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# Accuracy of body mass index in detecting an elevated alanine aminotransferase level in adolescents

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**Summary.** *Aim*: We evaluated the accuracy of body mass index (BMI) in detecting an elevated alanine aminotransferase (ALT) level in adolescents, taking into account the effects of gender, age, ethanol intake, hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, and drug consumption.
*Subjects*: A representative sample of 454 adolescents (11–17 years) from two cities in northern Italy was studied (the Dionysos Study).
*Methods*: *z*-BMI was calculated as the *z*-score of BMI using national growth charts. Logistic regression was used to quantify the contribution of the variables of interest to an elevated ALT ($>30\,\mathrm{U\,L^{-1}}$). Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated, and areas under receiver–operator characteristic curves (AUC) were used to evaluate accuracy.
*Results*: An elevated ALT was detected in 21 adolescents (4.6%). Among the studied variables, only male gender (OR = 6.7, 95% CI 2.0–23.2) and *z*-BMI (OR = 2.1, 95% CI 1.4–3.2) were significant predictors of elevated ALT. The accuracy of the prediction was 0.69 (95% CI 0.59–0.79) for gender and 0.71 (95% CI 0.59–0.81) for *z*-BMI. By combining gender and *z*-BMI, the accuracy rose to 0.80 (95% CI 0.71–0.89).
*Conclusion*: BMI is a good predictor of elevated ALT in Italian adolescents and gender adds to the accuracy of the prediction.

## 1. Introduction

Alanine aminotransferase (ALT) is the liver enzyme most frequently altered in asymptomatic individuals undergoing blood examinations (Pratt and Kaplan 2000). As detected by the Dionysos Study, nearly one in every five individuals in Northern Italy has an ALT higher than the upper normal value of $30\,\mathrm{U\,L^{-1}}$ (Bellentani *et al.* 1994). Ethanol intake, hepatitis B virus (HBV) and C virus (HCV) infections, and drug consumption are well-known risk factors for elevated ALT. However, overweight is being increasingly recognized as a major risk factor for altered liver enzymes (Pratt and Kaplan 2000). Among the adults of the Dionysos Study, body mass index (BMI) was the best single predictor of a value of ALT greater than two times the upper normal value (i.e. $>60\,\mathrm{U\,L^{-1}}$). The accuracy of the prediction increased, however, from 0.65 to 0.75 when gender, ethanol consumption, and HBV and HCV infections were considered as predictors together with BMI (Bedogni *et al.* 2003). Because alcohol consumption, and HBV and HCV infections are less common in adolescents, we hypothesized that BMI could be an even more important predictor of elevated ALT in adolescents. In the only available study performed in a representative sample of adolescents (Strauss *et al.* 2000), overweight and alcohol consumption were associated with elevated ALT, defined as a value $>30\,\mathrm{U\,L^{-1}}$. However, in that study, adolescents with HBV and HCV infections were excluded, and the possible confounding effects of gender and drug consumption were not

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considered. In this paper, we report on the contribution of BMI to elevated ALT in the adolescent population of the Dionysos study, taking into account the above confounding factors.

## 2. Materials and methods

### *2.1. Subjects*

The Dionysos Study was performed on 6917 out of 10150 inhabitants of two communities of Northern Italy (Campogalliano and Cormons) (Bellentani *et al.* 1994, Bellentani and Tiribelli 2001). For the purpose of the present study, an individual aged between 11 and 17 years was considered an adolescent. The analysis was performed on the 454 Dionysos adolescents (232 females and 222 males) for whom all the measurements of interest were available, corresponding to 97% of all the adolescent population enrolled. The full adolescent cohort included 70% of all the children living in the two cities.

### *2.2. Methods*

As reported previously (Bellentani *et al.* 1994), ALT was measured by common laboratory methods. Weight and height were measured following the *Anthropometric Standardization Reference Manual* (Lohman *et al.* 1988). BMI was calculated as weight (kg)/height $(m)^2$. Using the classification of the International Obesity Task Force (Bellizzi and Dietz 1999, Dietz and Bellizzi 1999), children with BMI $\geq$85th and $<$95th percentile for age were classified as 'at risk of overweight', and those with BMI $\geq$95th percentile for age as 'overweight'. *z*-scores were calculated from national reference values (Cacciari *et al.* 2002) using the LMS method and then converted to percentiles. Ethanol intake was assessed by interview, as described previously (Bellentani *et al.* 1994). Hepatitis B surface antigen (HbsAg) and anti-HCV antibodies were detected by using commercial kits (Abbott Laboratories, Chicago, IL, USA and second generation ELISA, Ortho Diagnostic Systems, Raritan, NJ, USA). Drug consumption was ascertained by interview and coded as the consumption of any drug.

### *2.3. Statistical analysis*

Continuous variables are given as medians and interquartile ranges (IQR) because of skewed distributions. Between-gender comparisons of continuous variables were performed with the Mann–Whitney *U*-test and those of ordinal variables with Fisher's Exact test. Univariable and multivariable logistic regression were used to establish the contribution of the variables of interest to elevated ALT, defined as a value greater than the upper normal limit of $30\,U\,L^{-1}$, detected at least two times over a month. This value corresponded to the 99th internal percentile. We chose a value of ALT $>30\,U\,L^{-1}$ to allow comparison with previous studies (Strauss *et al.* 2000) and because values greater than $60\,U\,L^{-1}$ (Sherwood *et al.* 2001, Bedogni *et al.* 2003) are uncommon in adolescents. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated and the goodness of fit of models including continuous predictors was evaluated using the Hosmer–Lemeshow statistic (Hosmer and Lemeshow 2000). Exact logistic regression was used for univariable models with dichotomous predictors and whenever feasible (Mehta and Patel 1995). The sensitivity (SN) and specificity (SP) of each model were calculated and receiver–operator characteristic (ROC) curves were drawn by plotting SN vs (1 – SP). The area under the ROC curve (AUC) was used as a measure of accuracy (Zhou *et al.*

Table 1. Measurements of the adolescents. Values of continuous variables are medians and interquartile ranges.

| | All ($n=454$) | Female ($n=232$) | Male ($n=222$) | Female vs. male $p$* |
|---|---|---|---|---|
| Age (years) | 15 (3) | 15 (3) | 15 (3) | 0.246 |
| Weight (kg) | 55.0 (16.0) | 54.0 (11.0) | 60.0 (21.0) | 0.0003 |
| Height (m) | 1.66 (0.13) | 1.63 (0.10) | 1.70 (0.16) | $<0.0001$ |
| BMI ($kg\,m^{-2}$) | 20.2 (4.0) | 20.1 (3.3) | 20.7 (4.5) | 0.277 |
| $z$-BMI (SDS) | $-0.22$ (1.32) | $-0.26$ (1.29) | $-0.19$ (1.37) | 0.921 |
| ALT ($U\,L^{-1}$) | 14 (7) | 13 (6) | 16 (9) | $<0.0001$ |
| Alcohol (yes/no) | 70/384 | 27/205 | 43/179 | 0.027 |
| HbsAg (+/−) | 1/453 | 0/232 | 1/221 | 0.489 |
| Anti-HCV (+/−) | 3/451 | 0/232 | 3/219 | 0.116 |
| Drugs (yes/no) | 80/374 | 48/184 | 32/190 | 0.086 |

*Mann–Whitney $U$-test for continuous variables and Fisher's Exact test for dichotomous variables. Abbreviations: $z$-BMI, $z$-score of BMI (Cacciari *et al.* 2002); SDS, standard deviation score; ALT, alanine aminotransferase; HbsAg, hepatitis B surface antigen; anti-HCV, antibodies against hepatitis C virus.

2002). Statistical significance was set to a value of $p<0.05$ for all tests. Statistical analysis was performed using SPSS 11 (SPSS, Chicago, IL, USA), and StatXact 5 and LogXact 4 (Cytel, Cambridge, MA, USA).

## 3. Results

The measurements of the 454 adolescents are given in table 1. The median (IQR) age was 15 (3) years, with no between-gender difference ($p=0.246$). Weight ($p=0.0003$) and height ($p<0.0001$) were higher in males than females. BMI, ranging from 13.2 to 33.7 $kg\,m^{-2}$, was similar in males and females ($p=0.277$), and the same was true for the $z$-score of BMI, or $z$-BMI ($p=0.921$), ranging from $-2.95$ to 2.7 standard deviation scores. Twenty-nine subjects (6.4%) were at risk of overweight and 27 (5.9%) were overweight. ALT levels were comprised between 1 and 65 $U\,L^{-1}$ and were higher in males than females ($p<0.0001$). While ethanol consumption was more frequent in males ($p=0.027$), HbsAg positivity ($p=0.489$), anti-HCV positivity ($p=0.116$), and drug consumption ($p=0.086$) were equally frequent in males and females.

An elevated ALT was detected in 21 adolescents (4.6%). The contributions of the variables of interest to elevated ALT are given in table 2. Age, analysed both as a continuous variable (OR = 0.98, 95% CI 0.75–1.29, exact-$p=0.931$) and quartiles (table 2), was not associated with elevated ALT. Males had an OR of 6.7 (95% CI 2.0–23.2) for elevated ALT. As compared with adolescents with BMI <85th percentile for age, those at risk of overweight had an OR 4.7 (95% CI 1.0–16.8) and those overweight had an OR of 5.1 (95% CI 1.1–18.4) for elevated ALT (table 2). Because of comparable OR, the subjects at risk of overweight and those overweight were pooled ($n=56$), with a resultant OR for elevated ALT of 4.9 (95% CI 1.7–13.6, exact-$p=0.004$). On the contrary, ethanol consumption (exact-$p=0.274$), HbsAg positivity (exact-$p=0.093$), anti-HCV positivity (exact-$p=1.000$), and drug consumption (exact-$p=0.608$) were not associated with elevated ALT (table 2).

The median (IQR) ethanol intake was 0 (0) $g\,day^{-1}$ in both females and males, ranging from 0 to 24 $g\,day^{-1}$ in females and from 0 to 32 $g\,day^{-1}$ in males (exact-$p=0.019$). Only three subjects drank more than 30 $g\,day^{-1}$—the lowest quantity of

Table 2. Univariable prediction of elevated ALT levels in adolescents.

| Predictor | OR (95% CI) | Exact *p*-value |
|---|---|---|
| Age | | |
| First quartile | 1 | |
| Second quartile | 0.6 (0.1–2.1) | 0.489 |
| Third quartile | 0.2 (0.0–1.4) | 0.143 |
| Fourth quartile | 1.2 (0.4–3.9) | 0.956 |
| Gender | | |
| Female | 1 | |
| Male | 6.7 (2.0–23.2) | 0.0008 |
| BMI | | |
| $<$85th pct | 1 | |
| $\geq$85th and $<$95th pct | 4.7 (1.0–16.8) | 0.044 |
| $\geq$95th pct | 5.1 (1.1–18.4) | 0.035 |
| Ethanol | | |
| No | 1 | |
| Yes | 0.3 (0.0–2.0) | 0.274 |
| HbsAg | | |
| − | 1 | |
| + | 20.6 (0.5 to $+\infty$) | 0.093 |
| Anti-HCV | | |
| − | 1 | |
| + | 5.4 (0–51.5) | 1.000 |
| Drugs | | |
| No | 1 | |
| Yes | 1.5 (0.4–4.4) | 0.608 |

Abbreviations: OR, odds ratio; 95% CI, 95% confidence intervals; pct, percentile for age; HbsAg, hepatitis B surface antigen; anti-HCV, antibodies against hepatitis C virus.

ethanol determined to be toxic by the Dionysos Study (Bellentani *et al.* 1994)—and all were males and aged $\geq$14 years.

The accuracy in detecting an elevated ALT was 0.69 (95% CI 0.59–0.79, $p = 0.003$) for gender and 0.64 (95% CI 0.50–0.77, $p = 0.036$) for dichotomized BMI. Because BMI should always be referred to sex and age in childhood (Bellizzi and Dietz 1999, Dietz and Bellizzi 1999, Cole *et al.* 2000), we tested whether *z*-BMI was a more accurate predictor. The OR for elevated ALT associated with an increase of 1 unit of *z*-BMI was 2.1 (95% CI = 1.4–3.2, $p = 0.001$). The model fitted well ($p = 0.839$, Hosmer–Lemeshow statistic) and was more accurate than the dichotomized BMI model (AUC = 0.71, 95% CI 0.59–0.81, $p = 0.001$). When gender and *z*-BMI were employed as predictors in a multivariable model (table 3), the fit was good ($p = 0.591$, Hosmer–Lemeshow statistic) and the accuracy greater than that of the univariable models (AUC = 0.80, 95% CI 0.71–0.89, $p < 0.0001$).

Table 3. Multivariable prediction of elevated ALT levels in adolescents.

| Variable | $\beta$ | SE ($\beta$) | *p*-value | OR (95% CI) |
|---|---|---|---|---|
| Gender (male) | 1.967 | 0.638 | 0.002 | 7.2 (2.0–25.0) |
| *z*-BMI | 0.783 | 0.228 | 0.001 | 2.2 (1.4–3.4) |

Abbreviations: $\beta$, regression coefficient; SE ($\beta$), standard error of regression coefficient; OR, odds ratio; 95% CI, 95% confidence intervals; *z*-BMI, *z*-score of BMI (Cacciari *et al.* 2002).

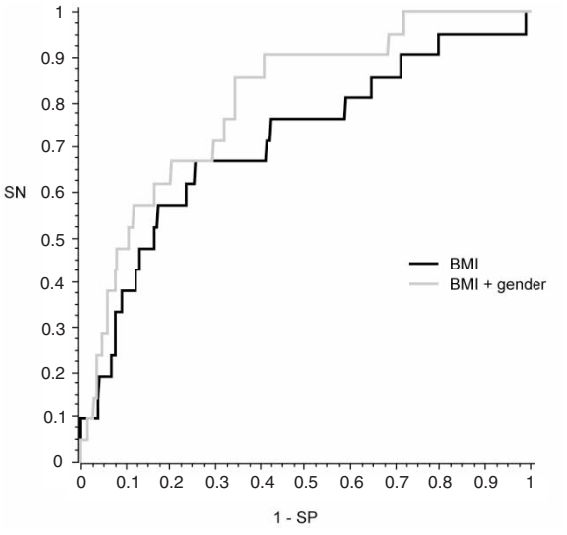


Figure 1. Accuracy of BMI alone and combined with gender in detecting elevated ALT levels in adolescents. Abbreviations: SN, sensitivity; SP, specificity.

In particular, there was an increase of 9% in accuracy as compared with the univariable BMI model (figure 1). This difference was not statistically significant ($p = 0.118$, Venkatraman–Begg procedure), but the study was not adequately powered to test it ($\beta = 0.65$ for $\alpha = 0.05$) because of the low number of adolescents with elevated ALT.

## 4. Discussion

We evaluated the accuracy of BMI in detecting an elevated ALT in a representative sample of Italian adolescents, taking into account the effects of gender, age, ethanol intake, HBV and HCV infections, and drug consumption. We defined elevated ALT as a value of ALT $> 30\,\mathrm{U\,L^{-1}}$ to allow comparison with previous studies and because values greater than $60\,\mathrm{U\,L^{-1}}$ (Sherwood *et al.* 2001, Bedogni *et al.* 2003) are uncommon in adolescents. The frequency of elevated ALT in our adolescents (4.6%) was not significantly different from that (3.2%) detected in a representative sample of US adolescents (Strauss *et al.* 2000; $p = 0.114$, Fisher's Exact test). In our study, *z*-BMI was the single most accurate predictor of elevated ALT (AUC = 0.71, $p = 0.001$). Contrarily to adults, age was not a risk factor for elevated ALT in our adolescents but, similarly to adults, male gender was (Bedogni *et al.* 2003). The contribution of hepatotropic viruses and ethanol intake to account for an elevated ALT was negligible, owing to the low prevalence of HBV and HCV infections and the low level of ethanol consumption. This is in contrast with the findings obtained in US adolescents, where a frequency of alcohol consumption greater than 4 days per month was a significant predictor of elevated ALT in addition to BMI (Strauss *et al.* 2000). As found in adults (Bedogni *et al.* 2003), drug consumption was not a predictor of elevated ALT. The use of both gender and *z*-BMI as predictors increased the accuracy of the estimate to a level (AUC = 0.80, $p < 0.0001$) usually regarded as excellent (Altman 2000). However, the relatively low number of adolescents with elevated ALT was responsible for a large 95% CI and for the low power achieved in testing the significance of the between-AUC difference.

The reason why BMI is a predictor of elevated ALT may be explained by the fact that non-alcoholic fatty liver (NAFL), i.e. fatty liver not attributable either to alcohol or HBV or HCV infection, is the most common variety of fatty liver in Western societies (Bellentani *et al*. 2000, Neuschwander-Tetri and Caldwell 2003). Overweight and its metabolic complications are in fact recognized as the most important risk factors for NAFL. Why gender adds to the prediction of an elevated ALT is less easy to explain. Previous studies have shown that at comparable weight and age, males have greater ALT levels than females (Pratt and Kaplan 2000). The greater frequency of ALT $>30\,\mathrm{U\,L^{-1}}$ in males may thus partly depend from the setting of a similar upper normal limit for both genders. However, this cannot explain why the prevalence of elevated ALT is greater in males than females at greater cut-points, e.g. $60\,\mathrm{U\,L^{-1}}$ (Bedogni *et al*. 2003). Whatever the reason why gender is a predictor of elevated ALT, the increase in 9% of accuracy obtained by considering gender together with BMI is practically relevant, even if the statistical significance of this finding needs to be tested in a larger sample of adolescents.

In conclusion, BMI is an accurate predictor of elevated ALT in Italian adolescents, and consideration of gender together with BMI increases the accuracy of the prediction. Even if this is the first study performed on a representative sample of European adolescents, it must be pointed out that our prediction model was developed in a population with a low prevalence of elevated ALT, ethanol consumption and HBV and HCV infections, and that it may not work properly in populations with different characteristics. The relevance of the BMI–ALT association in adolescents is that in many cases it may be indicative of underlying NAFL. However, population studies employing ultrasonography to diagnose fatty liver are needed to test this hypothesis.

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**Zusammenfassung.** *Ziel:* Wir untersuchten die Genauigkeit des Körpermasse-Index (body mass index, BMI) zur Erfassung eines erhöhten Alanin-Aminotransferase (ALT)-Spiegels bei Jugendlichen, und berücksichtigten dabei die Abhängigkeit von Geschlecht, Alter, Alkoholkonsum, Hepatitis B (HBV)- und C (HCV)-Virusinfektion, sowie Drogenkonsum.
*Probanden*: Es wurde eine repräsentative Stichprobe von 454 Jugendlichen (11–17 Jahre) aus zwei Norditalienischen Städten untersucht (Dionysos Studie).
*Methoden*: Z-BMI wurden als Z-Werte für BMI unter Verwendung nationaler Wachstumskurven gerechnet. Eine logistische Regression wurde verwendet, um den Anteil der interessierenden Variablen an der ALT-Erhöhung ( > 30 U/L) zu quantifizieren. Odds ratios (OR) und 95% Konfidenzintervalle (95%CI) wurden errechnet, und es wurde die Fläche unter der Receiver-operator characteristic-Kurve zur Bestimmung der Genauigkeit benutzt.
*Ergebnisse*: Ein erhöhtes ALT wurde bei 21 Jugendlichen (4,6%) gefunden. Unter den untersuchten Variablen waren nur männliches Geschlecht (OR = 6.7, 95%CI 2.0–23.2) und der Z-BMI (OR = 2.1, 95%CI 1.4–3.2) signifikante Vorhersageparameter für ein erhöhtes ALT. Die Genauigkeit der Vorhersage war 0.69 (95CI 0.59–0.79) für Geschlecht und 0.71 (95%CI 0.59–0.81) für Z-BMI. Wenn Geschlecht und Z-BMI kombiniert wurden, stieg die Genauigkeit auf 0.80 (95%CI 0.71–0.89).
*Zusammenfassung*: BMI ist ein guter Vorhersageparameter für erhöhte ALT bei Italienischen Jugendlichen, und Kenntnis des Geschlechts verbessert die Genauigkeit der Vorhersage.

**Résumé.** *But*: On a évalué la précision de l'indice de masse corporelle (IMC) pour la détection d'un niveau élevé d'aminotransférase alanine (ATA) chez les adolescents, en tenant compte des effets du sexe, de l'âge, de l'absorption d'éthanol, des infections virales par l'hépatite B (VHB) et C (VHC) et de la consommation de drogue.
*Sujets:* On a étudié un échantillon représentatif de 454 adolescents (11–17 ans) de deux villes du nord de l'Italie (Etude Dyonisos).
*Méthodes:* Un z-IMC a été calculé comme le z-score de l'IMC à partir des courbes de croissance nationales. La contribution des variables concernées à un niveau élevé d'ATA ( > 30 U/L) a été évaluée par régression logistique. On a calculé les Odds Ratios (OR) et les intervalles de confiance à 95% (IC95%) et la précision a été évaluée au moyen des aires sous-jacentes aux courbes caractéristiques receveur-opérateur.
*Résultats:* Un niveau élevé d'ATA a été détecté chez 21 adolescents (4.6%). Parmi les variables étudiées, seul le sexe masculin (OR = 6.7, IC95% 2.0–23.2) et le z-IMC (OR = 2.1, IC95% 1.4–3.2) sont des prédicateurs significatifs d' ATA élevée. La précision de la prédiction est 0.69 (95%IC 0.59–0.79) pour le sexe et 0.71 (IC95% 0.59–0.81 ) pour le z-IMC. En combinant le sexe et le z-IMC, la précision monte à O.80 (IC95% 0.71–0.89).
*Conclusion:* L'IMC est un bon prédicateur d'un niveau élevé d'ATA chez les adolescents italiens et le sexe accroît la précision de la prédiction.

**Resumen.** *Objetivo*: Evaluamos la precisión del índice de masa corporal (IMC) en la detección de niveles altos de alanina aminotransferasa (ALT) en adolescentes, teniendo en cuenta los efectos del género, la edad, la ingesta de etanol, las infecciones por virus de las hepatitis B (HBV) y C (HCV), y el consumo de drogas.

*Sujetos*: Se estudió una muestra representativa de 454 adolescentes (11–17 años) de dos ciudades de norte de Italia (Dionysos Study).
*Métodos:* Se calculó el valor z-IMC como la puntuación-z del IMC utilizando curvas de crecimiento nacionales. Se utilizó una regresión logística para cuantificar la contribución de las variables de interés a un elevado nivel de ALT ( > 30 U/L). Se calcularon las razones de productos cruzados (odds ratios, OR) y los intervalos de confianza al 95% (95% IC); las áreas bajo las curvas características receptor-operador (AUC) se usaron para evaluar la precisión.
*Resultados:* Se detectó un elevado nivel de ALT en 21 adolescentes (4.6%). Entre las variables estudiadas, solo el género masculino (OR = 6.7; 95% IC 2.0–23.2) y el valor z-IMC (OR = 2.1; 95% IC 1.4–3.2) fueron predictores significativos de un nivel de ALT elevado. La exactitud de la predicción fue de 0.69 (95% IC 0.59–0.79) para el género y de 0.71 (95% IC 0.59–0.81) para la z-IMC. Combinado el género y la z-IMC, la precisión ascendió a 0.80 (95% IC 0.71–0.89).
*Conclusión*: El IMC es un buen predictor de un alto nivel de ALT en adolescentes italianos y el género se suma a la exactitud de la predicción.