Prevalence of elevated alanine transaminase (ALT) in Australia and its relationship to metabolic risk factors: a cross sectional study of 9,447 people

Abstract

Objective: Elevated alanine transaminase (ALT) is a strong predictor of metabolic syndrome, but there are few data from the Australian population. We aimed to determine the prevalence of elevated ALT and association with metabolic risk factors.

Methods: In this cross sectional study including adult participants (N=9,447) from a nationwide, population based survey, we assessed the prevalence of elevated ALT [defined as ≥ 40 IU/L (males) and ≥ 30 IU/L (females) as baseline, and ALT as ≥ 30 IU/L (males) and ≥ 19 IU/L (females) as lower threshold], distribution of metabolic risk factors, and independent predictors of elevated ALT in logistic regression models. Analyses were weighted to the population with population weights.

Results: Elevated ALT levels were found in 11.2% of the Australian population. People with elevated ALT were younger (43 vs 46 yrs) with more truncal adiposity (100 vs 91 cm), higher pro-atherogenic lipids and glucose and exercised less (120 vs 160 minutes per week, $p<0.05$ for all analyses). Regression analyses indicated that younger age, male sex, diabetes, triglycerides, apolipoprotein B and waist circumference were independent predictors of elevated ALT. The population attributable fraction of elevated ALT due to truncal obesity was estimated at 47%.

Conclusion & Implications: These data demonstrate a high prevalence of elevated ALT in the general population that is closely associated with metabolic risk factors. Individuals with elevated ALT should be evaluated for co-existent metabolic disorders.

Keywords: ALT, population, metabolic syndrome, cross sectional study

Introduction

Elevations in alanine transaminase (ALT) are frequently associated with hepatic injury due to viral hepatitis, autoimmune hepatitis and nonalcoholic fatty liver disease, the latter predictive of future development of metabolic syndrome and type 2 diabetes in some populations(1, 2). Cross sectional data suggests that elevated ALT is also strongly associated with components of the metabolic syndrome, with a positive, linear correlation of ALT with BMI(3), fasting glucose(4) and pro-atherogenic lipids such as apolipoprotein B, VLDL and LDL(5). In addition, prospective data indicates that elevated ALT may predict future metabolic syndrome (14% excess risk for every 5 IU/L increase in ALT)(6) and type 2 diabetes(7) (16% excess risk for every 5 IU/L increase in ALT) although studies on the relationship of ALT and cardiovascular or all-cause mortality are conflicting(8-11) . Similarly, when nonalcoholic fatty liver disease (NAFLD) is defined by elevated enzymes (both ALT and GGT), an association is found between NAFLD and increased incidence of type 2 diabetes and metabolic syndrome(1, 12).

Despite these data suggesting that ALT may predict incident metabolic diseases, data on the prevalence of elevated ALT in the Australian population is scarce. Examination of evidence from the 1994 Busselton Health Survey, a population based cohort first examined in 1966 and followed through to 1994, suggested that elevated ALT was associated with metabolic syndrome and an overall prevalence of elevated ALT of 5.2%(13). Data from large epidemiological studies in the United States suggest that elevated ALT has been increasing, estimated at 7% in 1988(14), 8.9% in 1999 and 11% in 2008 (15), while studies in Asian populations where viral hepatitis is common, show a prevalence from 7.4% to 11.4%(16, 17).

The primary aims of this cross sectional study were to assess the prevalence of elevated ALT in the Australian population as a whole and in high risk subgroups including those with elevated BMI or waist circumference(18). We also aimed to determine the strongest metabolic predictors of elevated ALT, and to estimate the risk of elevated ALT attributable to truncal obesity using the population attributable fraction method.

METHODS

Survey design and conduct

The Australian Health Survey is a nationwide, population based survey conducted throughout 2011-2012. A detailed description of the survey methodology is provided elsewhere(19). Briefly, the survey used a multistage, stratified, probability sampling technique to identify random households within clusters that were representative of 97% of the Australian population. Within each cluster, homes were selected and approached for participation with introductory letters. In the event of non-response, five call backs were attempted before a household was classified as non-responding. Pre-specified exclusions were persons of Indigenous background (who were studied separately), people living in institutions or very remote areas, and members of the armed forces. There was no restriction by age. All participants provided written informed consent, and ethical approval was granted by the Australian Government Department of Health and Ageing's Departmental Ethics Committee.

Variable measurement

Trained interviewers used validated questionnaires to collect information on variables known or suspected to influence ALT levels. Clinical history included age, sex and smoking status (current, ex-

smoker or never user).Diabetic status was recorded according to whether respondents had ever been told by a doctor or nurse that they had diabetes or high glucose. For physical activity data, information was collected on both the average minutes of physical activity for fitness, recreation, sport or transport in the last week, and whether participants met recommended guidelines of ≥150 minutes/week of moderate exercise (i.e. that which incurred a moderate increase in physical exertion and heart rate/breathing, excluding walking). Blood pressure was recorded with two measurements on the left arm obtained while seated, using an appropriately sized cuff on an automated monitor. The second recording was used unless the difference was > 10mmHg, then a third measurement was taken and the second and third readings were averaged. Weight was determined by digital scales and a stadiometer measured height in centimetres. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Waist circumference was taken at the midpoint between the lowest rib and top of iliac crest as per World Health Organization recommendations using a metal tape measure, where a waist circumference ≥ 80cm for women and ≥ 94cm for men was considered “increased risk” and ≥88cm for women or ≥102 cm for men was considered “substantially increased risk”. For a subgroup of participants, adherence or non-adherence to recommended alcohol consumption guidelines of ≤20g/day on any given day was also recorded.

Fasting blood samples were collected in the morning by qualified phlebotomists either at home or the nearest Sonic Healthcare collection centre and analysed centrally in < 72 hours by Douglass Hanly Moir Pathology as a fresh sample. Samples were taken over a 12 month period to take into account seasonal variation. Serum ALT (U/L), GGT (U/L), triglycerides (mmol/L), high density lipoprotein (HDL, mmol/L), low density lipoprotein (LDL, mmol/L) and ferritin (µg/L) were analysed using an Architect Ci16200 analyser (Abbott Diagnostics). Serum apolipoprotein B (g/L) was analysed using an Integra 800 analyser

(Roche Diagnostics), and fasting glucose was measured in mmol/L using the hexokinase method (Integra 800 analyser, Roche Diagnostics). Vitamin D was measured as serum 25-hydroxy vitamin D using a mass spectrometry method, with levels ≥50 nmol/L considered adequate.

Determination of the threshold for an elevated ALT

As there is no consensus on what level constitutes an elevated ALT, the threshold was determined consistent with levels reported previously(20), and in accordance with the testing laboratory's reference range at ALT ≥ 30 IU/L for females and ≥40 IU/L for males(21). Baseline analyses were undertaken using these levels, and further analyses were repeated using a lower threshold that has been proposed in the literature (ALT ≥ 19 for females and ALT ≥ 30 for males)(22) to explore whether a lower threshold led to the same or different results.

Population attributable fraction

The population attributable fraction is a public health statistic that describes the contribution of a risk factor to a disease; in this case, the contribution of truncal obesity to the prevalence of elevated ALT, as this is known to be one of the strongest predictors(20). It is calculated by the following equation:

$$Fraction = \frac{\theta\,(Relative\ Risk-1)}{1 + \theta\,(Relative\ Risk\ -1)}$$

where θ represents the proportion of people who have truncal obesity (waist circumference ≥ 80cm for females and ≥94cm for males), and relative risk is approximated by the adjusted odds ratio of elevated ALT in people with truncal obesity compared to those with a normal waist circumference. The

population attributable fraction is useful for public health physicians and policy makers in determining the most important risk factors to target when addressing a problem of public health significance.

Statistical analysis

The prevalence of elevated ALT was estimated in the overall Australian population, and according to sex, BMI and waist circumference, as the latter are recognised as the strongest risk factors for development of metabolic diseases(23, 24). The population was then divided into 2 groups of normal versus elevated ALT, and the means of variables known or suspected to be associated with ALT levels were compared between groups. The t-statistic was used to test for a difference between normally distributed variables. For non-Normally distributed variables (serum triglycerides, ferritin and minutes per week of exercise) log transformations were undertaken and the means compared using the t-statistic. Proportions were compared using the chi-square statistic. Analyses were weighted to the general Australian population by the use of population weights as recommended by the Australian Bureau of Statistics (ABS) (25) . A set of 60 population weights are supplied by the ABS to facilitate a delete-a-group Jackknife approach to standard error estimation, to take into account the cluster design of the survey. This allows for extrapolation of study results to the wider population. Univariate logistic regression analyses were undertaken to assess the strength and direction of relationships between elevated ALT and explanatory variables. Variables which had a positively skewed non-Normal distribution were log transformed, and assumptions of linearity checked graphically, with all variables found to be linear. Multivariable logistic regression analysis was performed with the inclusion of all potential explanatory variables (excluding ferritin, Vitamin D and BMI as the latter demonstrates collinearity with waist circumference) in the baseline model and backwards stepwise elimination undertaken until all remaining variables were significant at the $p<0.05$ level. Additional models were fitted to determine whether the variables

selected for inclusion in the final model were sensitive to their coding as continuous or categorical (for diabetes, we used diabetic status or fasting glucose; for exercise we used minutes of exercise/week or whether participants adhered to exercise guidelines of > 150 minutes/week, and for waist circumference, we tested mean waist circumference or whether participants were in normal or at-risk categories). As the results were consistent irrespective of type of coding, categorical variables for diabetes and waist circumference category are presented in the final models. A two-way interaction term between age and sex was investigated in the baseline model but found to be not significant. Similar analyses were performed for the relationship between elevated GGT (defined as ≥ 50 U/L for males and ≥ 35 U/L for females) and metabolic co-factors, and are included as supplementary data (see supplementary tables). A p value <0.05 was considered statistically significant, and all analyses were undertaken in SAS v9.3 (SAS Institute, Cary, NC).

RESULTS

Study cohort and prevalence of elevated ALT

Of 27,636 people who participated in interviews, 10,184 provided blood samples and 9,447 were aged ≥ 18 and formed our study cohort (Figure 1). The majority (80%) of blood samples were fasting. The prevalence of elevated ALT in the Australian population overall was 11.2%, and higher for males (13.9%) than females (8.4%). The prevalence of elevated ALT was higher in people who were overweight or obese, estimated at 11.8% and 19.6% respectively, and increased in association with waist circumference (Figure 2). When the threshold for elevated ALT was lowered to 30 IU/L (males) and 19IU/L (females), the overall prevalence of elevated ALT was 32.1%, equivalent to approximately 1/3 of the Australian population.

Metabolic and demographic characteristics in those with normal and elevated ALT

People with an elevated ALT were more likely to be younger (43.3 vs 46.4 years), with higher BMI (30.0 vs 26.9 kg/m^2) and greater waist circumference (for males, 103.6 vs 96.1 cm and for females 93.6 vs 86.4cm). People with elevated ALT had increased levels of LDL and triglycerides, and undertook less exercise (221 vs 245 minutes/week)(Table 1). Mean systolic blood pressure was higher in those with elevated ALT (124 vs 121 mmHg), although smoking habits were similar in both groups. For the subgroup where alcohol data were available (n=5602), the proportion of people who exceeded national alcohol guidelines of >20g/day were not significantly different. Demographic characteristics were also compared when the threshold for elevated ALT was lowered to ALT 30 IU/L for males and 19 IU/L for females. Age and amount of exercise was similar in people with normal or elevated ALT, but the group with elevated ALT continued to show significantly higher levels of important metabolic risk factors such as BMI, waist circumference and LDL (Table A, Supplementary material).

Univariate and multivariable analyses using standard threshold

In univariate analyses, the strongest associations with elevated ALT were seen with male sex, triglycerides, apolipoprotein B and elevated waist circumference (Table 2). In the multivariable model, variables in the final model that remained independent predictors of elevated ALT after controlling for other predictors were younger age, male sex, presence of diabetes and higher triglycerides, apolipoprotein B, ferritin and elevated waist circumference (Table 2, Figure 3); of these, a substantially increased waist circumference (≥ 88cm for women and ≥102cm for men) was the most strongly associated predictor. Smoking habits, physical activity levels and blood pressure were not independently associated with elevated ALT.

Univariate and multivariable analyses using the lower ALT threshold (ALT 30 IU/L males, 19 IU/L females)

In univariate models, age, smoking status and exercise levels were not associated with elevated ALT, although similar associations to those seen for the standard threshold were demonstrated for other metabolic variables. As compared to the final multivariate model for the standard threshold, the final model also included blood pressure, however the effect of other independent variables such as increased waist circumference and triglycerides was similar (Table 3).

Population attributable fraction of truncal obesity to elevated ALT

The proportion of the Australian population with truncal obesity was 0.69, and the relative risk of elevated ALT in truncal obesity was approximated by the adjusted odds ratio of elevated ALT in those with waist circumference in the “at increased risk” or “substantially increased risk” categories, compared to those with a normal waist circumference (O.R. = 2.3).The population attributable fraction of truncal obesity to elevated ALT was calculated at 47%, indicating 47% of the risk of elevated ALT would be eliminated if all patients had waist circumference in the “not at risk” category.

DISCUSSION

The findings of this general population based study, derived from 9,447 measurements of ALT in community dwelling adults, indicate a high prevalence of elevated ALT at 11.2% for the overall population, 13.9% for males and 8.4% for females. The strongest determinant of elevated ALT was an increased waist circumference, with risk proportional to size. Other independent predictors were pro-

atherogenic lipids such as serum triglycerides and apolipoprotein B. Male sex was positively associated with higher ALT levels, while age was negatively associated, consistent with previous data(26), and may be explained by a loss of skeletal muscle mass in elderly populations as some ALT is muscle-derived; others propose that ALT may be a novel biomarker of ageing(27). Alcohol intake and exercise were not independently associated with ALT in our study, and the impact of exercise on ALT remains controversial, with some data suggesting that increased exercise reduces ALT(28, 29), while other data do not support this after adjustment for co-factors such as BMI(3).

As there has been a proposal to revise the threshold for elevated ALT downwards(15), we explored the use of a lower threshold, derived from the statistical mean ALT in young cohort with no metabolic risk factors, and its impact on independent predictors (22). Using a lower threshold resulted in 1/3 of the general population classified as having an elevated ALT. The group with elevated ALT continued to demonstrate a higher level of metabolic risk factors such as waist circumference, although age and exercise levels were not different, suggesting that perhaps the higher threshold teased out subtle differences in these characteristics. In regression analyses, the independent predictors of elevated ALT were similar using either threshold. Lowering thresholds for disease detection results in a trade-off of increased sensitivity but reduced specificity, and may be useful for detecting a disease where there is a readily available, inexpensive and highly effective treatment. However, given the underwhelming efficacy of pharmacotherapy of obesity related diseases, the cost of targeting 1/3 of the population, and the absence of a threshold that accurately predicts clinically important sequelae, we contend that there remains insufficient data to justify a lower threshold at present.

While the nature of our data does not allow assumptions of causality, the most likely reason for the increasing prevalence of elevated ALT is liver fat, known as non-alcoholic fatty liver disease (NAFLD), which has increased in parallel with the obesity epidemic. The prevalence of other causes of elevated ALT such as viral hepatitis and autoimmune hepatitis have remained unchanged in the population(30). As ALT is consistently predicted by obesity, we assessed the contribution of truncal obesity to elevated ALT by calculating the population attributable fraction. This was estimated at 47%, suggesting that 47% of the risk of elevated ALT would be eliminated if all patients had waist circumference in the "not at risk" category. This information is useful for policy makers and public health planners estimating the impact of obesity on liver health in the general population, given that data from countries with similar obesity demographics suggests that NAFLD will be the primary cause for liver transplantation by 2020(31).

Our results are consistent with reports of a high prevalence of elevated ALT in developed countries, estimated at 11% in US populations(15), and higher than historical cohorts from 1988 of 7.9%(14). The prevalence of elevated ALT has previously been estimated at 5.2% in a small (n=384) Australian population health survey from 1995, which is substantially lower than our findings(13). Studies that have assessed independent predictors of elevated ALT in diverse populations have also found obesity to be a major determinant in Caucasian(20), Hispanic(32) and Asian populations (17, 33), and hypertriglyceridemia is also consistently associated(32). Fasting insulin may also predict ALT(20) however this was not available in our study for evaluation. We did not find alcohol to be an independent predictor of ALT activity, in line with previous data indicating that BMI influences ALT levels significantly more than alcohol(34). While the bulk of available data consistently shows ALT to be a reliable and reproducible marker of metabolic health, whether it could prove clinically useful in prediction of diseases such as diabetes is unclear. A single study where ALT was added to variables of the German

Diabetes Risk Score shows a small incremental benefit in diabetes prediction(35), however this area requires further exploration.

This study has a number of strengths. It provides Australian data on the prevalence of elevated ALT and metabolic cofactors, and a benchmark for future comparison. The large sample size allowed a precise estimation of the relationship between ALT and cofactors, and weighting of statistical analyses allowed us to make inferences about the Australian population at large. Comprehensive data on alcohol and exercise was included in the models, and different variable formats tested, yet results were unchanged, strengthening the conclusion that alcohol intake is not a strong predictor of elevated ALT. A major limitation to this study is its cross-sectional design which does not allow inferences on causality or the temporal nature of relationships, however such large studies are challenging to conduct in a longitudinal format. Furthermore, as this cross sectional study has only just been completed, there has not been linkage to morbidity or mortality records which could provide information on longitudinal associations. The impact of residual selection bias on our results is also difficult to determine, despite techniques to minimise this such as five callbacks before non-response was recorded. Finally, misclassification of the cause of elevated ALT may have occurred due to misreporting of alcohol consumption or viral hepatitis. Serological testing for viral hepatitis was not performed, however the incidence of Hepatitis B and C infections in the Australian population has been reducing over the last decade(36) and misclassification due to viral hepatitis is unlikely to affect our conclusions.

Conclusion

These data indicate a high prevalence of elevated ALT in the general population, which is tightly associated with multiple metabolic risk factors. Community dwelling individuals with elevated ALT

should be assessed for presence of co-existing risk factors that may impact their metabolic health, and at a public health level, ALT may be regarded as an additional marker of impaired metabolic health.

REFERENCES

1. Ballestri S, Targher G, Romagnoli D, et al. Nonalcoholic fatty liver disease is associated with an almost two-fold increased risk of incident type 2 diabetes and metabolic syndrome. Evidence from a systematic review and meta-analysis. J Gastroenterol Hepatol. 2015. DOI: 10.1111/jgh.13264
2. Lonardo A, Ballestri S, Marchesini G, Angulo P, Loria P. Nonalcoholic fatty liver disease: a precursor of the metabolic syndrome. Dig Liver Dis. 2015;**47**:181-90.
3. Lawlor DA, Sattar N, Smith GD, Ebrahim S. The associations of physical activity and adiposity with alanine aminotransferase and gamma-glutamyltransferase. Am J Epidemiol. 2005;**161**:1081-8.
4. Fraser A, Ebrahim S, Smith GD, Lawlor DA. A comparison of associations of alanine aminotransferase and gamma-glutamyltransferase with fasting glucose, fasting insulin, and glycated hemoglobin in women with and without diabetes. Hepatology. 2007;**46**:158-65.
5. Siddiqui MS, Sterling RK, Luketic VA, et al. Association between high-normal levels of alanine aminotransferase and risk factors for atherogenesis. Gastroenterology. 2013;**145**:1271-9.
6. Kunutsor SK, Seddoh D. Alanine aminotransferase and risk of the metabolic syndrome: a linear dose-response relationship. PLoS ONE. 2014;**9**:e96068.
7. Fraser A, Harris R, Sattar N, et al. Alanine aminotransferase, gamma-glutamyltransferase, and incident diabetes: the British Women's Heart and Health Study and meta-analysis. Diabetes Care. 2009;**32**:741-50.
8. Goessling W, Massaro JM, Vasan RS, et al. Aminotransferase levels and 20-year risk of metabolic syndrome, diabetes, and cardiovascular disease. Gastroenterology. 2008;**135**:1935-44.

9. Ruhl CE, Everhart JE. Elevated serum alanine aminotransferase and gamma-glutamyltransferase and mortality in the United States population. Gastroenterology. 2009;**136**:477-85.

10. Kunutsor SK, Apekey TA, Khan H. Liver enzymes and risk of cardiovascular disease in the general population: a meta-analysis of prospective cohort studies. Atherosclerosis. 2014;**236**:7-17.

11. Kunutsor SK, Apekey TA, Seddoh D, Walley J. Liver enzymes and risk of all-cause mortality in general populations: a systematic review and meta-analysis. Int J Epidemiol. 2014;**43**:187-201.

12. Musso G, Gambino R, Cassader M, Pagano G. Meta-analysis: natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. Ann Med. 2011;**43**617-49.

13. Adams LA, Waters OR, Knuiman MW, Elliott RR, Olynyk JK. NAFLD as a risk factor for the development of diabetes and the metabolic syndrome: an eleven-year follow-up study. Am J Gastroenterol. 2009;**104**:861-7.

14. Clark JM, Brancati FL, Diehl AM. The prevalence and etiology of elevated aminotransferase levels in the United States. Am J Gastroenterol. 2003;**98**:960-7.

15. Ruhl CE, Everhart JE. Upper limits of normal for alanine aminotransferase activity in the United States population. Hepatology. 2012;**55**:447-54.

16. Hyun HJ, Shim JJ, Kim JW, et al. The prevalence of elevated alanine transaminase and its possible causes in the general Korean population. J Clin Gastroenterol. 2014;**48**:534-9.

17. Chen CH, Huang MH, Yang JC, et al. Prevalence and etiology of elevated serum alanine aminotransferase level in an adult population in Taiwan. J Gastroenterol Hepatol. 2007;**22**:1482-9.

18. Lonardo A , Argo CK, Ballestri S, et al. Epidemiological modifiers of non-alcoholic fatty liver disease: Focus on high-risk groups. Dig Liver Dis. 2015;**47**:997-1006.

19. Available from [cited 2015 July]: http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/4363.0.55.001Chapter2002011-13.

20. Ruhl CE, Everhart JE. Determinants of the association of overweight with elevated serum alanine aminotransferase activity in the United States. Gastroenterology. 2003;**124**:71-9.

21. ALT reference range [cited 2015 July]. Available from: http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/0247A7FA73DD3A31CA257C3D000D8A6B?opendocument.

22. Prati D, Taioli E, Zanella A, et al. Updated definitions of healthy ranges for serum alanine aminotransferase levels. Ann Intern Med. 2002;**137**:1-10.

23. Janiszewski PM, Janssen I, Ross R. Does waist circumference predict diabetes and cardiovascular disease beyond commonly evaluated cardiometabolic risk factors? Diabetes Care.2007; **30**:3105-9.

24. Wang Y, Rimm EB, Stampfer MJ, Willett WC, Hu FB. Comparison of abdominal adiposity and overall obesity in predicting risk of type 2 diabetes among men. Am J Clin Nutr.2005;**81**:555-63.

25. Replicate weights [cited 2015 July]. Available from: http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/4363.0.55.001Chapter2002011-13.

26. Dong MH, Bettencourt R, Barrett-Connor E, Loomba R. Alanine aminotransferase decreases with age: the Rancho Bernardo Study. PLoS ONE. 2010;**5**:e14254.

27. Le Couteur DG, Blyth FM, Creasey HM, et al. The association of alanine transaminase with aging, frailty, and mortality. J Gerontol A Biol Sci Med Sci. 2010;65:712-7.

28. Keating SE, Hackett DA, George J, Johnson NA. Exercise and non-alcoholic fatty liver disease: a systematic review and meta-analysis. J Hepatol. 2012;**57**:157-66.

29. Kim WR, Flamm SL, Di Bisceglie AM, Bodenheimer HC, et al. Serum activity of alanine aminotransferase (ALT) as an indicator of health and disease. Hepatology. 2008;**47**:1363-70.

30. Ngu JH, Bechly K, Chapman BA, et al. Population-based epidemiology study of autoimmune hepatitis: a disease of older women? J Gastroenterol Hepatol. 2010;**25**:1681-6.

31. Charlton MR, Burns JM, Pedersen RA, Watt KD, Heimbach JK, Dierkhising RA. Frequency and outcomes of liver transplantation for nonalcoholic steatohepatitis in the United States. Gastroenterology. 2011;**141**:1249-53.

32. Pan JJ, Qu HQ, Rentfro A, McCormick JB, Fisher-Hoch SP, Fallon MB. Prevalence of metabolic syndrome and risks of abnormal serum alanine aminotransferase in Hispanics: a population-based study. PLoS ONE. 2011;**6**:e21515.

33. Kim J, Jo I. Relationship between body mass index and alanine aminotransferase concentration in non-diabetic Korean adults. Eur J Clin Nutr. 2010;**64**:169-75.

34. Adams LA, Knuiman MW, Divitini ML, Olynyk JK. Body mass index is a stronger predictor of alanine aminotransaminase levels than alcohol consumption. J Gastroenterol Hepatol. 2008;**23**:1089-93.

35. Schulze MB, Weikert C, Pischon T, et al. Use of multiple metabolic and genetic markers to improve the prediction of type 2 diabetes: the EPIC-Potsdam Study. Diabetes Care. 2009;**32**:2116-9.

36. http://www.health.gov.au/internet/main/publishing.nsf/Content/ohp-bbvs-data. [cited 8 April 2016].