

Alanine Aminotransferase, γ -Glutamyltransferase, and Incident Diabetes

The British Women's Heart and Health Study and meta-analysis

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OBJECTIVE — To estimate and compare associations of alanine aminotransferase (ALT) and γ -glutamyltransferase (GGT) with incident diabetes.

RESEARCH DESIGN AND METHODS — ALT and GGT were studied as determinants of diabetes in the British Women's Heart and Health Study, a cohort of 4,286 women 60–79 years old (median follow-up 7.3 years). A systematic review and a meta-analysis of 21 prospective, population-based studies of ultrasonography, which diagnosed nonalcoholic fatty liver disease (NAFLD), ALT, and GGT as determinants of diabetes, were conducted, and associations of ALT and GGT with diabetes were compared.

RESULTS — Ultrasonography-diagnosed NAFLD was associated with more than a doubling in the risk of incident diabetes (three studies). ALT and GGT both predicted diabetes. The fully adjusted hazard ratio (HR) for diabetes per increase in one unit of logged ALT was 1.83 (95% CI 1.57–2.14, $I^2 = 8\%$) and for GGT was 1.92 (1.66–2.21, $I^2 = 55\%$). To directly compare ALT and GGT as determinants of diabetes, the fully adjusted risk of diabetes in the top versus bottom fourth of the ALT and GGT distributions was estimated using data from studies that included results for both markers. For ALT, the HR was 2.02 (1.59–2.58, $I^2 = 27\%$), and for GGT the HR was 2.94 (1.98–3.88, $I^2 = 20\%$), suggesting that GGT may be a better predictor ($P = 0.05$).

CONCLUSIONS — Findings are consistent with the role of liver fat in diabetes pathogenesis. GGT may be a better diabetes predictor than ALT, but additional studies with directly determined liver fat content, ALT, and GGT are needed to confirm this finding.

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Nonalcoholic fatty liver disease (NAFLD) is characterized by accumulation of fat in the liver, with or without inflammation, fibrosis, and cirrhosis, in the absence of substantial alcohol consumption or other causes of liver disease such as viral hepatitis. In large epidemiological studies, NAFLD and liver fat content (a continuum) are commonly revealed by elevations in alanine amino-

transferase (ALT), γ -glutamyltransferase (GGT), and ultrasonography.

High rates of elevated GGT levels were noted among diabetic patients over 40 years ago (1). Cross-sectional associations between abnormal GGT and dysglycemic states were also documented in the 1980s (e.g., the study by Ford et al. [2]). However, cross-sectional studies cannot determine causality because in most cases

it is impossible to ascertain the temporal sequence between the events studied. The first longitudinal study to examine the association of a biomarker of NAFLD with incident diabetes was published in 1998 (3). Since then, both ALT and GGT, even within the normal range, have been reported to predict incident diabetes. However, while some studies have demonstrated a stronger association between GGT and diabetes than between ALT and diabetes (4,5), other studies have reported the opposite (6).

To our knowledge, no previous publication has systematically reviewed and meta-analyzed all prospective studies of the association between NAFLD and its markers with future diabetes risk. We are also unaware of any studies that have compared the magnitude of the relative associations between ALT and GGT with diabetes risk, despite claims for one or the other being a better marker of liver fat and thus diabetes risk. We therefore examined the separate associations of ALT and GGT with incident diabetes in a population of older British women and undertook a systematic review and meta-analysis of prospective population-based studies assessing the associations of NAFLD, ALT, or GGT with diabetes. Of note, while aspartate aminotransferase has also been assessed in some studies (e.g., in the study by André et al. [4]), it is not as sensitive or specific to liver damage as ALT or GGT (7) and is therefore not addressed here.

RESEARCH DESIGN AND METHODS

British Women's Heart and Health Study

Full details of the selection of participants and measurements have been previously reported (8–10). A total of 4,286 women, aged 60–79 years, were randomly recruited from 23 British towns. Baseline data (self-completed questionnaire, research nurse interview, physical examination, and medical record review) were

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collected between 1999 and 2001. These women have been followed up for a median of 7.3 years, to September 2007, by a detailed review of their medical records conducted every 2 years and by a self-completed questionnaire. Informed consent was obtained from the women, and the approval of both the local and multi-center ethics committees was obtained for the study.

Levels of GGT and ALT were determined in fresh serum samples using an automated analyzer (Technicon Sequential Multiple Analyzer; Technicon Instruments Corporation, Tarrytown, NY). Waist and hip circumference, lipids, fasting glucose and insulin, and blood pressure were measured using standard methods as previously described. Information on smoking, physical activity, social class, and alcohol consumption was obtained from a self-completed questionnaire and nurse interview (9).

Insulin resistance was estimated according to the homeostasis model assessment (HOMA) as the product of fasting glucose (millimoles per liter) and insulin (microunits per milliliter) divided by the constant 22.5 (11). Baseline diabetes (for exclusion of these cases) was defined according to the World Health Organization criteria as any woman with a doctor's diagnosis of diabetes (based on medical records review and self-report) and/or with a fasting glucose concentration ≥ 7 mmol/l (12). Incident cases of diabetes were defined as either a self-report of a doctor diagnosis of diabetes or evidence of diabetes in the follow-up medical record reviews.

Cox proportional hazards regression models were used to examine associations of exposures with incident diabetes in those with no evidence of diabetes at baseline. In the Cox proportional hazards regression models, the participant's age was the time axis and risk was assessed from the date of baseline examination for each woman. ALT and GGT were expressed in units of SD of their respective distributions. Contributions to risk were censored at the date of diagnosis or death from any other cause or at the end of the follow-up period (30 September 2007) for those who remained alive and free of diabetes.

Systematic review and meta-analysis
PubMed and EMBASE (Excerpta Medica Database) were systematically searched by A.F. in February 2008 for all prospective population-based studies evaluating

Table 1—HRs (95% CI) of incident diabetes per SD change of natural logged ALT and GGT

	Model 1	Model 2	Model 3	Model 4
ALT	1.50 (1.27–1.74)	1.51 (1.29–1.77)	1.37 (1.15–1.64)	1.20 (0.99–1.44)
GGT	1.55 (1.34–1.79)	1.55 (1.35–1.79)	1.46 (1.25–1.71)	1.24 (1.04–1.48)

Model 1, adjusted for age; model 2, model 1 adjustment plus alcohol consumption; model 3, model 2 adjustments plus childhood and adult social class, physical activity, and smoking; model 4, model 3 adjustments plus HOMA, waist-to-hip ratio, triglycerides, HDL cholesterol, and systolic blood pressure.

the association among NAFLD (diagnosed by any imaging technique), ALT, GGT, and incident diabetes. No language restrictions were applied. Abstracts were scanned, relevant full-text publications were obtained, and inclusion criteria were applied (i.e., prospective studies conducted in general populations). Two independent reviewers (A.F. and D.A.L.) abstracted data. Reference lists of obtained articles were hand searched for additional potential studies. Study authors were contacted for additional data or clarification when required.

Two sets of meta-analyses were undertaken to reflect the two aims of this study. In the first set, a separate meta-analysis was conducted for each NAFLD marker, maximizing data use regardless of whether they provided data on ultrasound-defined NAFLD, ALT only, GGT only, or any combination of these. In these analyses, the assumption was that all study results for ALT (GGT or ultrasound) were part of the same distribution but not that the true effect was the same in all studies; therefore, a random-effects model was used, though we did also check our assumption for this random effect using the I^2 measure, which quantifies the percentage of total variation across studies that is due to heterogeneity rather than chance (13).

Because different studies presented results on different scales (e.g., risk ratios [RRs] for quantiles of ALT or GGT compared with the lowest quantile or per category or logged unit per liter), for the first meta-analysis (of all studies) a standard statistical method was used to estimate the log hazard ratio (HR) per log unit increase in ALT or GGT, together with its SE (14,15). Results are presented as the HR per unit change in ALT or GGT on a log scale.

When data were presented according to quantiles or categories of ALT or GGT, the median or mean in each group, when reported, was used. When these were not reported, the mean in each group was estimated based on the distribution of subjects across groups, as outlined by Chêne

and Thompson (15). All exposure (GGT and ALT) levels were converted to the log-normal scale if not already presented as such. The log HR per 1 unit/l increase was then estimated using the method of Greenland and Longnecker (14). This allows for correlations between HRs that are related to the same reference group.

The objective of the second meta-analysis was to directly compare the associations of ALT and GGT with diabetes. We decided a priori to limit this second analysis to results of studies that provided estimates for both ALT and GGT in the same population in order to ensure the comparability of the estimates for ALT and GGT. Furthermore, only studies for which we could obtain results in which ALT and GGT had been standardized (to account for their different distributions) were included. The most common method used to standardize ALT and GGT was to present results per fourths of the ALT and GGT distributions. Therefore, we combined the RRs in the top versus the bottom fourth of the ALT and GGT. A fixed-effects model was used, thus assuming that the true effect in all studies was the same and any difference between study results was due to chance alone, and this assumption was checked using the I^2 measure (13).

When possible, data were extracted separately for men and women. The effect of duration of follow-up on study results was assessed by meta-regression. Small-study effects such as publication bias were examined by using a funnel plot (16) and formally tested using the Egger test (17).

RESULTS

British Women's Heart and Health Study

Data on diabetes at baseline were available for 3,829 women (89% of 4,286), of whom 377 had diabetes and were excluded from the analysis. Of the remaining 3,452 women, 3,041 (88% of 3,452) had complete data on all covariables (Table 1). Characteristics of included women by diabetes status at the end of follow-up are presented

in Table A1 (available in an online appendix at <http://care.diabetesjournals.org/cgi/content/full/dc08-1870/DC1>). Women with diabetes at the end of follow-up were older; had higher age-adjusted mean BMI, waist-to-hip ratio, ALT, GGT, triglycerides, glucose, and HOMA; and had lower HDL cholesterol. More of the women with incident diabetes exercised for <2 h per week, and more also had a history of smoking.

During 281,081 person-years of follow-up, 112 women were diagnosed with diabetes, yielding a rate of 5.3 per 1,000 person-years (95% CI 4.4–6.4). Both ALT and GGT were associated with incident diabetes, even when adjustment was made for alcohol consumption (Table 1) and other potential confounders. When components of the metabolic syndrome were added to the model, the associations of both ALT and GGT with incident diabetes were attenuated toward the null. The 95% CI crossed the null for ALT but not for GGT. However, the magnitude of associations of ALT with diabetes and of GGT with diabetes was comparable in all four models, as was the degree of attenuation of age-adjusted estimates.

Systematic review and meta-analysis

The electronic search (crossing terms for ALT, GGT, liver steatosis, and diabetes) yielded 236 potentially relevant publications, of which 20 studied prospective population-based cohorts and assessed baseline ultrasonography-diagnosed NAFLD, ALT, and/or GGT and their associations with incident diabetes.

Ultrasound-diagnosed NAFLD

Three studies (18–20) (summarized in Table 2) assessed ultrasound-diagnosed NAFLD as a determinant of incident diabetes. No studies that used any other diagnostic test to ascertain NAFLD in its association with incident diabetes were retrieved. All three studies were conducted in Asian populations, and in all three there was evidence that ultrasound-diagnosed NAFLD was associated with diabetes risk. When estimates from these studies were meta-analyzed (using the estimate of mild vs. no NAFLD from the study by Kim et al. [18]), the pooled RR was 2.52 (95% CI 1.07–5.96), but there was evidence of considerable heterogeneity between studies ($I^2 = 90\%$).

ALT and GGT

Study characteristics of the 18 prospective population-based studies of the associations of ALT and/or GGT with incident

diabetes are also summarized in Table 2. Ten studies (4–6,21–28) (including the current analysis of the British Women's Heart and Health Study [BWHHS]) assessed both ALT and GGT as predictors of diabetes, an additional three studies looked at ALT only (29–31), and another four studies looked at the association of GGT with diabetes risk (3,32–34). Age-adjusted and fully adjusted study results examining (natural logged) ALT and GGT as determinants of incident diabetes were pooled (separately).

A change in one logged unit in ALT was associated with an HR of 3.05 (95% CI 2.59–3.59, $I^2 = 26\%$, 13 comparisons) and in GGT 2.56 (2.31–2.84, $I^2 = 32\%$, 17 comparisons) (online appendix Fig. A1). The meta-analysis of fully adjusted results for both ALT and GGT are presented in Fig. 1. The fully adjusted HR for diabetes per increase in one unit of logged ALT was 1.85 (1.57–2.18, $I^2 = 19\%$, 14 comparisons), and in one unit of logged GGT the HR was 1.92 (1.66–2.21, $I^2 = 55\%$, 18 comparisons).

No strong evidence was found for the presence of a small-studies effect for ALT or GGT. There was also no strong evidence of an association between duration of follow-up and study results (all $P > 0.69$).

Comparing associations of ALT and GGT with incident diabetes

Seven studies (including the BWHHS) contributed to the analysis of ALT and GGT categorized in fourths as predictors of diabetes (4,5,21,22,24,25). Additional studies assessed both ALT and GGT; however, one used fifths (26,27), another used tenths (6), and a final study (28) used fourths but did not present results in full and therefore could not be included in this analysis. Age-adjusted pooled analyses of the included studies are presented in online appendix Figure A2. The RR in the top versus the bottom quartile of ALT was 4.42 (95% CI 3.61–5.42, $I^2 = 42\%$), and for GGT it was 5.87 (4.63–7.44, $I^2 = 21\%$). The fully adjusted RR for ALT was 2.02 (1.59–2.58, $I^2 = 27\%$) and for GGT 2.94 (1.98–3.88, $I^2 = 20\%$) (Fig. 2). According to a formal statistical test for heterogeneity between estimates for ALT and GGT, there was some evidence suggesting that pooled estimates for GGT were larger than those for ALT (age-adjusted results, $P = 0.08$, and fully adjusted results, $P = 0.05$).

However, repeating the analysis after excluding results for women in the DESIR

(Data From the Epidemiological Study on the Insulin Resistance Syndrome) cohort (4), which was the only study that showed a potential protective effect of ALT, resulted in greater pooled estimates for GGT (HR 2.91 [95% CI 2.19–3.85]) than for ALT (2.12 [1.66–2.72]) but no strong evidence for heterogeneity between the estimates ($P \geq 0.10$ for both age-adjusted and fully adjusted results).

CONCLUSIONS — Ultrasound-diagnosed NAFLD, ALT, and GGT all predicted diabetes risk. NAFLD defined by ultrasound was associated with more than a doubling of the risk of incident diabetes. In a meta-analysis of fully adjusted results (albeit variably adjusted) of all population-based, systematically identified prospective studies, a 1 unit/l increase of natural logged ALT was associated with an 85% increase in diabetes risk and a 1 unit/l increase of natural logged GGT was associated with a 92% increase in diabetes risk.

A second meta-analysis that assessed the association of both ALT and GGT (using fourths of their distribution) with incident diabetes in the same populations was performed. Belonging to the top fourth of the GGT distribution was associated with a 194% increase in the risk of diabetes compared with risk increase associated with belonging to the bottom fourth. For ALT, the corresponding increase in the risk of diabetes was 102%, with formal evidence of heterogeneity between these two estimates (both based on fully adjusted models).

There are two possible explanations for the potentially stronger association of GGT with diabetes compared with that of ALT. First, both ALT and GGT are biomarkers of liver fat, but GGT may simply be the better marker. In light of the paucity of relevant evidence as to which liver enzyme better reflects liver fat content, this explanation cannot be ruled out. However, GGT is present on the surface of most cell types and is highly active in organs other than the liver, such as the kidney and pancreas (35). Therefore, ALT is considered a more liver-specific marker than GGT. GGT is the enzyme responsible for the extracellular catabolism of antioxidant glutathione (36) and may be linked to greater oxidative stress (37). Because oxidative stress has been implicated in insulin resistance, diabetes, and cardiovascular disease (37,38), GGT's potentially stronger association with diabetes may reflect its associations with several

Table 2—Summary of included studies

Exclusion criteria	Age (years)	n cases/n participants	Female sex (%)	Main results	Enzymes studied and categories	Follow-up (years)	Covariables
Diabetes, positive for hepatitis B virus surface antigen, hepatitis C virus antibody, ALT or AST > 3 times the upper normal limit, liver cirrhosis, and malignancy	20–79	203/3,670 men; 31/1,702 women	32	RR of mild fatty liver vs. nonfatty liver 1.55 (95% CI 1.05–2.31); RR of moderate-to-severe fatty liver vs. nonfatty liver 1.97 (1.23–3.16)	—	5	Age, sex, family history of diabetes, smoking, blood pressure, fasting glucose, BMI, ALT, HDL cholesterol, and triglycerides
Diabetes or fasting glucose > 110 mg/dl	43 ± 4.3	66/467 men; 16/373 women	44	OR of fatty liver vs. no fatty liver 1.83 (95% CI 0.95–3.51)	—	10	Age, sex, BMI, change in BMI, fasting plasma glucose, A1C, frequency of medical check-ups, alcohol intake, and family history of diabetes
Daily alcohol intake > 20 g, impaired glucose tolerance or diabetes, medications for hypertension, dyslipidemia, liver disease, thyroid disease positive for markers of viral hepatitis, CVD, and gastrectomy	≥40	109/3,189 men	0	HR of fatty liver vs. no fatty liver 5.5 (95% CI 3.6–8.5)	—	Mean: 4	Age and BMI
Diabetes	30–65	69/2,071 men; 30/2,130 women	51	—	ALT, AST, and GGT in quartiles	3	GGT: age, smoking, physical activity, and ALT; ALT: age and GGT
Diabetes	60–79	112/3,041 women	100	—	ALT and GGT	Median: 7.3	Age, childhood and adult social class, physical activity, smoking, alcohol intake, HOMA, waist-to-hip ratio, triglycerides, HDL cholesterol, and SBP

Table 2—Continued

	Exclusion criteria	Age (years)	n cases/n participants	Female sex (%)	Main results	Enzymes studied and categories	Follow-up (years)	Covariables
Doi, 2007 (ref. 21), Hisayama Study, Japan	Diabetes	40–79	71/719 men; 64/1,085 women	60	—	ALT, AST, and GGT in quartiles	Mean: 9	Age, family history of diabetes, fasting insulin, BMI, waist-to-hip ratio, total cholesterol, HDL cholesterol, triglycerides, CRP, hypertension, alcohol intake, smoking, and physical activity
Ford, 2008 (ref. 22), EPIC-Potsdam, Germany	Diabetes	40–65	787/3,011	57	—	ALT and GGT	Mean, 7; median 6.6	Age, sex, alcohol consumption, smoking, education, sports activity, occupational activity, waist circumference, BMI, SBP, total cholesterol, HDL cholesterol, CRP, and glucose
Hanley, 2004 (ref. 23), IRAS, U.S.	Diabetes	40–69	148/906	56	—	ALT, AST, and ALP in quartiles	Mean: 5.2	Age, sex, ethnicity, clinical center, alcohol intake, smoking, waist circumference, triglycerides, HDL cholesterol, impaired glucose tolerance, insulin sensitivity index, and acute insulin response
Lee, 2003 (ref. 24), Korea	Liver disease and diabetes	25–55	83/4,088 men	0	—	ALT, GGT, and AST in 6 categories (≤ 0.9 , 1.0–1.9, 2.0–2.9, 3.0–3.9, 4.0–4.9, and > 4.9 units/l)	4	Age, BMI, smoking, physical activity, family history of diabetes, fasting glucose, and alcohol intake

Table 2—Continued

	Exclusion criteria	Age (years)	n cases/n participants	Female sex (%)	Main results	Enzymes studied and categories	Follow-up (years)	Covariables
Lee, 2003 (ref. 32), CARDIA Study, U.S.	Diabetes	18–33	157/4,812	53	—	GGT in 25th, 50th, 75th, and 90th percentiles	15	Age, sex, race, study center, alcohol intake, BMI, smoking, physical activity, fasting glucose, and insulin
Lee, 2004 (ref. 33), Finland	Diabetes	25–64	212/9,771 men; 176/10,387 women	52	—	GGT in 25th, 50th, 75th, and 90th percentiles	Mean 12.7	Age, BMI, smoking, physical activity, alcohol intake, physical activity, and fasting glucose
Meisinger, 2005 (ref. 34), MONICA, Augsburg, Germany	Diabetes	25–64	172/1,851 men; 109/1,836 women	50	—	GGT in 25, 50, 75, and 87.5 percentiles	Mean 14.7	Age, hypertension, dyslipidemia, parental history of diabetes, regular smoking, alcohol intake, physical activity, and BMI
Monami, 2008 (ref. 25), FIBAR Study, Italy	Diabetes, liver disease other than NAFLD, metastatic cancer, severe heart failure, recent cholelithiasis, alcohol consumption >2 drinks a day, and hepatotoxic medication	40–75	36/2,662	57	—	ALT, AST, and GGT per increase in 10 units/l	Mean ± SD 3.3 ± 1	Age, sex, alcohol consumption, smoking, and fasting glucose
Nakanishi, 2003, 2004 (refs. 26,27), Japan	Hepatitis treatment, ALT >3 times the upper limit of the reference range, CVD, and diabetes	35–59	276/3,260 men	0	—	ALT, AST, GGT, and ALP in quintiles	7	Age, family history of diabetes, BMI, alcohol intake, smoking, physical activity, WBC, and all other liver enzymes
Nannipieri, 2005 (ref. 28), Mexico City Diabetes Study, Mexico	Type 1 diabetes, liver enzymes >3 SD above the mean, and alcohol intake >250 g/week	35–64	94/1,233	60	—	ALT, AST, GGT, and ALP in thirds	7	Age, BMI, waist, fasting insulin, and alcohol intake
Ohlson, 1988 (ref. 31), Sweden	Diabetes	54	47/766 men	0	—	ALT and AST in quintiles	13.5	Glucose, BMI, bilirubin, SBP, uric acid, and family history

Table 2—Continued

	Exclusion criteria	Age (Years)	n cases/n participants	Female sex (%)	Main results	Enzymes studied and categories	Follow-up (years)	Covariables
Perry, 1998 (ref. 3), British Regional Heart Study, U.K.	Diabetes	40–59	194/7,458 men	0	—	GGT in quintiles	Mean: 12.8	Age, BMI, physical activity, alcohol intake, smoking, preexisting CHD, SBP, heart rate, HDL cholesterol, uric acid, FEV ₁ , hematocrit, and glucose
Sattar, 2004 (ref. 29), WOSCOPS, Scotland	Diabetes, CHD, ALT >70 or AST >60 units/l, and all moderately hypercholesterolemic men	Mean 55	139/6,595	0	—	ALT in quintiles	4.9	Age, BMI, smoking, SBP, HDL cholesterol ratio, pravastatin treatment, triglycerides, alcohol intake, fasting glucose
Schindhelm, 2005 (ref. 30), Hoorn Study, the Netherlands	Diabetes	50–75	123/1,289	N/A	—	ALT in tertiles	6	Age, sex, follow-up duration, waist circumference, BMI, alcohol intake, fasting insulin, and 2-h postload glucose
Vozarova, 2002 (ref. 6), U.S.	Diabetes, impaired glucose tolerance, smoking, clinical or lab evidence of acute or chronic infection, and liver enzymes >3 times the upper limit	18–50	63/370	38	—	ALT, AST, GGT, and ALP in percentiles	Mean 6.9	Age, sex, % body fat, acute insulin response, and M-low
Wannamethee, 2005 (ref. 5), British Regional Heart Study, U.K.	Diabetes and ALT or GGT >3 times the upper limit of the reference range	60–79	100/3,500	0	—	ALT, AST, and GGT in quintiles	Mean 5	Age, social class, physical activity, smoking, alcohol intake, preexisting CHD or stroke, status, BMI, and HOMA-IR

Data for age are means \pm SD or range. Data for follow-up are *n* unless otherwise indicated. ALP, alkaline phosphatase; AST, aspartate aminotransferase; CARDIA Study, Coronary Artery Risk Development in Young Adults Study; CHD, cardiovascular heart disease; CRP, C-reactive protein; CVD, cardiovascular disease; EPIC-Potsdam Study, European Prospective Investigation Into Cancer and Nutrition–Potsdam Study; FEV₁, forced expiratory volume in 1 s; FIBAR Study, Firenze Bagno a Ripoli Study; HOMA-IR, HOMA of insulin resistance; IRAS, Insulin Resistance Atherosclerosis Study; M-low, glucose disposal during a low-dose insulin infusion; MONICA Study, Monitoring of Trends and Determinants in Cardiovascular Disease Study; N/A, not available; SBP, systolic blood pressure; WBC, white blood cell; WOSCOPS, West of Scotland Coronary Prevention Study.

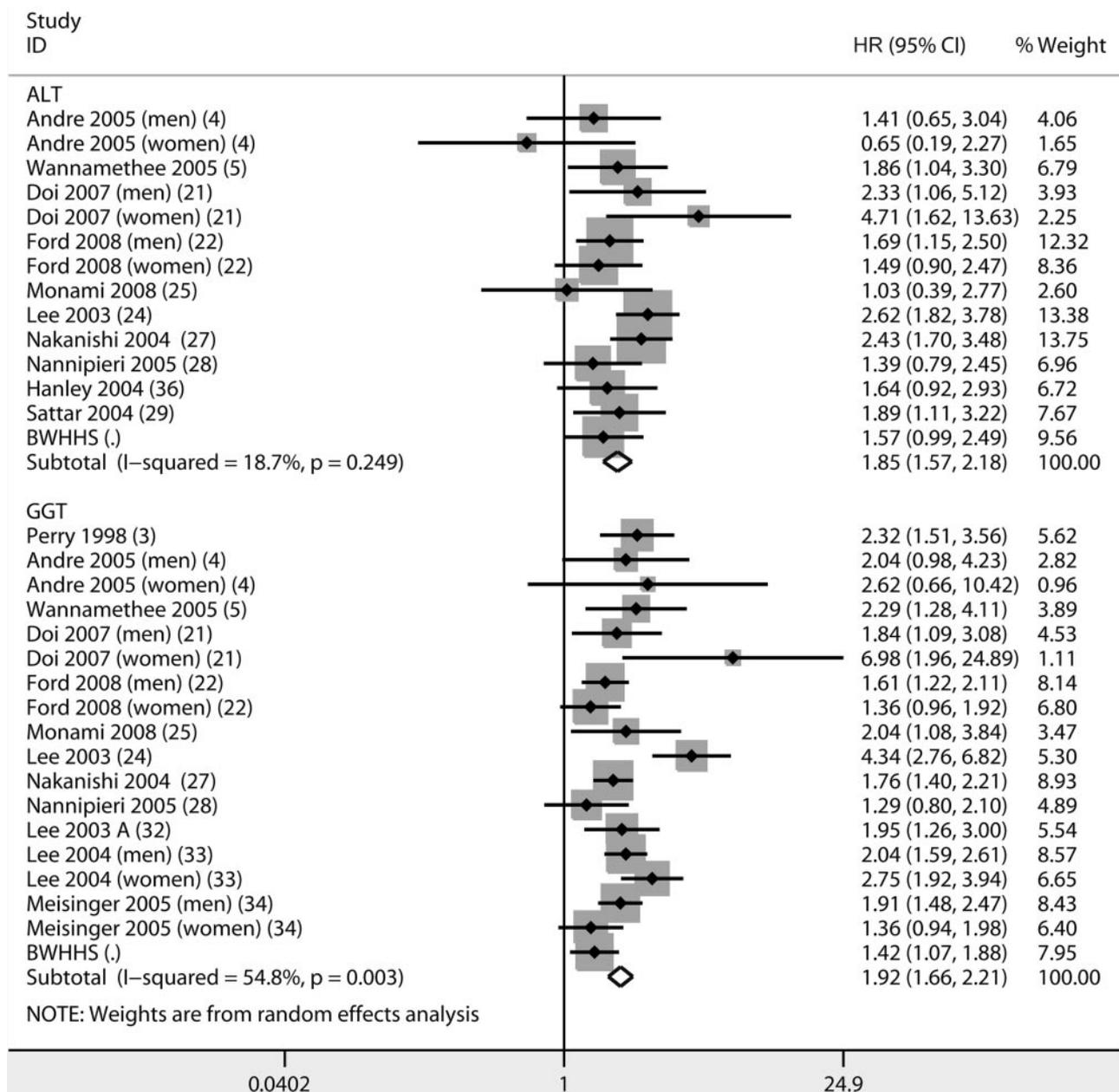


Figure 1— Meta-analysis of fully adjusted results of ALT and GGT as a determinant of incident diabetes.

different processes relevant to diabetes pathogenesis. This speculative suggestion requires more data.

Although a stronger association of GGT (compared with that of ALT) with diabetes is biologically plausible, our results should be interpreted with caution. The exclusion of a single observation substantially reduced the strength of evidence that the associations of ALT and GGT with incident diabetes were different. In addition, some limitations should be noted. Only 6 of the 10 studies that presented results for both ALT and GGT could be included in the meta-analyses of the risk estimates in the top fourth of the

ALT and GGT distributions versus the bottom fourth (despite our best efforts to contact and obtain relevant information from authors, results in the form necessary to include the additional three studies were not forthcoming). An additional limitation is that two of the studies included in the systematic review could not be included in the meta-analysis of all studies as a result of missing information. Attempts were made to obtain additional results from study authors, but this was not always possible. Limitations of the BWHHS include the lack of oral glucose tolerance testing at baseline, the use of self-reported medical diagnoses of diabe-

tes at follow-up, a less robust measure of insulin resistance (HOMA), and the inclusion of women only. The latter is also the study's strength because 6 of the 18 studies do not include any women.

In conclusion, NAFLD and associated elevations in liver enzymes are associated with incident diabetes above and beyond commonly measured diabetes risk factors. Results suggest that the association of GGT with diabetes risk may be of greater magnitude than that of ALT with diabetes, but further studies are needed to confirm this. In the meantime, raised levels of both enzymes in the context of other clinical features of insulin resistance (obe-

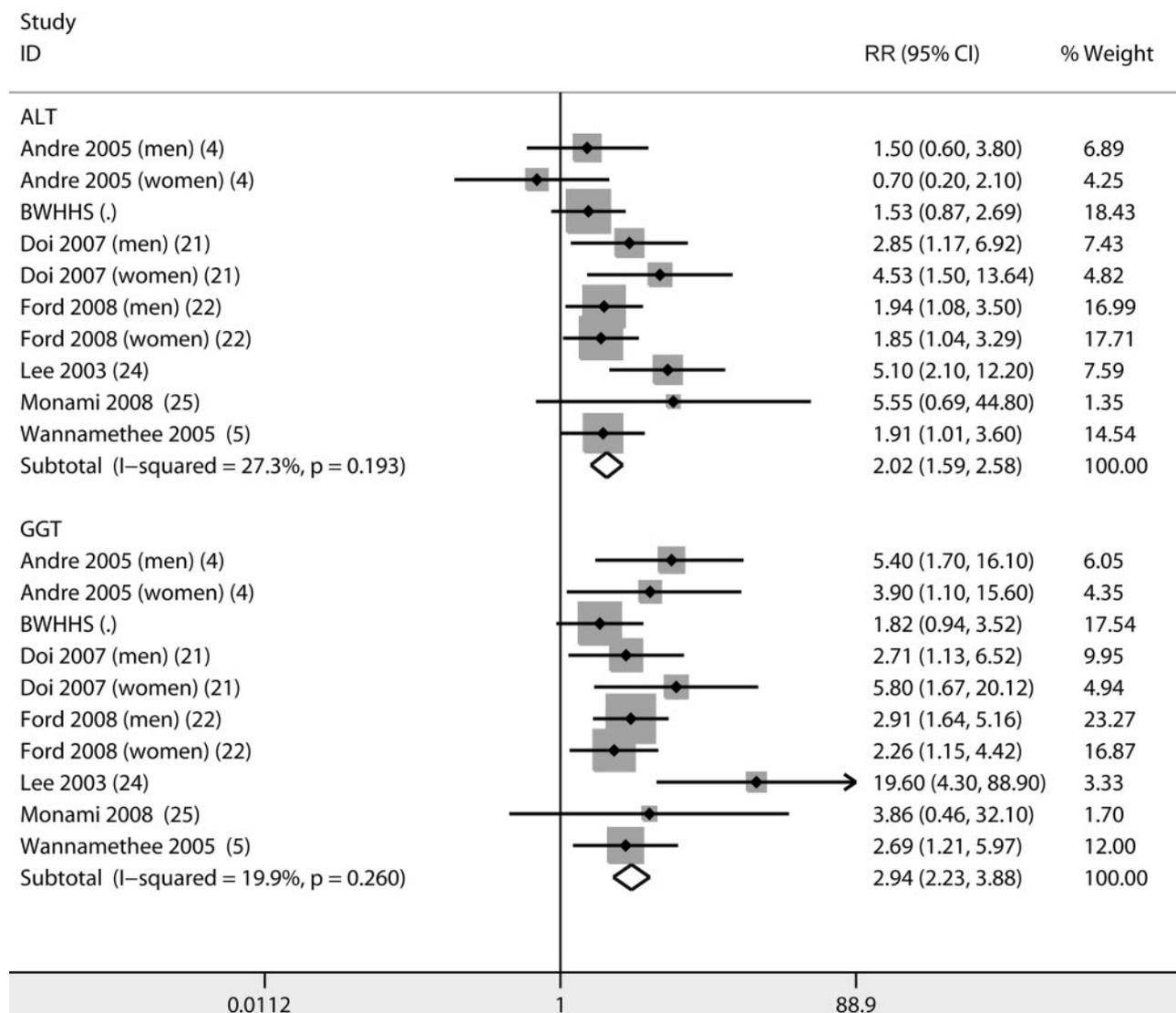


Figure 2—Meta-analysis of fully adjusted results (RR in top versus bottom fourth) of ALT and GGT as determinants of incident diabetes.

sity, hypertriglyceridemia, raised fasting glucose, etc.) give good insight into excess hepatic fat and thus elevated diabetes risk.

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