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# Persistent elevation of liver function enzymes within the reference range is associated with increased cardiovascular risk in young adults: the Bogalusa Heart Study

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**Abstract**

Elevations in alanine aminotransferase (ALT) and γ-glutamyl transferase (GGT), markers of liver dysfunction and nonalcoholic fatty liver, are considered as part of the metabolic syndrome and related diseases. However, information is limited regarding the persistence (tracking) in levels of these enzymes over time and their influence on cardiovascular (CV) risk in young adults. The study sample consisted of white and black subjects (N = 489, 40% male, 73% white; baseline age, 18-32 years) followed over a period of 12 years as part of the Bogalusa Heart Study, with repeat measurements of CV risk factor variables and liver enzymes. Both at baseline and follow-up, males vs females had higher ALT ($P < .01$ to .0001) and GGT ($P < .0001$); blacks vs whites had higher GGT ($P < .0001$). With respect to persistence in enzyme levels over time, of those individuals who had ALT and GGT at the top quintile specific for age, race, and sex at baseline, about 50% of them continued to remain so with high values after 12 years. Individuals with levels persistently in the highest quintile vs those in the lowest quintile showed higher ($P < .0001$) body mass index, waist circumference, triglycerides, low-density lipoprotein cholesterol, glucose, insulin, insulin resistance index, and systolic and diastolic blood pressures; lower ($P < .0001$) high-density lipoprotein cholesterol; and higher ($P < .05$ to .001) prevalence of obesity, hypertension, dyslipidemia, metabolic syndrome as defined by the National Cholesterol Education Program Adult Treatment Panel III, positive parental history of type 2 diabetes, and coronary heart disease. In addition, based on a multivariate analysis using 2 separate models for ALT and GGT, baseline levels of both enzymes were independent predictors of follow-up; insulin resistance index and baseline GGT were also predictive of follow-up systolic blood pressure. Elevations in liver enzymes ALT and GGT, within "reference" range, persist over time and relate to clinically relevant adverse CV risk profile in young adults.


## 1. Introduction

Nonalcoholic fatty liver (NAFL), a metabolic consequence of obesity, is increasingly being considered as a hepatic expression of metabolic syndrome [1-5]. Nonalcoholic fatty liver is commonly associated with long-term elevations in liver enzymes such as alanine aminotransferase (ALT) and γ-glutamyl transferase (GGT) [3,6,7]. These enzymes are suggested to have substantial clinical and epidemiological significance as useful noninvasive surrogate markers of NAFL and related liver dysfunction [6,7].

Recent epidemiological and clinical studies have reported a strong association of ALT and GGT with metabolic syndrome and related clinical manifestations including cardiovascular (CV) disease and type 2 diabetes mellitus [8-13]. However, information is limited regarding the persistence (tracking) of increased levels of these enzymes over time and their effect on CV risk in young adults. As part of the Bogalusa Heart Study, a biracial (black-white) community-based investigation of the early natural history of CV disease [14], the present study examines the tracking of ALT and GGT within "reference" range over time and their association with CV risk in terms of metabolic syndrome and parental histories of coronary heart disease and type 2 diabetes mellitus in apparently healthy young adults.

## 2. Methods

### 2.1. Study population

Three cross-sectional surveys were performed on young adults during 1985-1986, 1988-1991, and 2000-2001 in the

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community (65% whites, 35% blacks) of Bogalusa, LA. The study cohort (N = 489; 73% white, 40% male) was selected from those who were fasting and had data on ALT and GGT along with other risk factor variables, and participated in the baseline survey of 1985-1986 or 1988-1991 (baseline age: 25.6 year) as well as the follow-up survey of 2000-2001 (follow-up age, 37.9 years), with a follow-up period of at least 12 years or more. Individuals with liver enzyme values above the reference range (ALT, 0-55 IU/L; GGT, 0-65 IU/L) were excluded. The baseline characteristics of the study cohort were similar to the rest of the participants examined at the baseline survey with respect to liver enzyme levels and other risk factor variables (data not shown). This study was approved by the institutional review board of the Tulane University Health Sciences Center (New Orleans, LA). All participants gave their informed consent.

### 2.2. General examination

Standardized protocols were used by trained observers in all examinations. Subjects were instructed to fast for 12 hours before the screening, with compliance ascertained by an interview on the day of examination. Anthropometric and blood pressure measurements were made in replicate, and mean values were used in all analyses. Height and weight were measured to calculate body mass index (BMI; weight in kilograms divided by the square of height in meters) as a measure of overall adiposity. Waist circumference was measured midway between lower rib cage and iliac crest, as an indicator of visceral fatness. Replicate blood pressure measurements were obtained on the right arm of the subjects in a relaxed, sitting position. Systolic and diastolic blood pressures were recorded at the first and fifth Korotkoff phases, respectively, using a mercury sphygmomanometer. Study subjects were asked through a questionnaire whether either or both biological parents had histories of coronary heart disease (myocardial infarction, bypass surgery, balloon angioplasty, and angina) and type 2 diabetes mellitus, surrogate measures of CV risk. Individuals were considered smoker if they reported current use of cigarette or having stopped smoking only within the past year. Similarly, individuals were considered alcohol drinker if they reported current consumption of alcohol or having stopped alcohol drinking only within the past year.

### 2.3. Laboratory analyses

Cholesterol and triglyceride levels in the serum were assayed using enzymatic procedures on the Hitachi 902 Automatic Analyzer (Roche Diagnostics, Indianapolis, IN). Serum lipoprotein cholesterol levels were analyzed by a combination of heparin-calcium precipitation and agar-agarose gel electrophoresis procedures [15]. The laboratory is being monitored for precision and accuracy of lipid measurements by the Lipid Standardization and Surveillance Program of the Centers for Disease Control and Prevention (Atlanta, GA). A commercial radioimmunoassay kit was used for measuring plasma immunoreactive insulin levels (Phadebas; Pharmacia Diagnostics, Piscataway, NJ). Glucose, ALT, and GGT levels were measured as part of a multiple chemistry profile (SMA20) by enzymatic procedures with the multichannel Olympus Au-5000 analyzer (Olympus, Lake success, NY). Insulin resistance status was assessed using the homeostasis model assessment of insulin resistance (HOMA-IR) according to the formula described previously [16]: insulin ($\mu$U/mL) × glucose (mmol/L) ÷ 22.5.

### 2.4. Statistical analysis

All statistical analyses were performed with SAS version 9.1 (SAS institute, Cary, NC). Values of ALT, GGT, triglycerides, insulin, and HOMA-IR were log transformed in the analyses to improve normality. General linear models were used to examine race and sex differences in liver enzymes at baseline and follow-up. All *P* values were 2-tailed and adjusted for covariates where appropriate. To determine the persistence of ALT and GGT levels over time, the study subjects were ranked according to age-, race-, and sex-specific quintiles of ALT and GGT at baseline and follow-up. Subjects whose liver enzyme levels were persistently in the highest or lowest quintile during both baseline and follow-up surveys were categorized as having persistently high or low ALT or GGT levels. Follow-up risk factor characteristics (measures of obesity [BMI and waist circumference], systolic and diastolic blood pressures, lipids and lipoprotein variables [low-density lipoprotein cholesterol—LDL-C, high-density lipoprotein cholesterol—HDL-C, and triglycerides], and measures of glucose homeostasis

Table 1
Mean ± SD of the liver enzymes by race and sex at baseline and follow-up in young adults: the Bogalusa Heart Study

| Variable | Male | | Female | | Comparison (*P*) | |
|---|---|---|---|---|---|---|
| | White (n =150) | Black (n = 45) | White (n = 207) | Black (n = 87) | Sex | Race |
| Baseline | | | | | | |
| Age (y) | 25.7 ± 3.1 | 26.0 ± 3.03 | 25.6 ± 3.1 | 25.3 ± 3.0 | NS | NS |
| ALT (IU/L) | 27.2 ± 20.1 | 29.3 ± 25.3 | 14.2 ± 7.7 | 14.1 ± 8.7 | <.0001 | NS |
| GGT (IU/L) | 20.9 ± 19.1 | 34.3 ± 44.9 | 10.8 ± 8.3 | 18.4 ± 18.9 | <.0001 | <.0001 |
| Follow-up | | | | | | |
| Age (y) | 38.0 ± 3.1 | 38.3 ± 3.1 | 37.8 ± 3.1 | 37.6 ± 3.0 | NS | NS |
| ALT (IU/L) | 37.2 ± 24.7 | 30.5 ± 14.6 | 19.2 ± 13.0 | 16.9 ± 9.5 | <.01 | NS |
| GGT (IU/L) | 46.7 ± 52.2 | 55.8 ± 72.5 | 21.6 ± 18.2 | 35.5 ± 46.6 | <.0001 | <.01 |

NS indicates not significant.

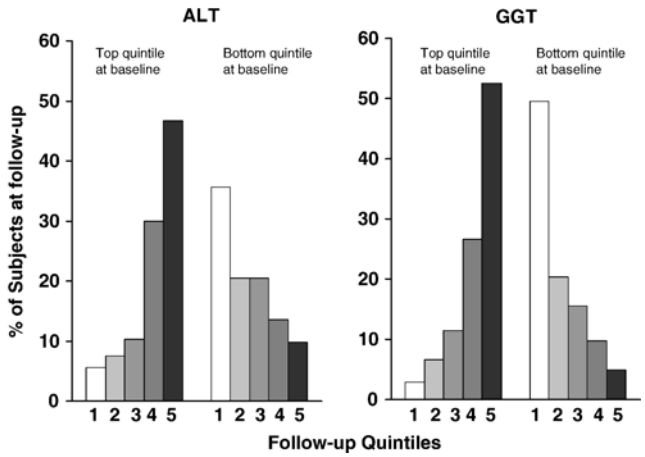


Fig. 1. Tracking of ALT and GGT over a 12-year period in young adults: the Bogalusa Heart Study. The degree of tracking was evaluated in terms of distribution by quintiles at follow-up of subjects who were in the extreme top or the bottom quintile specific for age, race, and sex at baseline. The percentage on the vertical axis denotes the proportion of subjects remaining in each quintile at follow-up.

[insulin, glucose, and HOMA-IR]) associated with persistently high vs persistently low ALT and GGT levels were compared after adjusting for age, race, and sex. Parental histories of type 2 diabetes mellitus and coronary heart disease were also compared between subjects with persistently high vs persistently low ALT and GGT levels.

The prevalence of obesity (BMI >30 kg/m$^2$), hypertension (systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg or being treated for the condition), dyslipidemia (total cholesterol >240 mg/dL or LDL-C >160 mg/dL or HDL-C <40 mg/dL or triglycerides >150 mg/dL or being treated for the condition), and metabolic syndrome (≥3 risk factors defined by National Cholesterol Education Program Adult Treatment Panel III [17]) were compared with the use of $\chi^2$ analysis between groups with persistently high and low levels of ALT and GGT to examine the status of abnormalities (high-risk) at follow-up.

In 2 separate multiple regression analyses, levels of ALT (model 1) and GGT (model 2) at baseline were evaluated as an independent predictor of follow-up level of risk factor variables. The model adjusted for age, race, sex, BMI, alcohol consumption status, and cigarette smoking status included either baseline ALT or GGT as the main predictor along with follow-up HOMA-IR, systolic blood pressure, triglyceride, HDL-C, and LDL-C as applicable. For example, when HOMA-IR was a dependent variable, other follow-up risk variables were used as covariates.

## 3. Results

Mean levels of ALT and GGT at baseline and follow-up are shown in Table 1 by race and sex. At baseline and follow-up, GGT levels were higher in blacks vs whites ($P <$ .0001 to .01) and males vs females ($P <$ .0001), whereas ALT levels were higher only in males vs females ($P <$ .0001 to .01).

Subjects with relatively high/low liver enzyme levels at baseline tended to have retained such levels 12 years later. As shown in Fig. 1, when subjects were grouped into quintiles according to age-, race-, and sex-specific rankings of ALT and GGT levels, a higher-than-expected number of individuals who ranked high (>80th percentile) or low (<20th percentile) in ALT and GGT levels at baseline maintained their respective ranks at follow-up. Of those individuals who had high levels of liver enzymes at baseline, about 50% continued to have elevated levels after 12 years. If there were no tracking of levels, one would expect only 20% in the highest or lowest quintile at follow-up by chance alone.

Follow-up risk factor characteristics of subjects with persistently high vs low levels of ALT and GGT are shown in Table 2. Subjects with persistently high vs low levels of

Table 2
Follow-up characteristics related to CV risk in young adults with persistently high vs low levels of liver enzymes over a 12-year period: the Bogalusa Heart Study

| Risk factor variables (mean ± SD) | ALT | | GGT | |
|---|---|---|---|---|
| | Persistently low[a] (n = 47) | Persistently high[b] (n = 50) | Persistently low (n = 51) | Persistently high (n = 55) |
| BMI (kg/m$^2$) | 26.8 ± 6.6 | 30.7 ± 5.4** | 27.6 ± 5.9 | 30.0 ± 5.9** |
| Waist circumference (cm) | 83.3 ± 13.3 | 101.9 ± 15.1** | 86.7 ± 15.9 | 100.3 ± 16.0** |
| Systolic BP (mm Hg) | 113.0 ± 13.2 | 123.4 ± 12.5** | 111.2 ± 10.8 | 125.6 ± 11.7** |
| Diastolic BP (mm Hg) | 75.8 ± 8.8 | 84.6 ± 9.9** | 74.5 ± 7.8 | 86.0 ± 9.7** |
| Triglyceride (mg/dL) | 99.7 ± 45.4 | 190.3 ± 143.6** | 107.3 ± 59.9 | 229.4 ± 192.4** |
| HDL-C (mg/dL) | 53.8 ± 13.6 | 41.9 ± 14.5** | 54.8 ± 11.5 | 47.5 ± 19.1* |
| LDL-C (mg/dL) | 113.3 ± 33.1 | 128.2 ± 39.8** | 115.6 ± 32.1 | 132.1 ± 40.5** |
| Insulin ($\mu$U/mL) | 9.3 ± 5.8 | 18.1 ± 12.0** | 9.0 ± 4.0 | 16.8 ± 10.5** |
| Glucose (mg/dL) | 82.0 ± 10.4 | 90.0 ± 24.7* | 80.6 ± 7.3 | 92.1 ± 26.5** |
| HOMA-IR | 2.0 ± 1.5 | 4.2 ± 3.1** | 1.8 ± 0.9 | 3.9 ± 2.7** |

Systolic BP indicates systolic blood pressure; diastolic BP, diastolic blood pressure.

[a] Less than age-, race-, and sex-specific 20th percentile.

[b] Greater than age-, race-, and sex-specific 80th percentile.

* $P <$ .001, persistently high vs low (adjusted for covariates where appropriate).

** $P <$ .0001, persistently high vs low (adjusted for covariates where appropriate).

Table 3
Prevalence of CV risk factors at follow-up according to liver enzyme status over a 12-year period in young adults: the Bogalusa Heart Study

| Prevalence (%) | ALT | | GGT | |
|---|---|---|---|---|
| | Persistently Low[a] (n = 47) | Persistently High[b] (n = 50) | Persistently Low (n = 51) | Persistently High (n = 55) |
| Obesity | 21.3 | 58.0** | 29.4 | 45.5* |
| Hypertension | 8.5 | 30.0** | 2.0 | 38.2** |
| Dyslipidemia | 4.3 | 14.0** | 21.7 | 61.8** |
| Metabolic Syndrome | 8.5 | 40.0** | 7.8 | 38.2** |

Obesity indicates BMI of >30; hypertension, systolic blood pressure of >140 mm Hg or diastolic blood pressure of >90 mm Hg or being treated for the condition; dyslipidemia, total cholesterol of ≥240 mg/dL or LDL-C of ≥160 mg/dL or HDL-C of <40 mg/dL or triglycerides of ≥150 mg/dL or being treated for the condition; metabolic syndrome, ≥3 risk factors defined by the National Cholesterol Education Program Adult Treatment Panel III.

[a] Less than age-, race-, and sex-specific 20th percentile.

[b] Greater than age-, race-, and sex-specific 80th percentile.

* $P < .05$.

** $P < .001$.

these enzymes had significantly higher BMI, waist circumference, systolic and diastolic blood pressures, triglycerides, LDL-C, insulin, glucose, and HOMA-IR ($P < .001$ to .0001), and lower HDL-C ($P < .001$). In addition, as shown in Table 3, individuals with persistently high vs low enzyme levels had increased prevalence of high-risk conditions of obesity, hypertension, dyslipidemia, and metabolic syndrome ($P < .05$ to .0001). With respect to metabolic syndrome, as shown in Fig. 2, significant ($P < .05$) clustering of 2 or more metabolic syndrome components occurred in subjects with persistent elevations in either ALT or GGT levels. On the other hand, the prevalence of individuals with no clustering was 2.4-fold ($P < .05$) higher among those with persistently low vs high levels of ALT or GGT.

Baseline levels of liver enzymes as predictors of adverse levels of CV risk factor variables at follow-up were examined in separate multivariate models. Baseline ALT as well as GGT was predictive of follow-up insulin resistance index (HOMA-IR) independent of other risk factors, whereas baseline GGT also predicted follow-up systolic blood pressure (Table 4).

Table 4
Baseline liver enzymes as predictors of follow-up risk factor variables in young adults: the Bogalusa Heart Study

| Follow-up risk variables | Baseline ALT (regression coefficient $\beta$[a]) | Baseline GGT (regression coefficient $\beta$[a]) |
|---|---|---|
| HOMA-IR | .006* | .004** |
| Systolic blood pressure | .043 | .062** |
| Triglyceride | .001 | .002 |
| HDL-C | .033 | .052 |
| LDL-C | −.154 | −.030 |

[a] The model adjusted for age, race, sex, BMI, alcohol consumption status, and cigarette smoking status included either baseline ALT or GGT as the main predictor along with follow-up HOMA-IR, systolic blood pressure, triglyceride, HDL-C, and LDL-C as applicable.

* $P < .05$.

** $P < .001$.

The prevalence of parental histories of type 2 diabetes mellitus and coronary heart disease is shown in Fig. 3 by the status of ALT and GGT. Among those with persistently high vs low ALT levels, parental type 2 diabetes mellitus and parental CHD occurred 2.0-fold ($P < .0001$) and 1.5-fold ($P < .001$), respectively. Likewise, parental type 2 diabetes mellitus and parental CHD occurred 1.7-fold ($P < .001$) and 1.8-fold ($P < .001$), respectively, among those with persistently high vs low levels of GGT.

## 4. Discussion

The present community-based study demonstrates that elevations in enzymes ALT and GGT, biomarkers of liver dysfunction and NAFL, persist over time and relate adversely to metabolic syndrome and its components as well as to parental histories of coronary artery disease and

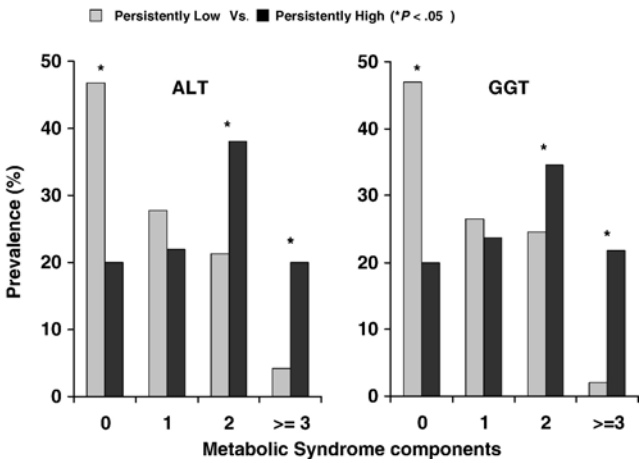


Fig. 2. Clustering of metabolic syndrome components at follow-up in young adults by liver enzyme status over a 12-year period: the Bogalusa Heart Study.

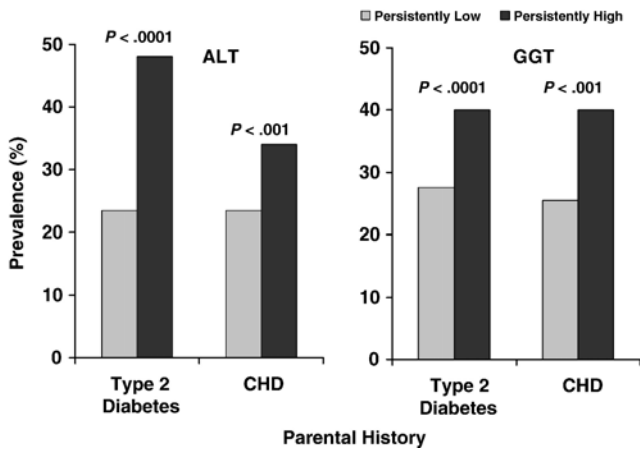


Fig. 3. Prevalence of parental history of type 2 diabetes mellitus and coronary heart disease at follow-up in young adults by liver enzyme status over a 12-year period: the Bogalusa Heart Study.

type 2 diabetes mellitus in asymptomatic, healthy young adults. These longitudinal observations in a relatively younger adult cohort are noteworthy in that they strongly support the notion of pathophysiologic link between NAFL, metabolic syndrome, and related CV risks, as part of the natural history of CV disease.

In this study, about 50% of the cohort maintained their baseline levels (high or low) after 12 years of follow-up. Although earlier studies have shown tracking of CV risk factor variables, individually or in combination, over time [18-21], no such data on ALT and GGT are available for comparison.

The adverse associations between NAFL disease (or related abnormal elevations in liver function enzymes) and pathophysiologically interrelated conditions of metabolic syndrome and its components have been found in previous studies [1-5,8-11]. In the present study, even within the reference range of ALT/GGT enzymes, excess prevalence of clinically high-risk conditions of obesity, dyslipidemia, hypertension, and metabolic syndrome was noted among those who were persistently in the highest vs lowest quintile distribution of either of these enzymes. Of note, in a multivariate analysis adjusted for adiposity and other CV risk factor variables, baseline ALT as well as GGT predicted follow-up measure of insulin resistance, the underlying feature of metabolic syndrome [22,23], in an adverse manner. In addition, GGT predicted systolic blood pressure. Although the observational nature of this study cannot address the issue of causality or the underlying mechanisms involved in the previously mentioned relationships, current knowledge on this subject provides some explanation.

The adverse relationship of liver enzymes to risk variables of metabolic syndrome may be the consequence of link between excess central (visceral) adiposity, NAFL, and hepatic insulin resistance mediated by increased hepatic free fatty acid flux from visceral fat leading to increased hepatic lipogenensis and triglyceride-rich lipoprotein secretion [2,3,24,25], which in part is due to induction of sterol-regulating binding protein and fatty acid synthase [26,27]. Furthermore, excess central adiposity (and by inference NAFL) enhances the expression of proinflammatory adipocytokines including tumor necrosis factor $\alpha$ and decreases the expression of insulin-sensitizing and anti-inflammatory adiponectin, resulting in increase in insulin resistance [28-30]. In turn, insulin resistance increases reactive oxygen species and oxidative stress by attenuating the inhibitory effect of insulin on lipid oxidation and by activating CYP2E1, a component of the cytochrome P-450 system [31].

The observed independent association of baseline GGT, but not ALT, with follow-up systolic blood pressure is consistent with the results of earlier reports [13,32,33] and may reflect the role of GGT in the dynamics of free radical generation, a factor involved in the pathogenesis of hypertension [34-36]. $\gamma$-Glutamyl transferase is considered to help maintain adequate levels of hepatic glutathione, an antioxidant [34,35]. Generation of excess free radicals associated with NAFL and central obesity may deplete glutathione levels thereby causing induction of GGT to counteract the adverse effect. However, the production of the GGT reaction in the presence of iron may itself lead to excess generation of free radicals [34,35].

A positive parental history is recognized as a surrogate indicator of future risk in the offspring, given the familial nature of CV disease and type 2 diabetes mellitus [37,38]. In addition, parental histories of CV disease and type 2 diabetes mellitus are shown to be associated with unfavorable CV risk factor profile in the offspring [39,40]. This study shows a significantly higher prevalence of parental histories of coronary heart disease and type 2 diabetes mellitus in the study cohort with persistently high vs low levels of ALT or GGT.

The observed higher ALT in blacks vs whites and males vs females are consistent with previous findings [6,11]. However, no such data are available for GGT for comparison. The race-sex differences in ALT and GGT may reflect the differences in the prevalence of NAFL noted previously [6].

This study has certain limitations in that it lacks direct assessment of body fat mass and distribution, liver fat content, and in vivo insulin action used in clinical and etiological studies. Instead, we used well-established measures that are appropriate to population studies. Furthermore, parental histories of coronary heart disease and type 2 diabetes mellitus were not verified in this study. Previous studies, including our own, noted a concordance of 78% to 83% between reported and verified cases [41,42]. It should be mentioned that nonsystemic misclassification of self-reported parental histories would most likely result in an underestimation of the strength of association.

In summary, elevations in levels of liver enzymes ALT and GGT persist over time and relate to higher prevalence of obesity, dyslipidemia, hypertension, and metabolic syndrome as well as parental histories of coronary heart disease and type 2 diabetes mellitus in apparently healthy young adults. When viewed in the context of upward secular trends in the prevalence of obesity [43,44] and ALT [45], and higher prevalence of metabolic syndrome [46] and NAFL [6] in the US population, these results underscore the potential utility of ALT and GGT as biomarkers in the evaluation of CV risk in asymptomatic young people.

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