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Pediatric RESEARCH

POPULATION STUDY ARTICLE

Low handgrip strength is associated with higher liver enzyme concentrations in US adolescents

José Francisco López-Gil[1], Robinson Ramírez-Vélez[2], Jorge Alarcón-Jiménez[3], Mikel Izquierdo[2] and Antonio García-Hermoso[2,4]

BACKGROUND: Increasing evidence highlights the role of muscular strength as a protective factor for cardiometabolic health in adolescents. However, it is not known the relationship between liver enzyme concentrations, liver disease risk factors, and muscular strength among young populations. The aim of this study was to determine the association between muscle strength and liver enzymes and chronic liver disease risk among US adolescents.

METHODS: Data from the NHANES cross-sectional study (2011–2014) was used. A total of 1270 adolescents were included in the final analysis (12–17 years old). Absolute handgrip strength (kg) was normalized according to body composition parameters by body weight [NHSw], whole-body fat [NHSf], and trunk fat [NHSt]).

RESULTS: In boys, handgrip strength was inversely associated with higher values of aspartate aminotransferase (AST) and gamma glutamyl transpeptidase (GGT) for all estimations of muscle strength (NHSw, NHSf, and NHSt) ($p < 0.050$). Likewise, boys with high and intermediate NHSw, NHSf, and NHSt presented lower AST and GGT than their counterparts with low handgrip strength ($p < 0.050$).

CONCLUSIONS: Our findings highlight the importance of muscular strength during adolescence since they could help in developing better liver enzyme profiles among adolescent population.

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IMPACT:

- Our research suggests that US adolescents with low handgrip strength have higher values of liver enzymes as well as a higher prevalence of chronic liver disease.
- These findings are clinically meaningful and highlight the importance of muscular strength during adolescence since they could help in developing better liver enzyme profiles among young populations.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) refers to a spectrum of liver disorders, such as hepatic steatosis (NAFL), steatohepatitis (nonalcoholic steatohepatitis (NASH)), fibrosis, and anticipated cirrhosis.[1] NAFLD is often accompanied by typical cardiovascular risk factors, such as arterial hypertension, type 2 diabetes, and low levels of high-density lipoprotein cholesterol.[1] The aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio is an indicator of hepatic liver function, and it has also been related to cardiovascular anomalies in adolescents.[2] Additionally, high levels of ALT and gamma glutamyl transpeptidase (GGT) and a low AST/ALT ratio can be used as substitute markers for NAFLD.[2] Numerous studies in middle- and older-aged populations have shown a positive relationship between liver enzyme values and both metabolic syndrome and type 2 diabetes.[3] Thus, it has been shown that adults with greater AST/ALT ratios are at risk of developing metabolic syndrome.[4] Likewise, it should also be noted that, while an AST/ALT level <1 is a marker for NASH, a ratio of ≥2 is associated with alcoholic liver disease.[5]

There is abundant scientific evidence demonstrating the relationships of high levels of physical fitness with a healthy status in youths.[6,7] Specifically, muscular fitness is prospectively associated with adiposity and cardiometabolic parameters, together with a positive association with bone health during childhood/adolescence.[6] Regarding liver enzymes, a previous study suggested that normative handgrip strength by body weight (NHSw) has moderating effect on the association between anthropometric and body composition parameters (including waist circumference, waist-to-height ratio, and visceral adipose tissue) and controlled attenuation parameter (as an indicator of liver fat) in Colombian adolescents with excess of adiposity,[8] suggesting the importance of promoting muscular fitness during childhood and adolescence to reduce the risk of developing NAFLD. The approach used in this investigation is similar to that used by Lee et al.[9] in a representative sample of Korean adolescents; the author suggests that handgrip strength has a moderating effect on the associations of body mass index and metabolic syndrome scores with NAFLD. In contrast, higher

[1]Departamento de Actividad Física y Deporte, Facultad de Ciencias del Deporte, Universidad de Murcia, Murcia, Spain; [2]Navarrabiomed, Complejo Hospitalario de Navarra (CHN), Universidad Pública de Navarra (UPNA), IdiSNA, Pamplona, Spain; [3]Physiotherapy Department, Universidad Católica de Valencia (UCV), Valencia, Spain and [4]Universidad de Santiago de Chile (USACH), Escuela de Ciencias de la Actividad Física, el Deporte y la Salud, Santiago, Chile
Correspondence: Antonio García-Hermoso (antonio.garciah@unavarra.es)

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cardiorespiratory fitness is linked to lower liver fat mass percentage, liver enzyme values, insulin resistance, and cardiometabolic risk in children with excess weight (overweight/obesity)[10] but is not related to muscular fitness parameters.

Early screening and promotion efforts for a healthy status among young populations are vital to mitigate the incidence of NAFLD and other preventable comorbidities. Moreover, longitudinal data have demonstrated that chronic alteration of liver enzymes and greater fat mass (i.e., two hallmark risk factors for NAFLD) are associated with diminished muscle quality and weakness.[11–13] Similarly, increasing evidence highlights the role of muscular strength preservation as a protective factor for cardiometabolic health in young populations.[8] However, much uncertainty still exists about the relationship between liver enzyme concentrations, liver disease risk factors, and muscular strength among young population.[14] Therefore, the aims of this study were to examine the associations of handgrip strength normalized to body composition parameters with liver enzymes and chronic liver disease risk in US adolescents.

METHODS

Design and participants

Data from the National Health and Nutrition Examination Surveys (NHANES) cross-sectional study was used. The NHANES has performed a series of nutrition and health surveys since the beginning of the 1960s and has been carried out periodically from 1971 to the present day. Each year, about 5000 participants (non-institutionalized civilian resident population of the United States) of all ages and phases have been interviewed in their homes and completed the health examination component of the survey. The NHANES design has been modified on a periodic basis to sample larger numbers of some subcategories of specific public health concerns to raise the reliability and accuracy of estimates of health status markers for these population subcategories. In the present study, we included data from waves 2011–2012 and 2013–2014. A total of 1270 participants were included in the final analysis. Information about the selection of the participants of the study is presented in Fig. 1.

All procedures carried out involving human participants were following the ethical standards of the institutional and/or national research committee (National Health and Nutrition Examination Survey, NCHS IRB/ERB Protocol Number: NHANES 2011–2012 (Protocol #2011-17); NHANES 2013–2014 (Continuation of Protocol #2011-17). No further authorization was solicited for our study because the data used lacked personal identifiers. We utilize the NHANES data from 2011 to 2014. The data were obtained through a simple stratified multi-stage probability sampling of non-institutionalized civilian residents of the US.

Procedures

Body measurements. Standing height was measured using a stadiometer. Weight was calculated by a digital weight scale. Body mass index values were determined using measured height and weight values as follows: weight (kg)/height (m^2). The prevalence of excess weight (overweight/obesity) was calculated according to the Centers for Disease Control and Prevention (CDC) criteria.[15]

Body fat. Whole-body fat and trunk fat were determined by dual energy X-ray absorptiometry (DXA) (Hologic QDR 4500A), which applies two different energy levels generated by an energy tube to evaluate bone mineral content and bone mineral density. In addition, DXA can offer an accurate estimation of the four components of body composition (body weight into mineral, fat, water, mineral, and protein) by segmenting the body by specific clear-cut lines. All DXA scans were conducted by a certified radiology technologist.

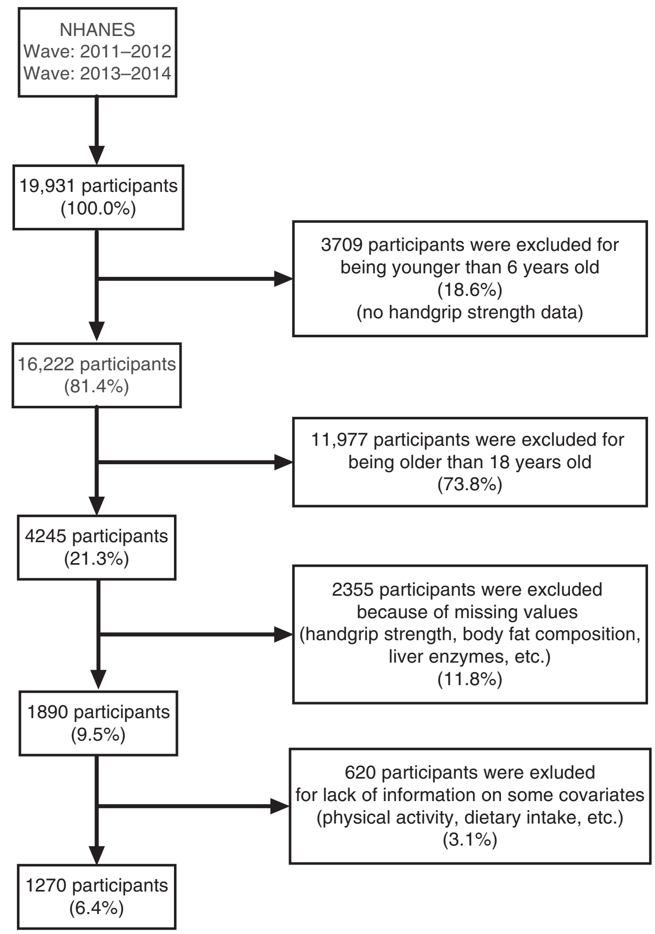

Fig. 1 Complete flow chart about the selection of the participants of the study. NHANES, National Health and Nutrition Examination Surveys (NHANES).

Blood sample. Participants were examined in the morning, after completing a fast of at least 9 h. The blood collection (venipuncture) procedure entails the following: (1) to fulfill a questionnaire to detect conditions that reject the participant from blood extraction; (2) to check fasting status; and (3) to execute the blood draw. Liver enzymes values (ALT, AST, and GGT) were obtained by DxC 800 chemistry analyzers through kinetic and enzymatic rate methods. Additionally, the previously ALT cut-off points proposed by Schwimmer et al.[16] for diagnosing chronic liver disease in adolescents were applied in the present study (>26 IU/L in boys and >22 IU/L in girls).

Handgrip strength. A comprehensive explanation of testing methods can be located in the NHANES Muscle Strength Procedures Manual.[17] To determine the maximum reading (kg) of the handgrip strength, a handgrip dynamometer was used (T.K. K. 5401, Grip-D, Takei, Japan), adjusted by sex and hand size for each participant, to evaluate the handgrip strength. The teenagers stood with their arms outstretched, gradually and continuously squeezing the dynamometer to its maximum strength for at least 2 s, performing the test twice and alternating with both hands. A rest period of 90 s was established between the different tests.[18] The absolute handgrip strength (kg) was computed as the mean of the left and right and then it was normalized to body composition parameters (normalized by body weight, NHSw], normalized by whole-body fat [NHSf], and normalized by trunk fat [NHSt]). In the absence of cut-off points for NHSw, NHSf, and NHSt, the different estimations of these normalized handgrip strength were categorized into tertiles by sex and age for the entire sample and categorized as: low handgrip strength (third tertile), intermediate handgrip strength (second tertile), and high handgrip strength (first tertile).

Covariates. Age, race/ethnicity, and ratio of family income to poverty were self-reported in participants aged >16 years, as well as in minors who are emancipated. A proxy provided data was applied in the case of participants aged <16 years. Participants were asked to complete questions created with the aim of estimating the time spent in physical activity (PA), both moderate PA (MPA) and vigorous PA (VPA) in three different circumstances (transportation, recreation, and work). Thus, the total weekly MET-minutes was computed following the recommendations of the NHANES National Youth Fitness Survey Time (Transportation = 4 Metabolic Equivalents [METS]; MPA = 4 METS; VPA = 8 METS). Dietary intake was computed by two 24-h dietary recall in-person interviews for each participant. Daily total energy and nutrient intakes from foods and beverages was calculated by averaging both 24-h dietary recalls. Lastly, a quantitative, automated hematology analyzer for in vitro diagnostic (UniCel DxH 800 analyzer) was used by determine the hemoglobin levels of the participants.

Statistical analyses

Descriptive data are offered as means and standard deviation for continuous variables and numbers and percentages for categorical variables. Student's *t* test and chi-square test were performed to compare continuous and categorical variables, respectively. Initial analyses indicate significant interactions between sex and handgrip strength categories in mean differences of liver enzymes ($p < 0.050$ for all); consequently, all analyses were carried out by sexes. Partial correlations were used to determine the relationship between variables. Due to the non-normal distribution of the liver enzymes values, the assumptions for executing an analysis of covariance (ANCOVA) were not met. Consequently, we chose bootstrapping as a trustworthy method to originate robust estimations of standard errors and confidence intervals (CIs) for measures of both central tendency and association. Thus, a robust bootstrapping ANCOVA with similar level of significance ($p < 0.050$) was performed to control for confounding variables. This ANCOVA was applied to assess differences between mean values of liver enzymes across handgrip strength categories (low, intermediate, or high) normalized by weight, trunk fat, or whole-body fat. Likewise, pairwise post hoc comparisons using Bonferroni was applied to verify the differences between mean values of liver enzymes across handgrip strength categories. Finally, multinomial logistic regression analyses were carried out in order to obtain the probability of having chronic liver disease according to the different handgrip strength category. All analyses were adjusted by age, race/ethnicity, ratio of family income to poverty, PA, dietary intake, and hemoglobin levels. Data analyses were carried out using the software Statistical Package for Social Sciences (SPSS) (Version 23.0). A *p* value <0.050 was considered statistically significant.

RESULTS

Table 1 shows the descriptive characteristics of the sample. The final sample had a mean age (standard deviation [SD]; [range]) of 14.5 years (1.7) with a range from 12 to 17 years (49.0% girls). Boys had greater levels of ALT, AST, GGT, risk of liver disease, and hemoglobin than girls (all $p < 0.05$). Statistically significant differences were shown in all estimations of handgrip strength between sexes (absolute handgrip strength, NHSw, NHSt and NHSf) ($p < 0.001$). Finally, the prevalence of the sum of overweight and obesity were 38.6% for the whole sample, according to the CDC criteria.

Table 2 presents crude and partial correlations between different estimations of handgrip strength and different values of liver enzymes, stratified by sex. Negative relationships were found between both AST and GGT and all of the normalized estimations of handgrip strength in the case of boys.

Figure 2 depicts differences in mean values of different liver enzyme concentrations according to the handgrip strength categories by sex. Our results show that boys with low NHS had higher values of AST and GGT in all of estimations of NHS than those with intermediate NHS and high NHS ($p < 0.001$).

Figure 3 presents the risk of having chronic liver disease according to the different relative handgrip strength categories. Low handgrip strength groups for all estimations of NHS were associated with an increased odds of chronic liver disease in boys but not in girls: NHSw (odds ratio (OR) = 4.41; CI 95% = 2.36–8.22), NHSf (OR = 2.77; CI 95% = 1.03–7.45), and NHSt [OR = 3.65; CI 95% = 1.39–9.60).

DISCUSSION

The current study aimed to explore the associations of handgrip strength with both liver enzymes and the prevalence of chronic liver disease in US adolescents. The main finding of our study was that high levels of liver enzymes (ALT and GGT) were found in adolescents with low handgrip strength, mainly in boys. Likewise, for all estimations of normalized handgrip strength, low handgrip strength groups were associated with an increased odds of chronic liver disease in boys. The absence of statistical significance in the case of girls could be explained by some factors. First, a higher levels of liver enzymes (ALT) has been found in several previous epidemiological studies in boys,[19,20] which was also corroborated in our study. Second, boys have greater levels of hemoglobin than girls, due to regular blood loss during the menstrual cycle could diminish the liver enzymes values.[21] However, further studies are required to elucidate the possible mechanism about how sex affects the liver function among adolescents.[21]

The role of physical exercise and its importance on liver enzyme concentrations is well known.[22] For example, González-Ruiz et al.[23] suggested physical exercise as an effective intervention for NAFLD progression by targeting hepatic lipid composition and visceral and subcutaneous adipose tissue in a pediatric obesity population. Regarding physical fitness, scientific evidence is conflicting. The present study revealed that higher normalized handgrip strength was related to lower liver enzymes (AST and GGT) among US adolescents. In contrast, Medrano et al.[10] reported no associations between handgrip strength and liver enzyme levels in excess weight children, but they did show that higher cardiorespiratory fitness was associated with lower percentages of hepatic fat and GGT and higher AST/ALT ratios. Nonetheless, these authors did not use handgrip strength values relative to adiposity levels as proposed in our study. In contrast, the findings of our study agree with those reported by previous studies in young[8,9] and adult populations.[24] For instance, Ramírez-Vélez et al.[8] found that NHSw moderates the associations between anthropometrics and body composition and fat deposits in the liver (determined by controlled attenuation parameters) in Colombian children and adolescents with higher body fat mass. These results are similar to those reported by Lee,[9] who suggested that higher handgrip strength may attenuate the risk of obesity and metabolic syndrome for NAFLD.

Over the past decade, scientific evidence has pointed to the benefits of strength training on different health parameters in both children and adolescents.[25] Additionally, prospective negative associations were observed between muscular fitness in childhood/adolescence and adiposity and cardiometabolic parameters in later life.[6] We also found a higher odds of chronic liver disease in those with lower handgrip strength, highlighting

Table 1. Main characteristics of the analyzed sample ($n = 1270$).

Variables	Boys		Girls		*p*
	n	*M* (SD)/*n* (%)	*n*	*M* (SD)/*n* (%)	
Sociodemographic					
Age, years	648	14.4 (1.7)	622	14.5 (1.7)	0.496
Race, Non-Hispanic White, *n* (%)	648	188 (29.0)	622	155 (24.9)	0.156
Family income to poverty ratio	648	2.10 (1.59)	622	2.09 (1.52)	0.908
Dietary intake					
Energy intake (kcal)	648	2188.3 (799.6)	622	1703.0 (628.7)	<0.001
Carbohydrates (g)	648	281.4 (104.6)	622	223.7 (85.3)	<0.001
Proteins (g)	648	84.4 (39.1)	622	62.2 (24.2)	<0.001
Fats (g)	648	82.5 (37.1)	622	64.2 (29.4)	<0.001
Physical activity					
Weekly PA (MET-min)	648	3213.7 (2960.9)	622	2985.2 (2963.1)	0.169
Daily PA energy expenditure (kcal)	648	530.4 (507.8)	622	465.4 (533.0)	0.026
Anthropometric data					
Weight, kg	648	66.89 (20.19)	622	61.90 (18.06)	<0.001
Height, m	648	1.68 (10.08)	622	1.60 (6.57)	<0.001
BMI, kg/m^2	648	23.38 (5.85)	622	24.13 (6.17)	0.025
Overweight/obese, *n* (%)	648	254 (39.2)	622	242 (38.9)	0.103
Body fat, kg	279	19.23 (10.27)	283	21.56 (10.29)	<0.001
Body fat, %	279	29.29 (8.78)	283	34.15 (6.52)	<0.001
Trunk fat, kg	292	7.65 (4.97)	280	8.77 (5.14)	<0.001
Trunk fat, %	292	11.33 (4.54)	280	13.55 (4.05)	<0.001
Muscular strength					
Absolute handgrip strength, kg	648	32.80 (9.10)	622	24.91 (5.00)	<0.001
Handgrip strength, kg/body weight, kg	648	0.51 (0.12)	622	0.42 (0.09)	<0.001
Handgrip strength, kg/whole-body fat, kg	279	2.37 (1.06)	283	1.32 (0.51)	<0.001
Handgrip strength, kg/trunk fat, kg	292	6.68 (3.27)	280	3.57 (1.73)	<0.001
Liver profile					
ALT, U/L	648	21.3 (15.1)	622	16.9 (14.4)	<0.001
AST, U/L	648	25.8 (10.2)	622	21.7 (7.9)	<0.001
GGT, U/L	648	15.3 (8.5)	622	12.6 (6.9)	<0.001
Risk of chronic liver disease, *n* (%)	648	96 (14.8)	622	63 (10.1)	0.012
Hemoglobin (g/dL)	648	14.4 (1.1)	622	13.0 (1.2)	<0.001

Data are expressed as mean (standard deviation) or numbers (percentages). Risk of having chronic liver disease was according to Schwimmer et al.[16]
ALT alanine aminotransferase, *AST* aspartate aminotransferase, *BMI* body mass index, *GGT* gamma glutamyl transferase, *MET, metabolic equivalet, PA* physical activity.

Table 2. Bivariate and partial correlations between different liver enzymes and different estimations of handgrip strength in US adolescent population.

Variables	Alanine aminotransferase		Aspartate aminotransferase		Gamma glutamyl transferase	
	Crude	Adjusted[a]	Crude	Adjusted[a]	Crude	Adjusted[a]
Boys						
Handgrip strength (kg)	0.179**	0.083	−0.108*	0.063	0.171**	0.043
Handgrip strength/body weight	−0.219**	−0.227**	−0.071*	−0.065	−0.189**	−0.181*
Handgrip strength/whole-body fat	−0.200**	−0.244**	−0.044	−0.079	−0.168*	−0.195*
Handgrip strength/trunk fat	−0.263**	−0.258**	−0.019	−0.077	−0.201**	−0.202*
Girls						
Handgrip strength (kg)	0.068	−0.024	−0.101*	−0.074	0.191**	0.071
Handgrip strength/body weight	−0.139**	−0.080	0.066	0.022	−0.211**	−0.109
Handgrip strength/whole-body fat	−0.092	−0.060	0.167*	0.068	−0.211**	−0.095
Handgrip strength/trunk fat	−0.136*	−0.069	0.165*	0.072	−0.237**	−0.090

*$p < 0.050$; **$p < 0.001$.
[a]Adjusted by age, race/ethnicity, ratio of family income to poverty, PA, dietary intake, and hemoglobin levels.

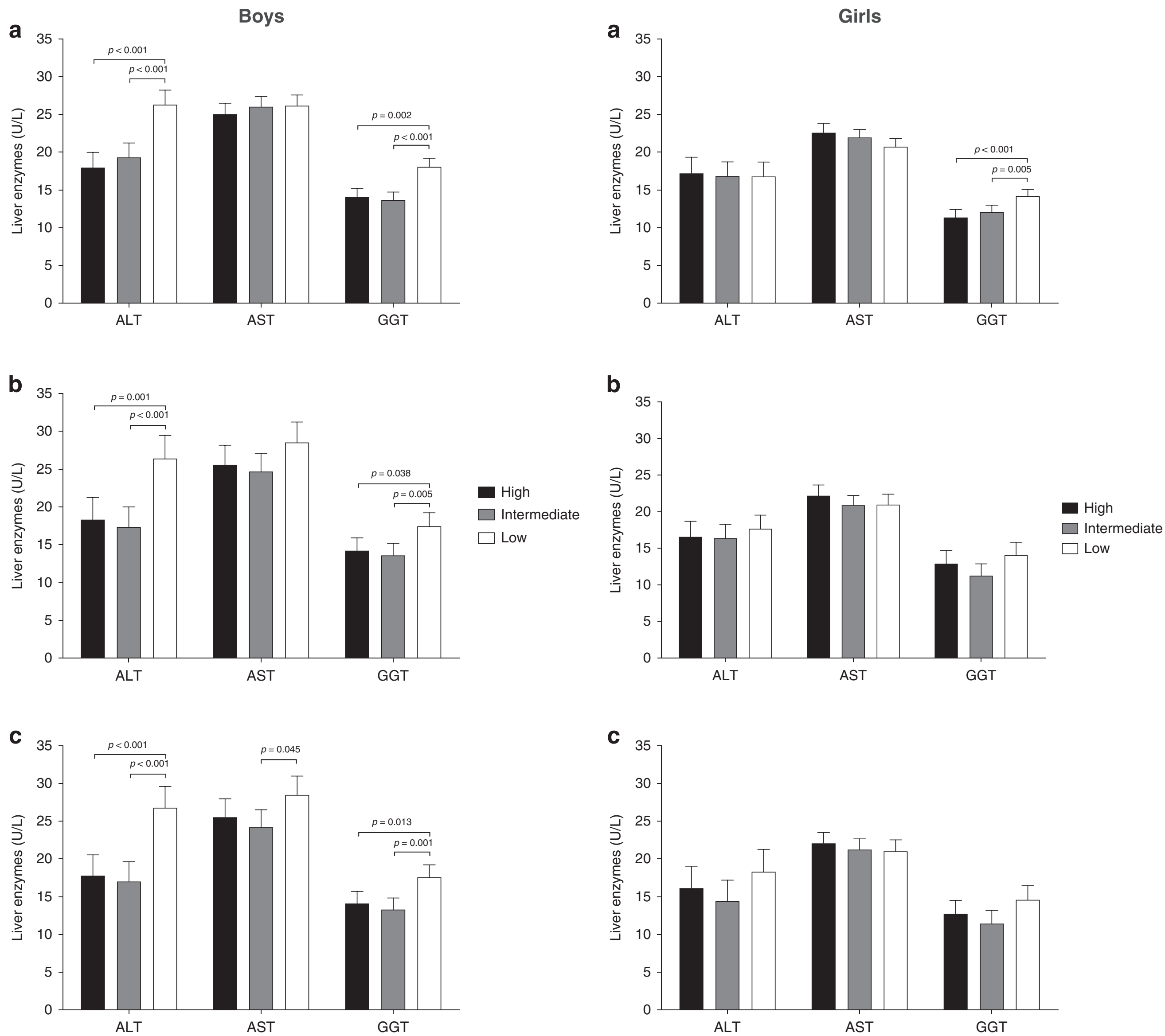

Fig. 2 Differences in mean values of different liver enzymes in blood level according to the different types of relative handgrip strength and adjusted for age, race/ethnicity, ratio of family income to poverty, physical activity, dietary intake, and hemoglobin levels. Data expressed as mean (bars) and standard error (lines). **a** Normalized handgrip strength by body weight; **b** normalized handgrip strength by whole-body fat; **c** normalized handgrip strength by trunk fat. ALT alanine aminotransferase, AST aspartate aminotransferase, GGT gamma glutamyl transferase, HS handgrip strength.

the importance of the level of muscular fitness in youth to achieve lower values of liver enzymes and diminish the possible risk of acquiring liver disease. A variety of physiological pathways exist whereby higher muscle strength could affect liver enzyme concentration: (a) increases in muscle strength may produce increases in the basal metabolic rate and a greater expenditure of energy, which may lead to a reduction in visceral fat tissue as well as fatty deposits in the liver[8]; (b) higher levels of normalized handgrip strength could reflect higher muscle quality (i.e., the capacity to produce force according to the mass or volume of musculoskeletal tissue),[26] which seems to influence the accumulation of fat in the liver,[8] which in turn could affect the release of hepatokines[27]; (c) skeletal muscles produce several myokines, biologically and metabolically active factors that regulate insulin resistance and lipid accumulation, all of which are associated with risk factors in the development of NAFLD[28]; and (d) other mechanisms such as low insulin-like growth factor 1 and osteocalcin level and increased insulin resistance and tumor necrosis factor-alpha may explain the link between low skeletal muscle mass and increased liver enzyme levels.[29]

This study had some limitations that must be declared. First, due to the cross-sectional design of this study, our findings are unable to reveal the causal associations between muscular strength and liver enzyme values as well as the risk of having liver disease. In this sense, longitudinal studies are needed to clarify the role of muscular strength in liver enzyme values moderating this multifarious relationship. Second, another limitation of this study is the lack of a biopsy, the gold standard for diagnosing hepatic steatosis. However, because of its cost, invasiveness, and potentially life-threatening complications, biopsies are not recommended for all subjects. Thus, several easy methods are used to diagnose NAFLD (e.g., ultrasonography and biochemical tests).[14]

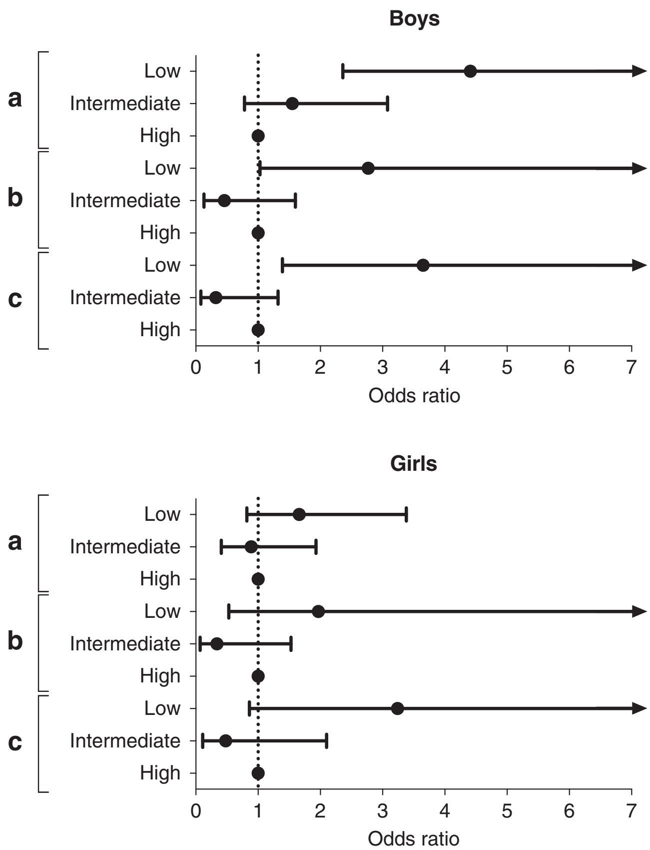

Fig. 3 Risk of having chronic liver disease according to the different relative handgrip strength categories. Data expressed as odds ratio (dots) and standard error (bars). Risk of having chronic liver disease was determined according to Schwimmer et al.[16] Adjusted for age, race/ethnicity, ratio of family income to poverty, physical activity, dietary intake, and hemoglobin levels. High handgrip strength (Q1) was considered as the reference category. **a** Normalized handgrip strength by body weight; **b** normalized handgrip strength by whole-body fat; **c** normalized handgrip strength by trunk fat.

Among the strengths of this study, we conducted a large population-based study on US adolescents. Another strength is the fact that, to our knowledge, this is the first study to explore the association between liver enzymes and the risk of chronic liver disease according to categories of handgrip strength relative to body composition. Moreover, different tools were used to determine body composition, among them DXA, considered the gold standard.

CONCLUSIONS

The present study suggests that US adolescents with low handgrip strength have higher values of liver enzymes as well as a higher odds of chronic liver disease, mainly in boys. Our findings are clinically meaningful and highlight the importance of muscular strength during adolescence since they could help in developing better liver enzyme profiles. Further prevention programs and tailored interventions targeted to adolescents are required to improve muscular strength during this period. In addition, the presented results are of interest for physical educators, researchers, trainers, fitness professionals, physical therapists, and coaches to identify the target population for primary prevention and to estimate the proportion of adolescents with high or low muscular strength level.[30]

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AUTHOR CONTRIBUTIONS

Conceptualization, J.F.L.-G. and A.G.-H.; methodology, J.F.L.-G., and A.G.-H.; software, J. F.L.-G. and A.G.-H.; validation, J.F.L.-G and A.G.-H.; formal analysis, A.G.-H.; data curation, J.F.L.-G. and A.G.-H.; writing—original draft preparation, J.F.L.-G., A.G.-H., J.A.-J., and R.R.-V.; writing—review and editing, R.R.-V., and M.I.; visualization, A.G.-H. and R.R.-V.; supervision, A.G.-H. and M.I.; all authors have read and agreed to the published version of the manuscript.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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REFERENCES

1. Sattar, N., Forrest, E. & Preiss, D. Non-alcoholic fatty liver disease. *BMJ* **349**, g4596 (2014).
2. Labayen, I. et al. Liver enzymes and clustering cardiometabolic risk factors in European adolescents: the HELENA study: liver enzymes and metabolic risk. *Pediatr. Obes.* **10**, 361–370 (2015).
3. Balkau, B., Lange, C., Vol, S., Fumeron, F. & Bonnet, F. Nine-year incident diabetes is predicted by fatty liver indices: the French D.E.S.I.R. study. *BMC Gastroenterol.* **10**, 56 (2010).
4. Hanley, A. J. G. et al. Liver markers and development of the metabolic syndrome: The Insulin Resistance Atherosclerosis Study. *Diabetes* **54**, 3140–3147 (2005).
5. Sorbi, D., Boynton, J. & Lindor, K. D. The ratio of aspartate aminotransferase to alanine aminotransferase: potential value in differentiating nonalcoholic steatohepatitis from alcoholic liver disease. *Am. J. Gastroenterol.* **94**, 1018–1022 (1999).
6. García-Hermoso, A., Ramírez-Campillo, R. & Izquierdo, M. Is muscular fitness associated with future health benefits in children and adolescents? A systematic review and meta-analysis of longitudinal studies. *Sports Med.* **49**, 1079–1094 (2019).
7. García-Hermoso, A., Ramírez-Velez, R., García-Alonso, Y., Alonso-Martinez, A. & Izquierdo, M. Association of cardiorespiratory fitness levels during youth with health risk later in life. A systematic review and meta-analysis. *JAMA Pediatr.* **174**, 1–9 (2020).
8. Ramírez-Vélez, R. et al. Grip strength moderates the association between anthropometric and body composition indicators and liver fat in youth with an excess of adiposity. *J. Clin. Med.* **7**, 347 (2018).
9. Lee, K. Moderation effect of handgrip strength on the associations of obesity and metabolic syndrome with fatty liver in adolescents. *J. Clin. Densitom.* **23**, 278–285 (2020).
10. Medrano, M. et al. Associations of physical activity and fitness with hepatic steatosis, liver enzymes, and insulin resistance in children with overweight/obesity. *Pediatr. Diabetes* **21**, 565–574 (2020).
11. Pandey, S. Association of nonalcoholic fatty liver disease with relative skeletal muscle mass: a public health perspective. *Hepatology* **68**, 1657–1657 (2018).
12. Kim, G. et al. Relationship between relative skeletal muscle mass and nonalcoholic fatty liver disease: a 7-year longitudinal study. *Hepatology* **68**, 1755–1768 (2018).
13. Fan, R., Wang, J. & Du, J. Association between body mass index and fatty liver risk: a dose-response analysis. *Sci. Rep.* **8**, 15273 (2018).
14. Kelishadi, R. et al. Association of alanine aminotransferase concentration with cardiometabolic risk factors in children and adolescents: the CASPIAN-V cross-sectional study. *Sao Paulo Med. J.* **136**, 511–519 (2018).
15. Kuczmarski, R. J., Ogden, C. L. & Guo, S. S. 2000 CDC growth charts for the United States: methods and development. Vital and health statistics. Series 11, Data from the national health survey. https://www.cdc.gov/nchs/data/series/sr_11/sr11_246.pdf (2002).
16. Schwimmer, J. B. et al. SAFETY Study: alanine aminotransferase cutoff values are set too high for reliable detection of pediatric chronic liver disease. *Gastroenterology* **138**, 1357–1364.e2 (2010).

17. Centers of Disease Control and Prevention. National Health and Nutrition Examination Survey (NHANES): muscle strength procedures manual. https://wwwn.cdc.gov/nchs/data/nhanes/2011-2012/manuals/Muscle_Strength_Proc_Manual.pdf (2011).
18. Ruiz, J. R. et al. Field-based fitness assessment in young people: the ALPHA health-related fitness test battery for children and adolescents. *Br. J. Sports Med.* **45**, 518–524 (2011).
19. Fraser, A., Longnecker, M. P. & Lawlor, D. A. Prevalence of elevated alanine aminotransferase among US adolescents and associated factors: NHANES 1999–2004. *Gastroenterology* **133**, 1814–1820 (2007).
20. Kim, J. W. et al. Prevalence and risk factors of elevated alanine aminotransferase among Korean adolescents: 2001–2014. *BMC Public Health* **18**, 617 (2018).
21. Chen, S. C.-C. et al. Gender difference of alanine aminotransferase elevation may be associated with higher hemoglobin levels among male adolescents. *PLoS ONE* **5**, e13269 (2010).
22. Baker, C. J. et al. Effect of exercise on hepatic steatosis: are benefits seen without dietary intervention? A systematic review and meta-analysis. *J. Diabetes* **13**, 63–77 (2021).
23. González-Ruiz, K., Ramírez-Vélez, R., Correa-Bautista, J. E., Peterson, M. D. & García-Hermoso, A. The effects of exercise on abdominal fat and liver enzymes in pediatric obesity: a systematic review and meta-analysis. *Child Obes.* **13**, 272–282 (2017).
24. Hao, L., Wang, Z., Wang, Y., Wang, J. & Zeng, Z. Association between cardiorespiratory fitness, relative grip strength with non-alcoholic fatty liver disease. *Med. Sci. Monit. Int. Med. J. Exp. Clin. Res.* **26**, e923015 (2020).
25. Stricker, P. R., Faigenbaum, A. D. & McCambridge, T. M. Resistance training for children and adolescents. *Pediatrics* **145**, e20201011 (2020).
26. Barbat-Artigas, S., Rolland, Y., Zamboni, M. & Aubertin-Leheudre, M. How to assess functional status: a new muscle quality index. *J. Nutr. Health Aging* **16**, 67–77 (2012).
27. Stefan, N. & Häring, H.-U. The role of hepatokines in metabolism. *Nat. Rev. Endocrinol.* **9**, 144–152 (2013).
28. Mizgier, M. L., Casas, M., Contreras-Ferrat, A., Llanos, P. & Galgani, J. E. Potential role of skeletal muscle glucose metabolism on the regulation of insulin secretion: organ crosstalk and insulin secretion. *Obes. Rev.* **15**, 587–597 (2014).
29. Poggiogalle, E., Donini, L. M., Lenzi, A., Chiesa, C. & Pacifico, L. Non-alcoholic fatty liver disease connections with fat-free tissues: a focus on bone and skeletal muscle. *World J. Gastroenterol.* **23**, 1747 (2017).
30. Laurson, K. R., Saint-Maurice, P. F., Welk, G. J. & Eisenmann, J. C. Reference curves for field tests of musculoskeletal fitness in U.S. children and adolescents: The 2012 NHANES National Youth Fitness Survey. *J. Strength Cond. Res.* **31**, 2075–2082 (2017).