

The association of elevated alanine aminotransferase and the metabolic syndrome in an overweight and obese pediatric population of multi-ethnic origin

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Abstract We studied the association between alanine aminotransferase (ALT) and features of the metabolic syndrome in a cohort of overweight and obese children aged 3–18 years. An oral glucose tolerance test was performed in 443 consecutive children from an obesity out-patient clinic (median age 11.2, range 3.1–18.0 years; $n=240$ boys) of multi-ethnic origin. The prevalence of the metabolic syndrome, insulin resistance, elevated ALT (>30 IU/L), and the association of ALT with (components of) the metabolic syndrome was assessed. The metabolic syndrome was present in 26.9%. Elevated ALT levels were found in 20.3%, with a higher prevalence in boys than in girls (25.8% versus 13.8%, $P<0.001$). ALT was

associated with the prevalence of the metabolic syndrome, insulin resistance, high triglycerides, and low HDL-cholesterol after adjustment for gender, age, and BMI. In conclusion, elevated ALT levels were highly prevalent and associated with the metabolic syndrome, insulin resistance, high triglycerides, and low HDL-cholesterol in an obese multiethnic pediatric population.

Keywords Pediatrics · Obesity · Metabolic syndrome · Insulin resistance · Alanine aminotransferase · Non-alcoholic fatty liver disease

Abbreviations

OR	Odds ratio
CI	Confidence interval
CVD	Cardiovascular disease
NAFLD	Non-alcoholic fatty liver disease
ALT	Alanine aminotransferase
SDS	Standard deviation score
IDF	International Diabetes Federation
Z-BMI	Standard deviation score of BMI
Z-WC	Standard deviation score of waist circumference

Introduction

As in adults, the prevalence of obesity in children worldwide as well as its cardiometabolic sequelae are rapidly increasing [27]. Although criteria for the metabolic syndrome in children and adolescents have only started to become formally defined, components of the adult metabolic syndrome, including central obesity, insulin resistance, glucose intolerance, hypertriglyceridemia, low HDL-choles-

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terol and hypertension have been reported in pediatric populations [16].

In adults, non-alcoholic fatty liver disease (NAFLD) and the more advanced stage, i.e. non-alcoholic steatohepatitis, are considered the hepatic manifestation of the metabolic syndrome and are associated with type 2 diabetes and a high risk of atherothrombotic cardiovascular disease [17]. Currently, NAFLD as a clinicopathologic condition is associated with childhood obesity and considered a major cause of abnormal liver function tests of unknown origin in pediatric populations [25]. Insulin resistance and hyperinsulinemia are regarded as critical factors in the pathogenesis of fatty liver disease. Conversely, fatty liver contributes to hepatic insulin resistance leading to increased glucose and triglyceride output by the liver and to lowered HDL-cholesterol levels [17].

In adults, the estimated prevalence of NAFLD ranges from 3% to 24% [8]. According to recently reported autopsy findings, fatty liver was present in 13% of 742 deceased children and adolescents aged 2–19 years [24]. After adjustment for age, gender, and ethnicity, the prevalence was 9.6%, increasing with age. Since obesity-related NAFLD may be associated with cardiometabolic risk factors in children, early identification of children at risk for developing type 2 diabetes and cardiovascular disease later in life is fundamental.

Alanine aminotransferase (ALT) is the liver enzyme with the closest association with liver fat accumulation [23], and consequently has been used as a circulating marker of NAFLD.

In this study, we established the prevalence of (components of) the metabolic syndrome, insulin resistance, and additional cardiometabolic risk factors in an obese population, and subsequently assessed the association of ALT with the presence of these cardiometabolic risk factors.

Methods

Data on a cohort of children aged 3–18 years who attended the pediatric obesity out-patient clinic at a general hospital in the Netherlands (Slotervaart Hospital, Amsterdam) in the period 2004–2007 were collected according to a prevailing treatment protocol. Severity of obesity was classified according to Dutch age- and gender-adjusted criteria from the ‘Fourth National Growth Study’ [11]. Children who used glucose- or lipid-lowering drugs, corticosteroids (chronically), drugs acting on the central nervous system, or children with (suspected) syndromes, type 1 diabetes, or secondary causes of obesity such as hypothyroidism, hypogonadism, and pituitary disorders were excluded from the study. In total, 443 children of multiethnic origin were included. None of the recruited subjects had a history of

alcohol abuse, and serologic tests for hepatitis B or C virus were negative in all. Each child underwent an oral glucose tolerance test (OGTT; 1.75 g glucose per kg of body weight, with a maximum of 75 g), with concomitant collection of blood samples for determination of fasting lipids, insulin, and ALT. At the same time, BMI, waist circumference, blood pressure, and Tanner’s pubertal stages were assessed. BMI values were standardized according to Dutch reference values using Z-scores (Z-BMI), which are standard deviation score (SDS) [11]. Children with a SDS from 1.1 to 2.3 were classified as overweight and children with ≥ 2.3 SDS were classified as obese. Waist circumference values were also standardized using Z-scores (Z-WC), applying Dutch reference values (cut-off values were 1.3 SDS for overweight and 2.3 SDS for obesity) [10].

Table 1 shows the definitions of the cardiometabolic risk factors and the metabolic syndrome. Glucometabolic disorders were defined by the presence of either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) or both, or type 2 diabetes, according to the IDF-criteria, with a cut-off point of 5.6 mmol/l for fasting glucose [2]. Hypertension was established according to previously reported European height- and gender-adjusted cut-off points [9], and lipid levels were assessed according to international criteria adjusted for age and gender [3]. The metabolic syndrome was defined according to the presence of overweight or obesity in addition to two of the components shown in Table 1 [28, 29]. Insulin resistance was assessed according to the homeostasis model assessment for insulin resistance (HOMA-IR): fasting plasma insulin ($\mu\text{U/l}$) \times fasting glucose (mmol/l) / 22.5 [18], with insulin resistance defined as HOMA-IR ≥ 3.5 [15].

Table 1 Definition of (components of) the metabolic syndrome

Component	Definition
1) Glucometabolic disorders	Impaired fasting glucose (IFG): fasting glucose ≥ 5.6 mmol/l Impaired glucose intolerance (IGT): 2 h-glucose ≥ 7.8 and < 11.0 mmol/l Diabetes: fasting glucose ≥ 7.0 or 2 h-glucose ≥ 11.0 mmol/l
2) Low HDL-cholesterol	$< p5$ for age and gender
3) High Triglycerides	$> p95$ for age and gender
4) High systolic or diastolic blood pressure	$> p95$ for height and gender

The metabolic syndrome includes overweight or obesity and two or more of the mentioned components

We chose a cut-off value of ALT >30 IU/l, which was shown to have the optimal sensitivity and specificity to predict NAFLD in a comparable population [21] and was further validated in the NHANES III study [26].

Laboratory analysis

Plasma glucose, ALT, and lipids were determined with SYNCHRON LX 20 (Beckman Coulter, Galway, Ireland), with intra-assay coefficients of variation (CV) of $\leq 3.5\%$ for ALT and $\leq 3\%$ for plasma glucose and fasting lipids. LDL-cholesterol was calculated with the Friedewald-formula [12]. Plasma insulin was determined with a chemiluminiscent immunometric assay (Immulite 200 system, Siemens Medical Diagnostics, Los Angeles, USA), intra-assay CV 3–6%, inter-assay CV 3–5%, detection-value 15 pmol/l.

Statistical analysis

Categorical data are presented as percentages, and continuous data are presented as means \pm standard deviation (SD), or median (interquartile range [IQR]) for variables with a skewed distribution. Differences in clinical and biochemical character-

istics were tested by Student's *t* tests for continuous variables and with χ^2 tests for categorical data.

The presence of cardiometabolic risk factors and the metabolic syndrome were determined according to gender, ethnicity, and ALT values (normal ALT group: ALT ≤ 30 IU/l and high ALT group: ALT >30 IU/l). To assess the association between ALT (as continuous variable) with (components of) the metabolic syndrome, logistic regression analyses were applied. To investigate the association between ALT and continuous metabolic variables, multivariate linear regression analyses were performed. In these models the individual metabolic parameter was entered as independent variable and ALT was entered as outcome variable, with additional adjustment for age, gender, and Z-BMI. Effect modification by pubertal stage, gender, and degree of obesity (overweight vs. obese) was tested by entering interaction terms (pubertal stage \times ALT, gender \times ALT, and degree of obesity \times ALT) into the models. Analyses were performed with SPSS software (version 15.0 for Windows, SPSS Inc., Chicago, IL). A two-sided *P* value <0.05 was considered statistically significant and a two-sided *P* value <0.1 was used to indicate effect modification.

Table 2 Baseline characteristics and prevalence of cardiometabolic risk factors, stratified according to normal and high ALT

	Total	ALT ≤ 30 IU/l	ALT >30 IU/l
<i>N</i>	443	353	90
Male/female	264 (54.2%) / 203 (45.8%)	178 (50.4%) / 175 (49.6%)	62 (68.9%) / 28 (31.1%)**
Pubertal	280 (63.2%)	217 (61.5%)	63 (70.0%)
Age (y)	11.2 (10.0–14.5)	11.2 (8.8–13.6)	11.5 (10.0–14.5)***
Z-BMI	2.8 \pm 0.5	2.8 \pm 0.5	2.9 \pm 0.5
Z-WC	3.9 \pm 1.2	3.8 \pm 1.2	4.3 \pm 1.1**
Systolic blood pressure (mmHg)	115 (108–122)	113 (108–121)	118 (110–127)
Diastolic blood pressure (mmHg)	70 (65–76)	70 (65–75)	73 (68–79)***
Fasting plasma glucose (mmol/l)	5.3 \pm 0.4	5.2 \pm 0.4	5.3 \pm 0.4
2-h plasma glucose (mmol/l)	5.8 \pm 1.0	5.8 \pm 0.9	6.0 \pm 1.2
Fasting plasma insulin (pmol/l)	102 (64–162)	96 (62–145)	131 (84–198)**
HOMA-IR	3.3 (2.0–5.4)	3.2 (2.0–5.0)	4.5 (2.5–6.7)**
Total cholesterol (mmol/l)	4.3 \pm 0.8	4.3 \pm 0.8	4.4 \pm 0.8
HDL-cholesterol (mmol/l)	1.1 (0.9–1.2)	1.1 (0.9–1.3)	1.0 (0.8–1.2)**
LDL-cholesterol (mmol/l)	2.8 \pm 0.7	2.8 \pm 0.7	2.9 \pm 0.6
Triglycerides (mmol/l)	0.8 (0.6–1.2)	0.8 (0.5–1.2)	1.0 (0.7–1.4)**
(Components of) the metabolic syndrome and insulin resistance			
Metabolic syndrome	115 (26.9%)	77 (22.7%)	38 (43.3%)*
Glucometabolic disorders	101 (23.5%)	71 (20.7%)	30 (34.4%)**
High triglycerides	78 (17.6%)	51 (14.4%)	27 (30.0%)**
Low HDL-cholesterol	141 (31.8%)	102 (28.9%)	39 (43.3%)***
Hypertension	102 (23.3%)	77 (21.8%)	26 (28.9%)
Insulin resistance	209 (47.2%)	155 (43.9%)	54 (60.0%)**

Data are mean \pm SD and *n* (%) or median (interquartile range) for variables with a skewed distribution

P values are given for comparisons between normal and high ALT groups tested with independent sample *t* tests, nonparametric tests, and χ^2 tests
SD standard deviation, Z-BMI standard deviation score of BMI, Z-WC standard deviation score of waist circumference, ALT alanine aminotransferase, HOMA-IR homeostasis model assessment for insulin resistance

P*<0.001; *P*<0.01; ****P*<0.05 for comparisons between the ALT ≤ 30 and ALT >30 IU/l groups

Results

General characteristics of the study population

Table 2 shows the baseline characteristics of the study population. The cohort comprised mainly four different ethnic groups: Dutch native (19.0%), Turkish (27.5%), Moroccan (25.5%), and Surinamese (9.7%). The remaining children (18.3%) were of diverse origins, including Asian, African, and South-American or had parents with different ethnic backgrounds.

The median age of the participants was 11.2 years, with ages ranging from 3.1 to 18.0 years. Boys had a higher mean Z-BMI (2.9 vs. 2.7, $P=0.002$) as well as a higher Z-WC compared to girls (4.3 vs. 3.5, $P<0.001$). Seventy children (15.8%) were classified as overweight (12.9% boys, 19.2% girls) and 373 (84.2%) as obese (87.1% boys, 80.8% girls).

The metabolic syndrome was detected in 26.9% of the children, with a similar prevalence in boys and girls.

Glucometabolic disorders were present in 23.5%, high triglycerides in 17.6%, low HDL-cholesterol in 31.8%, and hypertension in 23.3% of the participants. Of the children with glucometabolic disorders, 20.5% had IFG, 1.6% had IGT, and 0.5% had type 2 diabetes. Insulin resistance was present in 47.2% of the children. Elevated ALT levels (>30 IU/l) were found in 20.3% of the study population, with a higher prevalence found in boys than in girls (25.8% vs. 13.8%, $P<0.001$). In addition, male subjects had higher median ALT values in comparison with their female peers (median 28, IQR 18–31 vs. median 23 IQR 15–26 IU/l, $P<0.001$). The difference in prevalence of abnormal ALT values between the pubertal and prepubertal group was not statistically significant (22.5% vs. 16.6%, $P=0.14$).

There were no significant differences in prevalence of (the components of) the metabolic syndrome or high ALT between the overweight and obese group (data not shown). Therefore, overweight and obese children were pooled for the univariate and multivariate analyses. Among the ethnic groups, no significant differences in prevalence of elevated ALT values or mean ALT values were found. In addition, no ethnic-related differences were found in the prevalence of the various cardiometabolic risk factors, except for the prevalence of insulin resistance and the metabolic syndrome, both of which were highest in Turkish children, as compared to their peers of other origins (56.4% vs. 43.4%, $P=0.019$ and 35.2% vs. 23.7%, $P=0.016$, respectively).

Apart from obesity, 38.8% of the children had no components of the metabolic syndrome, while 34.3% had one component. The prevalence of the number of children who had two components was 19.6%, and for more than two the occurrence was 7.3%.

Prevalence and associations of cardiometabolic risk factors and insulin resistance according to ALT

Table 2 shows the biochemical variables and prevalence of the different cardiometabolic risk factors in the two ALT groups (high ALT group [>30 IU/l] and normal ALT group [≤ 30 IU/l]). The prevalence of the metabolic syndrome and three of its components (high triglycerides, low HDL-cholesterol, and glucometabolic disorders) were significantly higher in the high ALT group, in comparison with the normal ALT group ($P<0.001$ for the metabolic syndrome, $P=0.001$ for high triglycerides, $P=0.011$ for low HDL-cholesterol, and $P=0.008$ for glucometabolic disorders). In addition, insulin resistance was more abundant in the high ALT group ($P=0.007$). The mean number of components of the metabolic syndrome was 0.9 in the low ALT group and 1.4 in the high ALT group ($P<0.001$).

Z-BMI was more strongly associated with ALT than the Z-values of waist circumference (beta, 0.05; 95% confidence interval (95% CI); 0.01–0.09 vs. beta, 0.02; 95% CI, 0.004–0.04, respectively). We found a strong association between ALT and the metabolic syndrome (odds ratio (OR), 7.1; 95% CI, 2.3–21.5), adjusted for age, gender, and Z-BMI, which remained significant after additional adjustment for insulin resistance (OR, 3.6; 95% CI, 2.1–6.1). With regard to the individual components of the metabolic syndrome, ALT was associated with high triglycerides and low HDL-cholesterol (OR, 10.3; 95% CI, 3.0–35.3 and OR, 3.9; 95% CI, 1.4–11.0, respectively), but not with glucometabolic disorders and hypertension. Moreover, ALT was

Table 3 Associations of ALT with metabolic variables and blood pressure

Variable	Beta (95%CI)	P value
Fasting glucose (mmol/l)	−0.002 (−0.03 to 0.02)	0.865
2-hour glucose (mmol/l)	0.08 (0.01–0.14)	0.017
HOMA-IR		
- Prepubertal	0.42 (0.18–0.65)	0.001
- Pubertal	0.48 (0.25–0.71)	<0.001
Total cholesterol (mmol/l)	0.04 (−0.006 to 0.09)	0.088
HDL-cholesterol (mmol/l)		
- Male	−0.02 (−0.04 to 0.007)	0.163
- Female	−0.04 (−0.07 to −0.008)	0.013
LDL-cholesterol (mmol/l)	0.04 (0.003–0.09)	0.036
Triglycerides (mmol/l)		
- Prepubertal	0.04 (−0.01 to 0.10)	0.130
- Pubertal	0.06 (0.004–0.11)	0.037
Systolic blood pressure	0.30 (−0.38 to 0.98)	0.390
Diastolic blood pressure	0.26 (−0.23 to 0.76)	0.297

All variables are tested with regression analyses
Beta values are given for each ten unit increase in ALT after adjustment for age, gender, and Z-BMI
Z-BMI standard deviation score of BMI, ALT alanine aminotransferase, HOMA-IR homeostasis model assessment for insulin resistance

associated with insulin resistance (OR, 4.1; 95% CI, 1.3–13.1).

Table 3 shows the beta values for the association of ALT and different metabolic variables including glucose, lipids, HOMA-IR, and blood pressure, per increase of ten units of ALT, adjusted for age, gender, and BMI. These associations were significant for all lipid levels (except for total cholesterol), as well as for fasting insulin levels, 2h-glucose levels, and HOMA-IR, after adjustment for age, gender, and Z-BMI. Interestingly, no significant association was found between ALT and fasting plasma glucose in obese children, and a negative association was even seen in overweight children.

It is of notice that the association between ALT and several different variables (fasting insulin levels, HOMA-IR, and triglycerides) were significantly influenced by pubertal status (effect modifier), while the association between ALT and low HDL-cholesterol was influenced by gender. After stratification of these data, the association between elevated ALT and triglycerides remained significant only in the pubertal group, while fasting insulin levels and HOMA-IR remained significant in both the prepubertal and pubertal groups. HDL-cholesterol was only significantly associated with ALT in females.

Discussion

The main findings of this observational study are the high prevalence of cardiometabolic risk factors, including the metabolic syndrome and elevated ALT, as a marker of NAFLD in an obese multi-ethnic pediatric cohort.

There is no consensus regarding the definition of the metabolic syndrome in children, due to a lack of uniformity in the components and their cut-off values, taking into account age, gender, pubertal status, and ethnicity. In a previous report among 86 prepubertal and 105 pubertal children, with comparable criteria for the metabolic syndrome as in our study, the prevalence of the metabolic syndrome varied from 12.0% (moderately obese) to 31.1% (severely obese) [7]. It is of notice that, when the recently proposed IDF-criteria are applied [2], the prevalence of the metabolic syndrome in our population would equal 25.7%. Still, the two definitions have no total overlap; only 72.0% of the children would meet the criteria for both definitions of the metabolic syndrome (data not shown). In addition to the high prevalence of the lipid criteria of the metabolic syndrome, which include low HDL-cholesterol and high triglycerides, we found elevated total cholesterol in 12.0% and high LDL-cholesterol levels in 16.3% of children, both corrected for age and gender.

Our study is the first to report the prevalence of cardiometabolic risk factors in a large number of children

of multiethnic origin in the Netherlands. In a recent Dutch study in adults, the prevalence of the metabolic syndrome (IDF-criteria) was highest in Hindustani Surinamese men followed by African Surinamese and Dutch men, occurring in 51.0%, 31.2%, and 19.4%, respectively, and for women, both the Hindustani and African Surinamese participants had a higher prevalence of the metabolic syndrome than those of Dutch origin [5]. Among obese Turkish children living in Turkey [1], hypertension was present in 15.7% and the metabolic syndrome in 21.0%, whereas 29.2% had either low HDL-cholesterol or high triglycerides (in our study nearly 50%, with no significant differences among ethnicities). These numbers indicate less dyslipidemia among Turks living in Turkey, presumably due to different dietary habits. According to our findings, Turkish children are more insulin resistant (as determined by HOMA-IR) and have higher prevalence of the metabolic syndrome than their peers from other ethnic groups. In a previous study, the metabolic syndrome, but not HOMA-IR, independently predicted subclinical atherosclerosis and incident cardiovascular disease [4]. Thus, although insulin resistance is correlated with the metabolic syndrome, it may not enclose all the cardiometabolic risk factors associated with insulin resistance. Still, given the high prevalence of the metabolic syndrome in our Turkish children, they may be at greater risk for developing cardiovascular disease later in life.

Hyperinsulinemia and insulin resistance, as confirmed by hyperinsulinemic-euglycemic clamps, are generally more abundant among pubertal children in comparison with prepubertal populations. Decreased glucose oxidation and increased free fatty acid (FFA) oxidation characterize pubertal insulin resistance, partially mediated by the growth hormone/insulin-like growth factor-I (GH/IGF-I) axis. We found a high prevalence of IFG in our cohort (13.5% in prepubertal and 24.6% in pubertal children). This may be due to the cut-off value of 5.6 mmol/l for fasting glucose which might be too low (especially in prepubertal children) [30], but could also indicate impaired basal insulin secretion and hepatic insulin resistance in these children [19].

ALT is regarded as a marker of NAFLD [23]. Whereas the sole determination of ALT does not prove the existence of NAFLD, a strong correlation was found between ALT and hepatic steatosis measured by proton magnetic resonance spectroscopy (¹H-MRS) even after adjustment for BMI, ethnicity, gender, and age [6]. Conversely, in the same study, only 48% of subjects with a fatty liver had abnormal ALT levels, indicating that our data may underestimate the prevalence of NAFLD in our population. To note, the prevalence of NAFLD in obese children in Western populations ranges from 9.5% (according to ALT >30 IU/l) [26] to 38% (based on >5% hepatocytes containing fat) [24] and 44% (based on liver ultrasound) [21].

We confirmed a higher prevalence of elevated ALT in pubertal boys, as compared to girls [25]. This gender-difference may be explained by the preferential intra-abdominal location of fat in males which may predispose for the development of NAFLD [25]. Also, the lower levels of sex hormone binding globulin in men, which, together with the ensuing higher levels of free, metabolically active androgens, are associated with insulin resistance and a high risk of NAFLD [13]. Finally, the difference in prevalence of NAFLD between boys and girls may be due to a larger liver mass in males. The role of pubertal stage in the development of fatty liver remains controversial since contradictory findings have been reported. Apparently, other factors beside insulin resistance are involved in the pathogenesis of NAFLD.

Previous studies have shown that ethnicity can influence the risk for developing NAFLD; Hispanic populations were shown to carry a high risk [25]. In our study, we found no differences in ALT values or the presence of high ALT among the ethnic groups.

As supported by previous published data [17, 21], ALT was independently associated with insulin resistance. Interestingly, we found no association between ALT and fasting glucose, which is regarded as a result of the contribution of hepatic insulin resistance, but most importantly, of beta-cell dysfunction. Overall, it may be concluded that, although previous reports have described beta cell dysfunction in obese pediatric populations [14], beta-cell dysfunction at a young age may be less explicit. The significant association of ALT and fasting plasma triglycerides in pubertal but not prepubertal children indicates a sequence of the developmental stages of hepatic insulin resistance over time.

In a longitudinal study in adults, elevated ALT was associated with an increased incidence of the metabolic syndrome [14], a finding which sheds light on the possible causative role of NAFLD in the development of the clustered cardiometabolic risk factors. In young adults, ALT predicted cardiometabolic risk factors, even within the ALT reference range [20], and ALT was shown to predict cardiovascular disease in adults with and without type 2 diabetes [22]. The ‘portal hypothesis’, which implicates that abundant insulin-resistant visceral fat increases lipolytic activity and, consequently, the delivery of free fatty acids to the liver, as well as an important role for dietary fat, as a major contributor to the development of NAFLD, are among the explanations of the pathophysiology of NAFLD [20, 22].

This study has several limitations, including the lack of a normal-weight control group, which precluded generalization of our results. Also, since the cut-off points for the various components of the metabolic syndrome may not be totally applicable to our population, some misclassification cannot be ruled out. In addition, other forms of liver disease

that could result in elevated ALT levels besides hepatitis B and C (such as alpha-1 antitrypsin deficiency) have not been excluded in this study. Finally, the amount of dietary fat intake, as a risk factor for NAFLD, was not assessed.

In conclusion, in an obese multiethnic pediatric population, elevated ALT, suggestive of the presence of NAFLD, was highly prevalent and associated with (components of) the metabolic syndrome and insulin resistance. These associations were independent of ethnicity, but in part depended on gender and pubertal stage. Longitudinal large-scaled studies in children and adolescents should establish the predictive value of elevated ALT for the risk of developing type 2 diabetes and cardiovascular disease in adulthood.

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