcohol consumption, BMI, HOMA-IR, and components of the MetS (waist circumference, blood pressure, fasting glucose, and triglyceride 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 ([men/women] 0.12/0.17), ALT (0.51/0.44), AST (0.30/0.25), alcohol consumption (0.24/0.11), and 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) as well as components of the MetS: waist circumference (0.29/0.20), triglycerides (0.29/0.20), FPG (0.14/0.06), systolic blood pressure

Table 1—*Characteristics of men and women at baseline: the DESIR study*

	Men	Women	*P* value
n	1,656	1,889	
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 (g/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-to-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
FPG (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 (mmHg)	132 ± 13	126 ± 15	0.0001
Diastolic blood pressure (mmHg)	81 ± 9	77 ± 9	0.0001

Data are means ± SD.

(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 MetS

Over 3 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 with the first quartile group, the age-adjusted odds ratio 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, and ALT) attenuated the association, but it remained significant in both sexes. In men, after further adjustment on fasting plasma insulin or HOMA-IR, the odds ratios for the MetS increased across GGT quartile groups, and the highest quartile group had a significantly higher odds ratio compared with 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 odds ratios with other MetS definitions or after excluding participants exposed to drugs that modify GGT level (oral contraceptives, carbamazepine, etc.) or those exposed to hypolipidemic drugs that decrease triglycerides (data not shown).

Impact of ALT activity on the GGT-MetS association

The risk of developing the MetS increased across quartiles of baseline ALT (Table 2).

Table 2—*Odds ratios (95% CIs) of 3-year incident metabolic syndrome (IDF definition) with GGT and ALT levels at baseline, adjusted on baseline covariates: the DESIR study*

	Q1	Q2	Q3	Q4	*P* for trend
Men					
GGT (IU/l)	<19.7	≥19.7 to <26.6	≥26.6 to <41.2	≥41.2	
Cases/individuals 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)	<19.5	≥19.5 to <25.4	≥25.4 to <33.4	≥33.4	
Cases/individuals at risk	25/408	36/410	45/417	47/421	
Odds ratio adjusted for age	1	1.46 (0.85–2.49)	1.92 (1.14–3.21)	2.16 (1.29–3.61)	0.002
Odds ratio adjusted for 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					
GGT (IU/l)	<12.6	≥12.6 to <16.4	≥16.4 to <23.0	≥23.0	
Cases/individuals 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)	<13.5	≥13.5 to <17.2	≥17.2 to <21.3	≥21.3	
Cases/individuals at risk	19/458	28/463	38/444	71/453	
Odds ratio adjusted for age	1	1.30 (0.71–2.38)	1.87 (1.05–3.31)	2.87 (1.68–4.90)	0.0001
Odds ratio adjusted for 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, and ALT; model 3: adjusted as described for model 2 plus fasting insulin; and model 4: adjusted as described for model 2 plus HOMA-IR.

Table 3—*Age-adjusted odds ratios (95% CIs) for the 3-year incidence of each MetS component (IDF definition) according to quintiles of GGT at baseline: the DESIR study*

	Q1	Q2	Q3	Q4	*P* for trend
Men					
GGT (IU/l)	<19.7	≥19.7 to <26.6	≥26.6 to <41.2	≥41.2	
Central obesity					
Cases/individuals at risk	22/378	33/377	36/343	52/336	
Odds ratio	1	1.50 (0.86–2.63)	1.77 (1.02–3.09)	2.72 (1.61–4.61)	0.002
Low HDL					
Cases/individuals at risk	24/407	38/460	37/496	39/597	
Odds ratio	1	1.43 (0.84–2.43)	1.27 (0.75–2.17)	1.10 (0.65–1.87)	0.91
High triglycerides					
Cases/individuals at risk	31/403	61/425	69/425	100/436	
Odds ratio	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/individuals at risk	42/191	42/155	47/151	46/135	
Odds ratio	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/individuals at risk	57/296	67/276	75/277	88/280	
Odds ratio	1	1.32 (0.89–1.98)	1.47 (0.99–2.18)	1.80 (1.22–2.65)	0.0002
Women					
GGT (IU/l)	<12.6	≥12.6 to <16.4	≥16.4 to <23.0	≥23.0	
Central obesity					
Cases/individuals at risk	48/367	44/388	54/369	64/316	
Odds ratio	1	0.80 (0.52–1.24)	1.04 (0.68–1.59)	1.49 (0.98–2.26)	0.02
Low HDL					
Cases/individuals at risk	38/423	49/498	44/507	61/544	
Odds ratio	1	1.15 (0.74–1.80)	1.04 (0.66–1.63)	1.42 (0.92–2.20)	0.08
High triglycerides					
Cases/individuals at risk	18/439	32/507	34/508	59/540	
Odds ratio	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/individuals at risk	40/302	44/292	63/280	58/270	
Odds ratio	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/individuals at risk	32/387	36/458	62/453	70/449	
Odds ratio	1	0.93 (0.57–1.53)	1.71 (1.08–2.69)	1.97 (1.26–3.09)	0.0001

Compared with subjects in the first quartile, the odds ratios of incident MetS increased from 1.46 (95% CI 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 odds ratios to develop the MetS increased across quartiles of GGT activity (1, 2.08 [95% CI 1.09–3.92], and 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], and 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-MetS association

In nonalcohol drinkers, the odds ratios to develop the MetS increased across quartiles of GGT (1, 2.93 [95% CI 0.69–12.46], 1.82 [0.35–9.61], and 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], and 1.67 [0.70–3.92] in women, *P* for trend <0.11).

GGT and the incidence of individual components of the MetS (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 (central obesity, high triglycerides, high arterial blood pressure, and impaired fasting glycemia) (Table 3). These associations were linear, and at least the fourth quartile group had a significantly higher 3-year risk of developing an individual component of the MetS than the first quartile group. In participants free of IFG at baseline, 487 developed IFG, including 68 diabetic subjects, and the odds ratios to develop IFG at 3 years increased across GGT quartiles from 1.32 (95% CI 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 3-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 HOMA-IR, the association differed between sexes. In men, while MetS incidence still increased across quartiles, the association was no longer significantly linear; however, men with the highest values of GGT (quartile 4) had an odds ratio significantly higher than 1. The majority of these men had GGT levels above the upper limit of the normal range (>30 IU/l).

In women, the risk of developing the MetS no longer increased across quartiles. The odds ratios 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; however, it remained associated in women. GGT was significantly associated with the 3-year incidence of individual components of the MetS, except 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 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 7-year risk to develop the MetS, independently of potential confounding factors, such as alcohol consumption, other hepatic enzymes, and BMI. These results, using an adapted National Cholesterol Education Program definition with BMI replacing waist circumference, agree with our results in men. A recent analysis from the Insulin Resistance Atherosclerosis Study, which 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 National Cholesterol Education Program (22). Men and women were combined in this analysis, and these results concord 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 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, except 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 a marker of hepatic steatosis or visceral obesity (19,28,29) and 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, support the hypothesis that GGT is a marker of insulin resistance, whatever the etiology, and that ALT is a specific marker of hepatic insulin resistance. ALT is an epidemiological marker of nonalcoholic fatty liver disease; therefore, MetS and type 2 diabetes incidences could be related, specifically to hepatic insulin resistance due to the hepatic steatosis of nonalcoholic fatty liver disease, independently of alcohol intake and other classical hepatic diseases (22). This hypothesis is supported by the Insulin Resistance Atherosclerosis 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 etiologies, 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 hypertriglyceridemia 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 nonspecific insulin resistance, associated with the oxidative stress process, whatever the organ localization, 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 that 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 DESIR cohort were volunteers and certainly not representative of the general population, with an underrepresentation 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 subclinical hepatic dis-

eases 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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APPENDIX

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