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Prevalence of elevated alanine-aminotransferase (ALT) among US adolescents and associated factors: NHANES 1999-2004

Abigail Fraser¹, Matthew P. Longnecker², and Debbie A Lawlor¹

¹Department of Social Medicine, University of Bristol, Canynge Hall, Whiteladies Rd., Bristol BS8 2PR, UK

²Epidemiology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, NC, USA

Abstract

Background & aims—Non-alcoholic fatty liver disease (NAFLD) is a common cause of liver disease in children and adolescents. The majority of studies of NAFLD in children have been in select populations of the clinically obese. Study aims were to estimate the prevalence of elevated alanine-aminotransferase (ALT, as a marker of NAFLD) in a general contemporary adolescent population and to identify leading risk factors for ALT elevation (> 30 U/L).

Methods—We analysed data of adolescent participants (age 12-19, N=5586) in NHANES 1999-2004, a representative sample of the civilian non-institutionalized U.S population.

Results—The prevalence of elevated ALT (>30 U/L) was 7.4% among white adolescents, 11.5%, among Mexican Americans, and 6.0%, among black adolescents. It was prevalent in 12.4% of males compared to 3.5% of females. Multivariable associations with elevated ALT were found for sex (OR male versus female = 7.7, 95%CI: 3.9, 15.1), ethnicity (OR black versus white=0.6, 95%CI: 0.3, 1.3; OR Mexican American versus white=1.6, 95%CI: 1.0, 2.6), waist circumference (OR per 1 SD=1.4, 95%CI: 1.0, 2.0), and fasting insulin (OR per 1 SD=1.6, 95%CI: 1.2, 2.1). Age, C-reactive protein and triglycerides were also positively, and socio-economic position inversely associated with elevated ALT. The magnitude of associations with ALT was similar across ethnic groups.

Conclusions—ALT is associated with waist circumference and insulin resistance even in a young population. These characteristics could be utilized to identify adolescents who may benefit from screening for NAFLD, offering an opportunity to prevent disease progression at an early age.

Introduction

Non-alcoholic fatty liver disease (NAFLD) consists of a range of liver abnormalities in the absence of other established causes of liver damage, and is the commonest liver disorder in developed countries. In its mildest form (steatosis) it is characterised by an accumulation of triglycerides in hepatocytes, and its more advanced form, non-alcoholic steatohepatitis (NASH), is characterised by liver cell injury.^{1, 2}

Author for correspondence: Abigail Fraser, Department of Social Medicine, University of Bristol, Canynge Hall, Whiteladies Road, Bristol, BS8 2PR. Tel.: +44-117-3313803, Fax: +44-117-3313815, Email: Abigail.fraser@bristol.ac.uk.

Conflict of interest statement

No conflict of interest exists.

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With the epidemic of childhood obesity, and the recognition that the antecedents of obesity, insulin resistance and of NAFLD begin in early life, and that duration of NAFLD probably affects the likelihood of progression to more severe disease, concerns about NAFLD in children and adolescents have become a focus of public health researchers and practitioners.³⁻⁵ The whole spectrum of NAFLD has been described in children,⁴ with NASH first described in a paediatric population in the literature in the 1980s.⁶ Presentation with, and progression to, cirrhosis in children has also been described.^{4, 7, 8}

The diagnosis of NAFLD should be suspected when there is a raised level of alanine-aminotransferase (ALT) and/or echogenic liver detected by ultrasound together with the absence of any established causes of liver disease.⁹ A definitive diagnosis, and determination of severity, requires a liver biopsy, which is not feasible in large-scale epidemiological studies. In epidemiological studies, ALT is the most useful biomarker of NAFLD as it is the liver enzyme most closely correlated to liver fat accumulation.¹⁰ Most studies of the associations between obesity, insulin resistance and NAFLD in children and adolescents have been in select populations of the clinically obese.^{4, 11} Studies of these associations in general population samples of children/adolescents are important because clinical populations may not be representative of associations in obese children who are not referred for medical care. For example, in the US NHANES-III survey overweight and obesity were associated with elevated ALT levels in 12-18 year olds, but the prevalence of elevated levels in those who were obese (10%) was considerably lower than reported levels in clinically based studies (commonly between 25-30%).¹²

In addition to associations with obesity and components of the metabolic syndrome,¹³ other factors may be related to variation in liver enzymes in early life. Limited evidence of early life determinants of NAFLD suggests that NAFLD is more common in males compared to females and amongst adolescents of Hispanic origin (compared to white and black adolescents) and white compared to black adolescents.¹⁴ Similar differences in the prevalence of NAFLD and elevated ALT by ethnic group have been consistently documented in adults.¹⁵⁻¹⁸

Intrauterine factors are important determinants of components of the metabolic syndrome,¹⁹ and there is evidence that intrauterine factors are also important in liver development and function. According to the fetal programming hypothesis, fetal undernutrition in mid and late gestation results in maintaining the brain at the expense of the growth of the trunk, including the liver,²⁰⁻²² which may result in permanent alterations to liver function.²³ In a cohort of older British women, inverse associations between birthweight and levels of ALT, gamma-glutamyltransferase (GGT) and alkaline phosphatase (ALP) were found even when controlling for potential confounders.²⁴

The aims of this study were to estimate the prevalence of ALT elevation in a general adolescent population; to examine whether a range of early life characteristics are associated with elevated ALT in adolescence; and to determine the magnitude and strength of these associations in adolescent participants (defined as age 12-19) in NHANES 1999-2004.

Methods

NHANES is a complex, multistage probability sample of the civilian non-institutionalized population of the U.S.²⁵ Since 1999 NHANES has become a continuous survey. Data from 3 cross-sectional surveys: 1999-2000, 2001-2 and 2003-4 are included here. For our main analyses we included all participants aged 12-19 years. Blood samples were available for participants 12 years old and older and information on birthweight and maternal smoking during pregnancy were available for those aged up to 15 years. Information on ethnicity and family income were obtained from a family member. A poverty-income ratio (PIR) was

calculated for each family based on self-reported family income in relation to poverty threshold, family size and calendar year. Values below 1 are below the official poverty threshold while PIR values of 1 or greater indicate income above the poverty level (range 0-5). Data on age, birthweight and maternal smoking during pregnancy were obtained from an in-person administered questionnaire. The questionnaire was completed by a family member of at least 18 years old who was the most knowledgeable about the child (usually the mother or father).

Participants underwent a medical examination in which weight, standing height and waist circumference were measured in a standardized fashion. Seated resting blood pressure was measured by a physician calculated as the average of available measurements (min 1 max 4), excluding the first measurement if more than one was available. In addition, subjects aged 12 years and older were asked to provide a blood sample that was analyzed for liver enzymes.

ALT, aspartate aminotransferase (AST) and gamma-glutamyltransferase (GGT) were measured using an enzymatic rate method. HDL-c was measured by direct immunoassay. A high sensitivity C-reactive protein assay was conducted using latex-enhanced nephelometry. Fasting insulin, glucose and triglycerides were available for a random subgroup of adolescents who attended the morning clinics (N=2655). Fasting insulin was measured in 1999-2000 using a radioimmunoassay and in subsequent surveys using a two-site immunoenzymometric assay (Pharmacia method in 2001-2002 and using a Tosoh method in 2003-2004). A linear regression model was used to adjust 2001-2002 values to 2003-4 values. The distribution of insulin values in all 3 surveys were comparable. Plasma glucose was measured using an enzyme hexokinase method. The homeostasis model assessment of insulin resistance (HOMA-R) was calculated as the product of fasting glucose (mmol/l) and insulin ($\mu\text{U}/\text{ml}$) divided by the constant 22.5.²⁶ Triglycerides were measured using a timed-endpoint method. Tests for Hepatitis B surface antigen were performed using a sandwich radioimmunoassay (Abbot Laboratories) and specimens were tested for antibody to hepatitis C using direct solid-phase enzyme immunoassay with the anti-HCV screening ELISA. Positive specimens were repeated in duplicate according to the same procedure. Repeatedly positive specimens are tested supplementally using the Chiron RIBA Processor System (Chiron Corporation, Inc.).^{27, 28}

Statistical Analysis

In all analyses both the sampling probability (via weights) and cluster effects due to the correlation of observations among subjects from a given area were accounted for by using the 'svy' procedures in Stata version 9 (Stata corporation, Texas, 2005). ALT, AST, GGT, C-reactive protein, fasting insulin and HOMA-R and triglycerides were naturally log transformed in order to normalize distributions. Fasting insulin and HOMA-R are nearly perfectly correlated (Pearson's $r=0.99$). We report result for fasting insulin, however all results are the same if fasting insulin is replaced with HOMA-R. Logistic regression was used to assess associations of characteristics with elevated ALT, defined as ALT > 30 U/L, the value previously used to define elevated ALT in adolescents in NHANES III (1988-1994).¹² This threshold had a sensitivity of 0.92 for detecting the fatty-fibrotic pattern proven by ultrasound among obese children.²⁹

We conducted a secondary analysis using 40 U/L as a threshold defining elevated ALT for the sake of comparison, as this and similar thresholds have been previously used in studies in adolescents^{13, 30}, and to indicate NAFLD in adults^{15, 18, 31}. In addition, linear regression was used to assess associations of characteristics with ALT as a continuous variable as in general population studies of adults, associations of liver enzymes with BMI and components of the metabolic syndrome are linear and do not demonstrate threshold effects.^{32, 33}

Of 7,205 12-19 year-old adolescents in the 1999-2004 NHANES, 6339 (88%) had data on ALT. Of these, 5 adolescents were positive for Hepatitis B surface antigen and 12 were positive

or indeterminate for Hepatitis C antibody and were subsequently excluded from all analyses. Complete data on all measurements that did not require fasting, except for birthweight and maternal smoking during pregnancy were available for 5,586 adolescents (78% of all adolescents). Data on birthweight and maternal smoking during pregnancy was available only for adolescents 12-15 years old (N=2,686, 95% of 12-15 year-olds with complete data on all other variables). Of the 5,586 adolescents included in this study, 2,655 attended the morning clinics and also had data on fasting insulin, fasting glucose and triglycerides. All analyses included adolescents for whom complete data on all variables were available.

As fasting measurements were only available for a random sub-sample of adolescents, multivariable analyses excluding terms for fasting measurements were constructed for a) all adolescents and b) adolescents for whom fasting measurements were available. This allowed us to compare associations between the whole sample and the sub-group of adolescents who attended the morning clinics. Fasting measurements were then added into the model for the fasting sub-sample and all 3 models are displayed.

Results

Elevated ALT (defined as ALT>30 U/L) was present in 8.0% of the study population. Mean ALT was 19.3 U/L (SD=15.6, IQR: 5-196, range: 5-526). Characteristics of the study population by ALT elevation are presented in Table 1. Among white adolescents the prevalence was 7.4%, among Mexican Americans, it was 11.5%, among blacks adolescents it was 6.0%, and among adolescents classified as 'other' (other race, including multi-racial, other Hispanics) it was 10.6% (Figure 1). Elevated ALT was prevalent among 12.4% of males compared to 3.5% of females. Adolescents with elevated ALT were older, and had higher waist circumference, BMI, systolic blood pressure, CRP, fasting glucose, insulin, triglycerides, AST and GGT. They were also more likely to be poor and had lower HDL-c.

The multivariable associations of characteristics and non-fasting measurements with elevated ALT were comparable for the full sample and the fasting sub-sample, though confidence intervals were wider in the smaller sub-sample (Table 2). Elevated ALT was strongly associated with being older, male, and of Mexican American origin. Elevated ALT was also associated with greater waist circumference, C-reactive protein and systolic blood pressure and more weakly with being poor. When fasting measurements were added, evidence was found for positive associations of fasting insulin and triglycerides with elevated ALT, but not of fasting glucose. As waist circumference was more strongly associated with ALT than BMI, this measure was used in the multivariable models as a marker of adiposity and BMI was not simultaneously included in models containing waist circumference. Replacing waist circumference with BMI did not alter results, except that there was stronger evidence that black ethnic origin was associated with less ALT elevation compared to white ethnic origin (OR=0.5, 95%CI: 0.3, 1.0, p=0.06 in the model including BMI compared to OR=0.7, 95%CI: 0.3, 1.3, p=0.20 in the model including waist circumference). When birthweight and maternal smoking during pregnancy were included in the models, there was no evidence of associations with elevated ALT. Furthermore the associations of other characteristics with elevated ALT were not substantially altered. Therefore models including birthweight and maternal smoking (available only for a sub-group of adolescents 12-15 years old) are not presented. The multivariable model including the fasting measures (fasting sub-sample, model 2, Table 2) was re-run entering standardized continuous variables (i.e. each value of a given characteristic is divided by the standard deviation of that characteristic). This was done in order to compare the strength of the association of each characteristic with elevated ALT. The strongest associations with elevated ALT were for sex (OR male versus female = 7.7), ethnicity (OR black vs. white adolescents=0.6; OR Mexican American vs. white adolescents =1.6), age (OR per 1 SD change =1.7; SD=2.3 years), fasting insulin (OR per 1 SD change =1.6; SD=2.0 µU/l), waist

circumference (OR per 1 SD change =1.4; SD=14.5 cm), C-reactive protein (OR per 1 SD change =1.3; SD=4.2 mg/dl) and triglycerides (OR per 1 SD change =1.2; SD=1.6 mmol/l).

We also repeated the main analysis defining elevated ALT as >40 U/L. The prevalence of ALT>40 in the whole study population was 3.6%. Among males it was 5.6% and among females the prevalence was 1.6%. Among white adolescents it was 3.1%, among Mexican Americans it was 6.1%, and among black adolescents it was 2.3%. Table 3 presents the multivariable model for the fasting sub-sample (equivalent to 'fasting sub-sample 2, Table 2). Results were similar to those obtained for ALT>30 U/L: male sex, Mexican ethnic origin, greater waist circumference, fasting insulin and triglycerides were all associated with ALT>40. C-reactive protein and poverty were no longer associated with the outcome using this higher threshold.

We also repeated the analysis including fasting measures treating ALT as a continuous variable, as opposed to a binary, elevated versus not elevated variable. In this analysis black ethnic origin was associated with lower mean ALT levels (compared to white adolescents). Mexican ethnic origin, male sex, waist circumference, fasting insulin and glucose were positively associated with mean ALT levels. Age, triglycerides, C-reactive protein and PIR were not associated with mean ALT levels.

Finally, as the prevalence of elevated ALT was different among the different ethnic groups we examined the associations in each ethnic group separately. The magnitude and strength of associations did not differ by ethnic group and were not different than those obtained in the models that included the whole sample or the fasting sub-sample (results not shown).

Discussion

Our study aims were to estimate the prevalence of elevated ALT in a general contemporary adolescent population, to examine associations between a range of early life factors with ALT levels and to identify leading risk factors for ALT elevation. We found that the prevalence of elevated ALT, a surrogate marker of NAFLD in the absence of other causes of liver disease, was 8.0% among US adolescents 12-19 years of age. To the best of our knowledge there are only two other published studies in which the prevalence of NAFLD was estimated in a general pediatric or adolescent population and this is the first estimate of the prevalence of ALT elevation in a US adolescent population. Tominaga et al. reported a 2.6% prevalence of NAFLD (based on ultrasound) among Japanese children 4-12 years old.³⁴ Park et al. found a 3.2% prevalence of NAFLD among Korean adolescents 10-19 years old, using ALT with a cut-off value of 40 U/L.¹³ When we applied this threshold to the adolescent participants in NHANES 1999-2004, a similar prevalence of 3.6% was found. In another study, Schwimmer et al. examined liver tissue from autopsies performed on children 2-19 years of age at time of death in the county of San Diego.³⁵ The prevalence of histologically proven NAFLD was 9.6%. Although the sample in that study may not be representative of the community, authors report that the distribution of race, ethnicity and weight in the study population and the county of San Diego were well matched. Other studies assessing the prevalence of NAFLD have done so in select populations, predominantly obese and overweight clinic populations (e.g. 36-38). We found evidence of positive associations between sex (male compared to female), waist circumference, BMI, Mexican ethnic origin, and C-reactive protein and elevated ALT, and weaker evidence that fasting insulin, triglycerides, and poverty were associated with elevated ALT, findings that are consistent with other studies in both general^{12, 13, 34} and select adolescent populations,^{14, 36, 38} as well as in adult populations.^{14, 35, 39, 40}

When associations of participants' characteristics were examined separately per ethnic group, no differences in the magnitude of associations were found. This finding is important since it

suggests that although the prevalence of elevated ALT differed by ethnic group, greater waist circumference and/or BMI is detrimental among all ethnic groups. These findings highlight the importance of greater central or general adiposity as a risk factor for potential liver damage that is manifest at a young age in all ethnic groups.

Although there is some evidence of a developmental origin of NAFLD, we found no association of birthweight or maternal smoking during pregnancy with elevated ALT in this study population. Our findings suggest that childhood obesity is a more important determinant of elevated ALT, an indicator of NAFLD, than factors affecting intrauterine growth.

For our main analyses we used a binary outcome of elevated ALT. In clinical practice it is useful to have a threshold to define normal and abnormal states for risk factors (for example hypertension, overweight or obesity) since this can be used to identify those individuals who would most benefit from preventive interventions (medical or lifestyle). However, in terms of aetiology many risk factors such as blood pressure, blood glucose and lipids do not demonstrate threshold effect, but have linear associations with disease outcomes such as cardiovascular disease across their distribution. There is evidence that this is likely to be the case for ALT, which in adults is linearly associated with diabetes risk³². Furthermore, the threshold for defining elevated ALT in adolescents (or indeed adults) remains unclear. For these reasons we have undertaken analyses with two thresholds that have been previously used in adolescents and also with ALT as a continuous variable. Our results were consistent whether we examined ALT as a continuous outcome or used a threshold of 30U/L or 40 U/L to define ALT elevation.

Several limitations of this study should be mentioned. NAFLD was assessed using a proxy – elevated ALT levels - and not more rigorous diagnostic methods such as imaging techniques or biopsies. However, ALT is a useful biomarker of NAFLD in children²⁹ which is the most common cause of ALT elevation in the absence of other causes of liver disease.⁴¹ In addition, only one ALT measurement was available and ALT levels may fluctuate over time.

Furthermore we could not identify all potential causes of ALT elevation, which is important since higher levels of ALT are seen as a marker of NAFLD in the absence of other specific causes of ALT elevation. Individuals with hepatitis B and C were excluded but other causes such as autoimmune hepatitis and alcohol consumption have not. However, it is unlikely that such occurrences are common and would affect results and when analyses were limited to participants 12-15 years old in which alcohol consumption is probably rare, results were essentially the same as those presented here. Fasting measurements were only available for a random subgroup, therefore power to detect associations with these measures was substantially reduced and estimates are less precise than those available for measures that do not require fasting.

In conclusion, elevated ALT, a marker of NAFLD is prevalent in 8.0% of US adolescents 12-19 years of age. Although the natural history of NAFLD is relatively benign, progression to fibrosis and cirrhosis has been demonstrated in children and adolescents.⁴ Furthermore increasing ALT levels in adults predict incident diabetes and CVD,^{32, 39} and in this study of adolescents were associated with elevated fasting insulin and triglyceride levels and lower HDL-c levels; findings that are consistent with a small number of other studies in children and adolescents.^{7, 13} We found that ALT is associated with BMI, waist circumference and insulin resistance even in a young population, stressing the importance of fighting childhood obesity. Of note, although the prevalence of elevated ALT differed by ethnicity, the magnitude of the associations of all characteristics with ALT were similar across ethnic groups. These characteristics could be utilized by clinicians to identify adolescents who may benefit from screening for NAFLD, thus offering an opportunity to intervene and prevent disease progression at an early age.

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Figure 1.
Prevalence of elevated ALT (>30 U/L) by ethnic group and sex

Table 1

Characteristics by ALT levels (N=5,586, weighted sample N= 25,991,934).

Characteristic	ALT≤30 U/L N=5,095	ALT>30 U/L N= 491	p-value
Continuous variables *			
Age (years)	15.4 (0.1)	16.3 (0.2)	<0.01
Birth weight (kg) [‡]	3.4 (0.0)	3.4 (0.1)	0.64
Waist circumference (cm)	79.7 (0.4)	95.0 (1.1)	<0.01
BMI (kg/m ²)	22.8 (0.14)	28.3 (0.4)	<0.01
Systolic blood pressure (mmHg)	108.1 (0.28)	115.9 (1.0)	<0.01
HDLc (mmol/l)	1.3 (0.3)	1.2 (0.3)	<0.01
CRP (mg/dl) ^{**}	0.05 (1.0)	0.13 (1.1)	<0.01
Fasting glucose (mmol/l) [‡]	5.1 (0.0)	5.4 (0.1)	0.03
Fasting insulin (μU/l) ^{**‡}	8.1 (1.0)	14.2 (1.1)	<0.01
Triglycerides (mmol/l) ^{**‡}	0.9 (1.0)	1.3 (1.1)	<0.01
AST (U/L) ^{**}	21.7 (1.0)	34.3 (1.0)	<0.01
GGT (U/L) ^{**}	13.1 (1.0)	25.8 (1.0)	<0.01
Categorical variables			
Sex			<0.01
Male (%)	87.6	12.4	
Female (%)	96.5	3.5	
Ethnicity (%)			<0.01
White	92.6	7.4	
Black	94.0	6.0	
Mexican-American	88.5	11.5	
Other	89.4	10.6	
Maternal smoking in pregnancy [‡] (%)			0.20
Yes	93.3	6.7	
No	94.8	5.2	
Beneath poverty threshold (%)			0.03
Yes	91.8	8.2	
No	90.0	10.0	

* Means (SE)

** Geometric mean

[‡] Fasting sub-sample N=2655[‡] Available for adolescents 12-15 years old (N=2,686)

Table 2

Multivariable analysis of associations with elevated ALT (>30 U/L)

Variable	Complete data sample N=5,586		Fasting sub-sample, model 1 N=2655		Fasting sub-sample, model 2 N=2655	
	Odds ratio (95%CI)	p-value	Odds ratio (95%CI)	p-value	Odds ratio (95%CI)	p-value
Age (years)	1.1 (1.0, 1.2)	0.03	1.2 (1.1, 1.3)	<0.01	1.3 (1.1, 1.4)	<0.01
Sex (male vs. female)	3.8 (2.6, 5.4)	<0.01	6.7 (3.3, 13.6)	<0.01	7.7 (3.9, 15.1)	<0.01
Ethnicity (vs. White)						
Black	0.9 (0.5, 1.2)	0.23	0.7 (0.3, 1.3)	0.21	0.6 (0.3, 1.3)	0.20
Mexican	1.5 (1.1, 2.0)	<0.01	1.7 (1.0, 2.8)	0.03	1.6 (1.0, 2.6)	0.24
Other	1.7 (1.0, 3.0)	0.07	2.1 (0.8, 5.9)	0.15	2.0 (0.8, 5.1)	0.53
Waist circumference (cm)	1.05 (1.0, 1.1)	<0.01	1.05 (1.04, 1.11)	<0.01	1.05 (1.02, 1.09)	0.04
Systolic blood pressure (mmHg)	1.02 (1.00, 1.04)	0.04	1.02 (0.99, 1.05)	0.27	1.01 (0.98, 1.04)	0.58
HDLc (mmol/l)	0.7 (0.4, 1.3)	0.77	0.4 (0.1, 1.3)	0.12	0.6 (0.2, 1.7)	0.33
CRP (mg/dl)	1.2 (1.1, 1.3)	<0.01	1.2 (1.0, 1.4)	0.05	1.2 (1.0, 1.4)	0.05
PIR (over vs. under poverty threshold)	0.7 (0.5, 1.0)	0.08	0.8 (0.5, 1.6)	0.10	0.8 (0.5, 1.5)	0.07
Fasting glucose (mmol/l)					1.0 (0.8, 1.2)	0.53
Fasting insulin (μU/l)*					1.9 (1.3, 2.8)	0.09
Triglycerides (mmol/l)					1.5 (0.9, 2.4)	0.10

* on a log scale

Table 3

Multivariable analysis of associations with ALT>40

Variable	Fasting sub-sample N=2655	
	OR (95%CI)	p-value
Age (years)	1.3 (1.1, 1.5)	<0.01
Sex (male vs. female)	5.0 (1.6, 15.4)	<0.01
Ethnicity (vs. White)		
Black	0.8 (0.3, 2.0)	0.58
Mexican	2.9 (1.5, 5.7)	<0.01
Other	3.0 (1.0, 8.9)	0.05
Waist circumference (cm)	1.03 (1.01, 1.05)	0.01
Systolic blood pressure (mmHg)	1.0 (1.0, 1.0)	0.90
HDLc (mmol/l)	0.6 (0.1, 2.6)	0.50
CRP (mg/dl) *	1.2 (0.9, 1.7)	0.17
PIR (over vs. under poverty threshold)	1.5 (0.7, 3.2)	0.31
Fasting glucose (mmol/l)	1.0 (0.8, 1.3)	0.70
Fasting insulin (μU/l) *	2.2 (1.2, 4.2)	0.01
Triglycerides (mmol/l) *	1.8 (1.0, 3.4)	0.07

*
on a log scale