Research Article

Temporal changes of liver function tests in relation to adiposity in the community: The CoLaus|PsyCoLaus Study

Manon Scyboz[1], Noushin Sadat Ahanchi[2], Montserrat Fraga[3], Julien Vaucher[2,4*]

[1]*Faculty of Sciences and Medicine, University of Fribourg, Fribourg, Switzerland*
[2]*Department of Internal Medicine and Specialties, Division of Internal Medicine, Fribourg Hospital and University of Fribourg, Fribourg, Switzerland*
[3]*Division of Gastroenterology and Hepatology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland*
[4]*Department of Medicine, Division of Internal Medicine, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland*

Article Info

[*]***Corresponding Author:***
Julien Vaucher
Department of Internal Medicine and Specialties, Division of Internal Medicine, Fribourg, Hospital and University of Fribourg
Ch. des Pensionnats 2-6, CP-1708 Fribourg, Switzerland
E-mail: Julien.vaucher@h-fr.ch

Keywords
liver function tests, obesity, age, gender

Abstract

Background: Liver function test (LFT; including alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, and alkaline phosphatase) results are modulated by multiple factors, but their temporal changes have been insufficiently explored, especially in relation to aging and adiposity. First, we assessed the trends of LFTs levels over time across different age groups and sexes. Second, we tested the cross-sectional and longitudinal associations between levels of LFTs and anthropometric measurements capturing various degree of adiposity.

Methods: 5171 participants (2393 males), aged 35-75 years at baseline (2003-2006), from a prospective population-based cohort (CoLaus|PsyCoLaus study), were included and followed up until 2019-2023. Anthropometric measurements included body mass index, waist-to-height ratio, waist-to-hip ratio, relative fat mass, body shape index, body roundness index, waist-to-weight ratio and body surface area. Boxplots presented changes of LFTs across age groups. Multiple linear regressions and multilevel mixed models were used to analyze the cross-sectional and longitudinal associations between levels of LFTs and anthropometric measurements, adjusting for a large range of variables.

Results: LFTs values showed distinct temporal changes between age groups and sexes. Anthropometric measurements capturing various degree of adiposity demonstrated a strong and significant association ($p<0.001$) with all four LFTs in both cross-sectional and longitudinal analyses. These associations remained robust even after adjusting for multiple covariates.

Conclusion: In a population-based study, LFTs changed over time according to age and sex. These changes were independently associated with markers of adiposity, showing the importance of interpreting LFTs based on the clinical context, especially in presence of overweight or obesity.

Introduction

Liver function tests (LFTs; including alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, and alkaline phosphatase) are frequently performed in clinical practice [1-6], reflecting either hepatocyte integrity or cholestasis [2, 7-10]. Obesity and closely linked metabolic dysfunction-associated fatty liver disease (MAFLD) are widespread public health issues globally [3, 8-9, 11-14]. MAFLD arises from lipid accumulation in liver tissue, in the absence of significant chronic alcohol consumption, viral infection, or other chronic liver disease causes [11-12, 15]. MAFLD encompasses two entities that are: i) metabolic dysfunction-associated fatty liver (MAFL), characterized by steatosis; and ii) metabolic dysfunction-associated steatohepatitis (MASH), representing an inflammatory phase which involves various degrees of steatohepatitis and fibrosis potentially leading to cirrhosis and hepatocellular carcinoma [9, 11-13, 15-17]. However, MAFLD does not necessarily present with abnormal liver tests [12, 18], with 80% of affected people having normal alanine aminotransferase (ALT) levels [11]. A large body of evidence shows an increase in liver enzyme levels associated with the rising prevalence of obesity [4-6, 8, 11-13, 18], but there is still a lack of comprehensive understanding regarding their change over a prolonged period of time and their correlation with different clinical measures of obesity (such as body mass index [BMI], body shape index [BSI], body surface area [BSA], relative fat mass [RFM], weight-adjusted-waist index [WWI], waist-to-hip ratio [WHR] and waist-to-height ratio [WHtR]) [8, 13, 18-20].

Additionally, the relationship between LFTs and age and sex, which can blur any interpretation of longitudinal change of LFTs with another factor, remains unclear [19, 21-22]. While age was usually not considered as impacting LFTs levels, recent studies have shown ambiguous results [22]. A study by Dong et al showed a reduction of LFTs with increasing age [22]. Moreover, in the US National Health and Nutrition Examination Surveys, older age was associated with lower ALT values than at a younger age [5, 9, 12]. Regarding sexes, another study concluded that there exists a significant age-related correlation in ALT values among males, with higher levels of ALT observed in males aged 25-34 and 65-74 years [21]. The age-related correlation in ALT values among females was notably weaker, with only a slight increase observed around age 50. The levels of gamma-glutamyl transferase (GGT) rose until the age of 60 in males, while in females, they continue to increase throughout life [21]. However, most of these studies have been carried out in people with active medical conditions that can affect the interpretation of the evolution of liver tests [5, 9, 12, 21-22]. In general, most studies clearly show that ALT levels are higher in males than in females, regardless of age or BMI [4-6, 12, 18].

In this study, we first aimed to assess the changes of LFTs levels over time across different age groups and sexes. Second, we investigated the cross-sectional and longitudinal associations between levels of LFTs and anthropometric measurements capturing various degree of adiposity.

Methodology

CoLaus|PsyCoLaus Study

The CoLaus|PsyCoLaus study is an ongoing population-based prospective study conducted in the city of Lausanne, Switzerland, aiming to assess the biological and genetic determinants of cardiovascular disease, together with psychiatric disorders [23]. Briefly, a random sample of 6733 individuals aged 35-75 years from the population of Lausanne, Switzerland, was recruited between 2003 and 2006. Subjects were included if they consented to participate in the study. The first follow-up was performed between April 2009 and September 2012, the second follow-up between May 2014 and April 2017 and the third follow-up between April 2019 and September 2023. The information collected at follow-ups was the same as that collected during the baseline examination. For this study, data from the baseline (2003-2006), first (2009-2012), second (2014-2017) and third (2019-2023) follow-ups were used. The cantonal Ethics Commission of the Canton of Vaud approved the CoLaus|PsyCoLaus study ((http://www.cer-vd.ch) project number PB_2018-00038, reference 239/09), and all participants provided written informed consent.

Selection of participants

Participants were excluded based on missing data at baseline and follow-up and if high-sensitivity C-reactive protein (hs-CRP) level was ≥ 10 mg/L, indicative of an ongoing inflammatory process that might modify levels of LFTs.

Liver function tests

Blood analyses were conducted using fasting venous blood samples drawn from patients [23]. LFTs, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP), were measured at Lausanne University Hospital clinical laboratory.

Anthropometric measurements and LFT body weight and height were measured with participants barefoot and in light indoor clothes. Body weight was measured in kilograms to the nearest 100 g using a Seca® scale (Hamburg, Germany). Height was measured to the nearest 5 mm using a Seca® (Hamburg, Germany) height gauge. Body Mass Index (BMI) was calculated as the ratio of weight (in kilograms) to height squared (in meters). Waist-to-Height Ratio (WHtR) was determined by dividing waist circumference (in meters) by height (in meters). Waist-to-Hip Ratio (WHR) was obtained by dividing waist circumference (in meters) by hip circumference (in meters). Relative Fat Mass (RFM) was calculated using the formula [64 - (20 × height / waist circumference) + (12 × sex)], where sex is coded as 0 for males and 1 for females. Body Shape Index (BSI) was measured as

[waist circumference / weight$^{(-2/3)}$ × height $^{(5/6)}$]. Body Roundness Index (BRI) was calculated with the formula [364.2 - 365.5 × (1 - (0.5 × waist circumference / π)^2 / (0.5 × height)2)$^{0.5}$]. Waist-to-Weight Ratio (WWR) was calculated by dividing waist circumference by body weight. Body Surface Area (BSA) was calculated using the formula [weight$^{0.425}$ × height$^{0.725}$ × 0.007184]. Weight-adjusted waist index (WWI) was calculated by dividing waist circumference (cm) by the square root of weight (kg).

Covariates

Blood pressure and heart rate were measured thrice on the left arm, with an appropriately sized cuff, after at least 10 minutes' rest in the seated position using an Omron® HEM-907 automated oscillometric sphygmomanometer (Matsusaka, Japan). The average of the last two measurements was used for analyses. Serum lipids were measured using enzymatic colorimetric assays. Hs-CRP was assessed by immunoassay. Information on age, lifestyle, medical history of diabetes, alcohol consumption was obtained through a questionnaire. Alcohol consumption was obtained by asking if participants regularly consumed alcohol and their weekly consumption of wine, beer, and spirits in units per week. Smoking was categorized as never, former, and current.

Statistical analysis

Statistical analyses were performed using Stata version 17. Baseline characteristics of the study population are described as frequencies and percentages for categorical variables, mean and standard deviation, or median and 25th–75th percentile for continuous variables. The normality of continuous variables was assessed through histogram visualization and the Shapiro-Wilk test. Variables that exhibited skewness, such as LFTs, anthropometric measurements and hs-CRP, were log-transformed to approximate a normal distribution.

Cross-sectional analysis

For the cross-sectional analysis of baseline LFTs, confounders and anthropometric measurements were included. We compared LFTs, anthropometric measurements, sociodemographic characteristics, blood pressure levels (systolic blood pressure (SBP) and diastolic blood pressure (DBP)), lipid status (total cholesterol (TC), low-density lipoprotein cholesterol (LDL)), and hs-CRP levels between males and females using independent-samples t-tests. T-test or Mann–Whitney U test were used for continuous variables, and the chi-squared test for categorical variables. Multiple linear regression models were used to investigate the association of LFTs levels (each as independent variables) with anthropometric measurements (as dependent variables). Two models were used: 1) adjusting for age and sex; and 2) adjusting additionally for smoking, alcohol use, prevalence of diabetes, SBP, DBP, LDL, TC and hs-CRP. Results were expressed as beta coefficient and 95% confidence interval. As a sensitivity analysis, we stratified all analyses by sex.

Longitudinal analysis

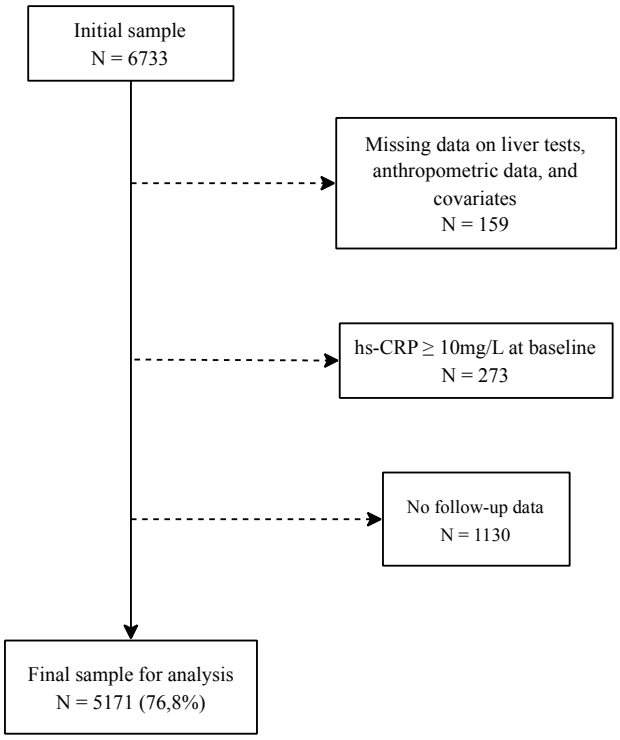
To explore the temporal changes in LFTs values across different age groups, boxplots were used to visually compare the patterns of values for each LFT in males and females. The participants were categorized into four age groups: < 40 years, 40-54 years, 55-69 years, and ≥ 70 years. For each age group, LFTs values were plotted for each survey.

To investigate the longitudinal association between LFTs and anthropometric measurements, we used a multilevel mixed-model approach for baseline, first, second and third follow-ups, including the same baseline confounders as in the cross-sectional analysis. Our model incorporated both fixed and random effects to comprehensively account for individual variability and potential confounding factors. The fixed effects included anthropometric measurements, follow-up time, and their interaction term, together with the same baseline confounders as in the cross-sectional analysis. The fixed effects elucidated how changes in LFTs were associated with anthropometric measurements over time. The random effects comprised random intercepts and random slopes, capturing individual-level variability in baseline LFTs levels and their rates of change over time. As a sensitivity analysis, we stratified all analyses by sex.

Results

Out of 6733 participants who completed the baseline survey, 159 (2.4%) were excluded due to missing information on LFTs and anthropometric data, and 273 (4%) due to a hs-CRP level ≥ 10 mg/L. Additionally, 1130 participants (16.8%) were excluded due to absence of follow-up data. The final sample size eventually comprised 5171 participants (76.8%) (Figure 1).

Figure 1: Enrolment flow chart for study population.



hs-CRP, high-sensitivity C-reactive protein

Baseline characteristics of participants

Baseline characteristics of participants indicated that males were slightly younger than females (mean age: 51.57 vs 52.7 years, p = 0.003). Males showed higher levels of LFTs (ALT, AST, ALP, and GGT) compared to females, highlighting sex-specific patterns in LFTs. Additionally, males had higher anthropometric measurements of adiposity, a higher prevalence of diabetes, a higher blood pressure (systolic and diastolic), higher LDL-cholesterol and alcohol consumption. In contrast, females exhibited higher HDL-cholesterol and hs-CRP levels (Table 1). The comparison between included and excluded participants showed that the included participants were younger, smoked less, had a higher education, drank more alcohol, were less likely to have diabetes and had a higher HDL-cholesterol. In excluded participants, their BMI was higher, and they presented higher hs-CRP and blood pressure levels. Total cholesterol, LDL-cholesterol, waist-to-hip ratio and the body surface area were similar between the two groups. All four LFTs, ALT, AST, ALP, and GGT, were significantly higher in the excluded people than included ones (24 vs 23 IU/L, p-value 0.001; 28 vs 27 IU/L, p-value 0.003; 68.2 vs 61.9 IU/L, p-value 0.002; 24 vs 20 IU/L, p-value 0.005, respectively) (Supplementary Table 1).

Table 1: Baseline characteristics of participants.

Variable	Total	Males	Females	P value*
	N = 5171	N = 2393	N = 2778	
Age (years)	52.1 (10.6)	51.57 (10.5)	52.7 (10.5)	0.003
Smoking status (n, %)				<0.001
Never	2126 (41.1)	835 (34.8)	1291 (46.4)	
Former	1729 (33.4)	920 (38.4)	809 (29.1)	
Current	1316 (25.4)	638 (26.6)	678 (24.4)	
Education level (n, %)				<0.001
High	1102 (21.3)	623 (26.03)	479 (17.2)	
Middle	1321 (25.5)	577 (24.1)	744 (26.7)	
Low	2748 (53.1)	1193 (49.8)	1555 (55.9)	

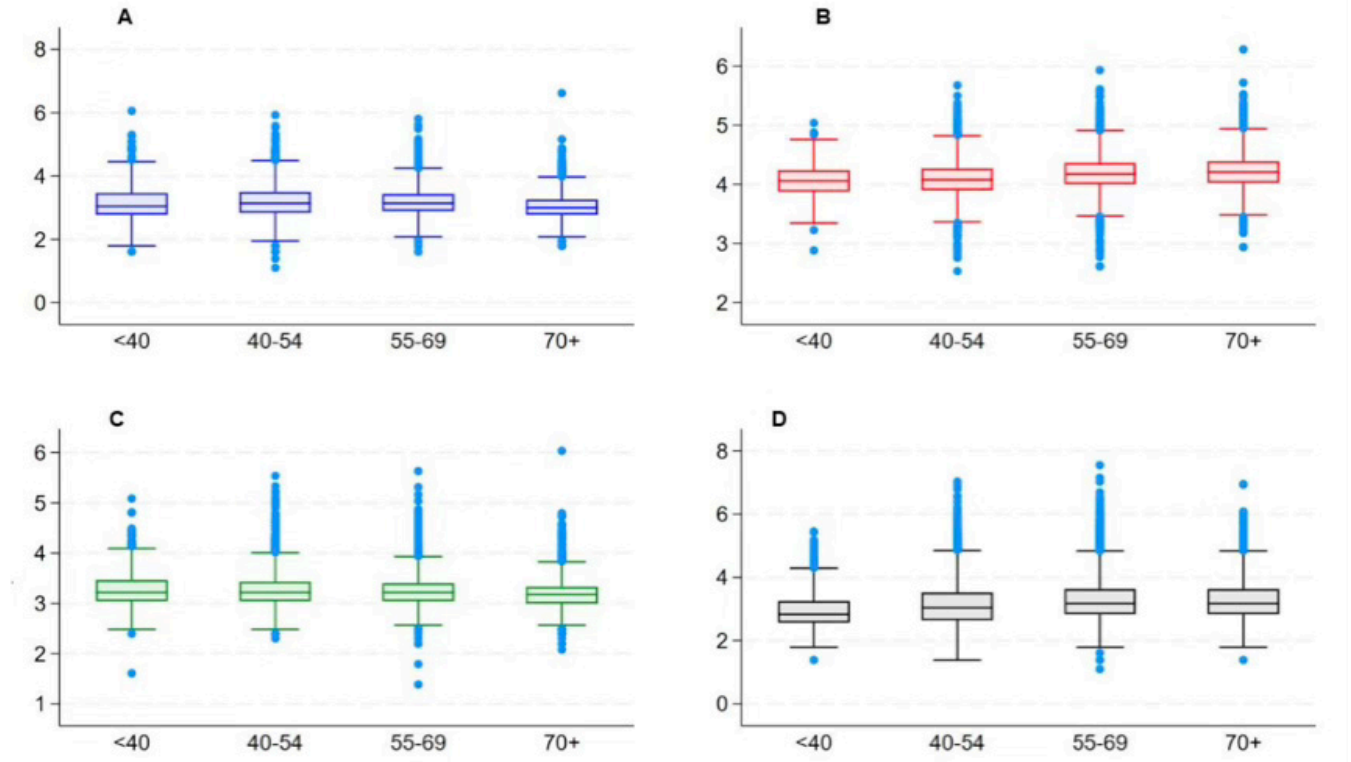
Alcohol drinker (weekly consumption)	4 (0-10)	7 (2-14)	2 (0-6)	0.04
Excessive alcohol consumers (n, %)	1029 (19.9)	566 (23.6)	463 (16.6)	0.02
BMI (kg/m2)	24.4 (4.23)	26.3 (3.81)	24.7 (4.45)	<0.001
BSI (m11/6kg-2/3)	0.078 (0.074; 0.082)	0.081 (0.078; 0.083)	0.075 (0.072; 0.079)	0.004
BSA (m0.725kg0.425)	0.006 (0.005; 0.007)	0.006 (0.006; 0.007)	0.0059 (0.0056;0.0063)	<0.03
RFM	31.02 (22.9; 38.35)	38.69 (36; 41.38)	23.49 (19.49; 27.57)	<0.001
WWI (m/kg2)	10.34 (9.82; 10.87)	10.55 (10.11; 11.01)	10.10 (9.58, 10.71)	0.002
WHtR (ratio)	0.51 (0.46; 0.56)	0.53 (0.5; 0.57)	0.49 (0.44; 0.54)	0.001
WHR (ratio)	0.86 (0.80-0.92)	0.92 (0.88-0.96)	0.81 (0.77- 0.86)	<0.001
hs-CRP (mg/l)	1.18 (0.6-2.4)	1.17 (0.6-2.1)	1.2 (0.6-2.5)	0.01
Diabetes (yes/no)	274 (5.3)	191(7.9)	83 (2.9)	0.03
SBP (mmHg)	126.8 (17.3)	130.8 (16.2)	123.4 (17.51)	<0.001
DBP (mmHg)	78.8 (10.7)	80.92 (10.7)	77.09 (10.48)	<0.001
HDL-C (mmol/L)	1.6 (0.4)	1.4 (0.35)	1.82 (0.42)	<0.001
TC (mmol/L)	5.51 (1)	5.53 (0.99)	5.57 (1.01)	0.05
LDL (mmol/L)	3.3 (0.9)	3.4 (0.8)	3.2 (0.91)	<0.001
Liver tests (IU/L)				
Alanine aminotransferase	23 (17-32)	29 (29-39)	15 (15-24)	<0.001
Aspartate aminotransferase	27 (23-33)	30 (25-37)	24 (21-29)	<0.001
Alkaline phosphatase	61.9 (51-75)	64 (54-75.6)	60.9 (49.3-75.6)	<0.001
Gamma-glutamyl transpeptidase	20 (14- 32)	27 (19-43)	16 (12-23)	<0.001

BMI, body mass index; BSA, body surface area; BSI, body shape index; RFM, relative fat mass; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; WWI, weight-adjusted-waist index; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; CRP, C-reactive protein; HDL-C, High-Density Lipoprotein; TC, Total Cholesterol; LDL, Low-Density Lipoprotein Cholesterol. Continuous variables shown as mean (SD) with p according to t-test; categorical variables as % with p according to $\chi 2$, median (25th-75th percentile) with p according to Mann–Whitney U-test (§). *Comparing males and females.

Distribution of liver function tests according to age

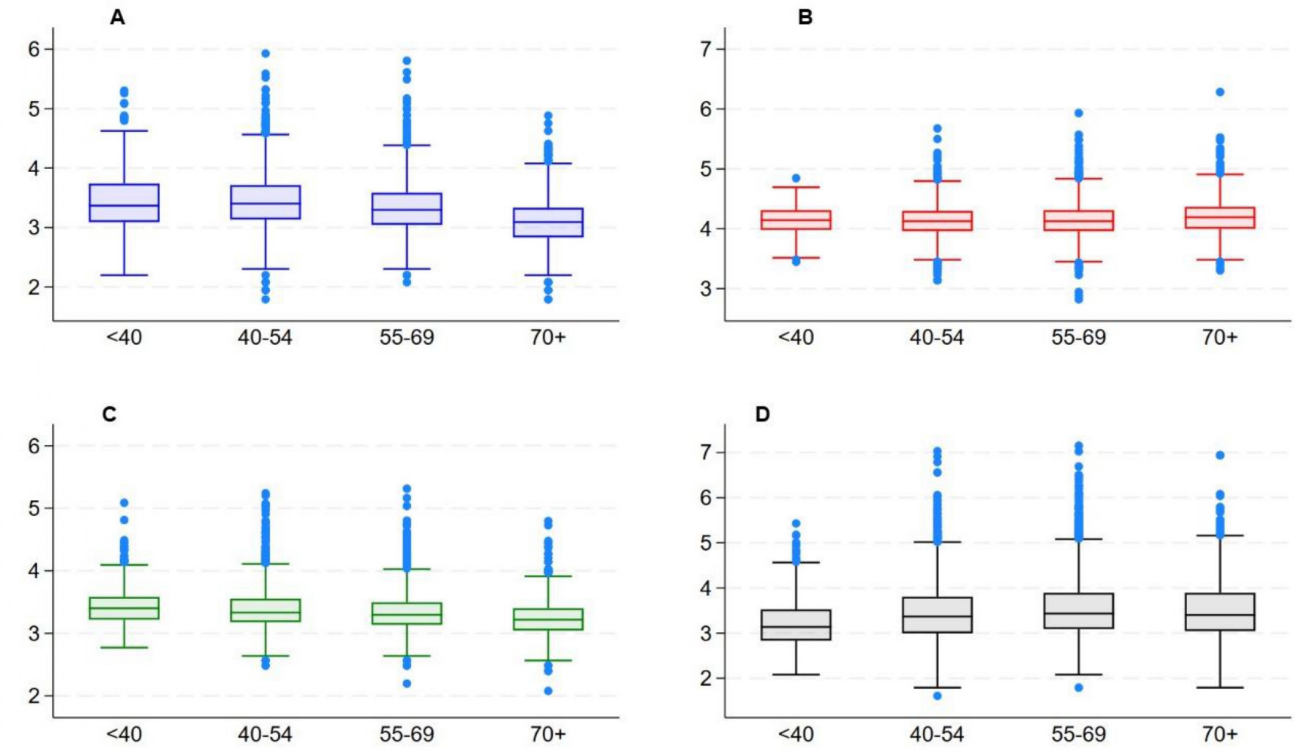
To analyze the trend in LFTs values based on age, boxplots were generated for different age groups (< 40 years, 40-54 years, 55-60 years, > 70 years) across all follow-up periods. Figure 2 illustrates that the progression of liver test values varies with age for both males and females, with distinct patterns observed for each LFT. Concisely, ALT levels either slightly increased or remained stable in middle-aged people (40-70 years) and decreased after 70 years. AST and GGT levels showed a consistent increase with age, while ALP levels remained relatively stable but exhibit a slight decrease after 70 years. The prospective change of LFTs levels by age and sex is depicted in Figures 3 and 4.

Figure 2: Distribution of liver function tests according to age ranges in total population.



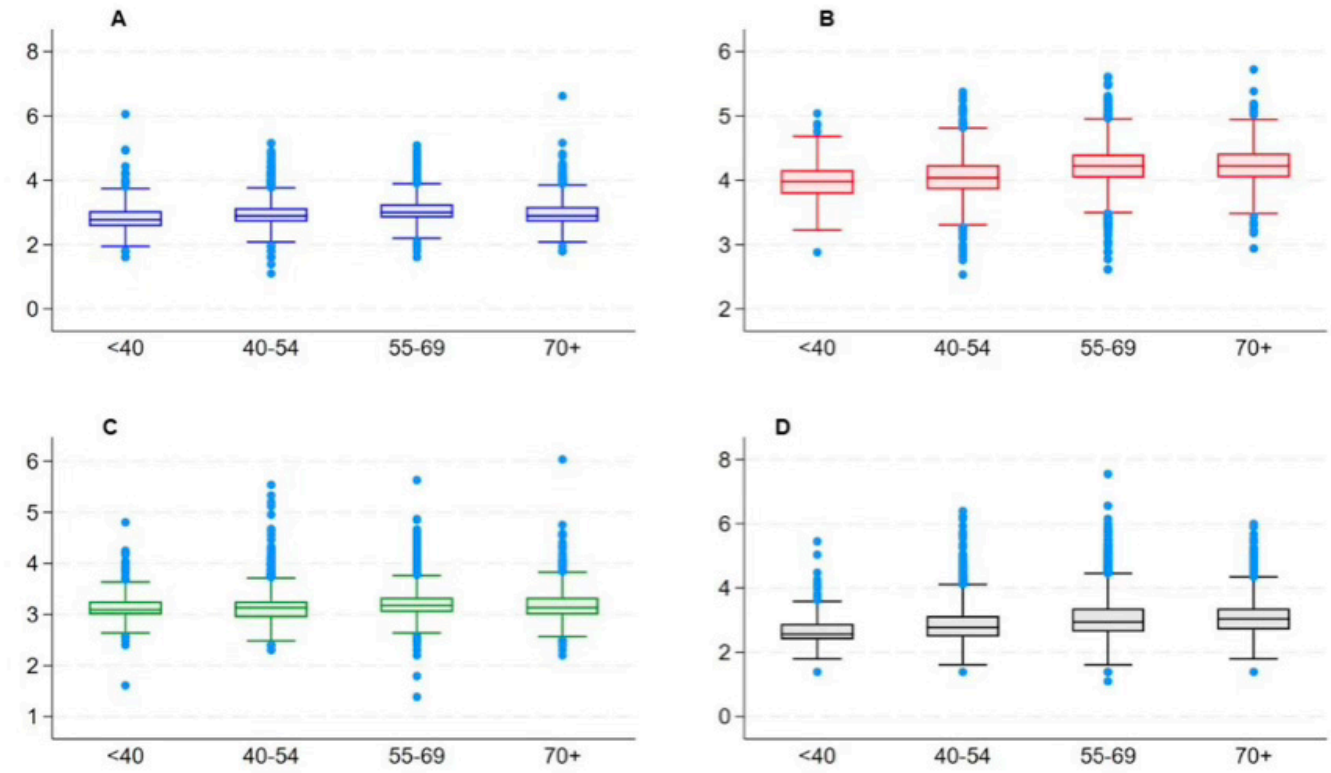
Panels A, B, C and D show the distribution of log-transformed alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and gamma-glutamyl transpeptidase, respectively, by age groups.

Figure 3: Distribution of liver function tests according to age ranges in males.



Panels A, B, C and D show the distribution of log-transformed alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and gamma-glutamyl transpeptidase, respectively, by age groups.

Figure 4: Distribution of liver function tests according to age ranges in females.



Panels A, B, C and D show the distribution of log-transformed alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and gamma-glutamyl transpeptidase, respectively, by age groups.

Association between liver function tests and anthropometric variables of adiposity

The associations between LFTs and anthropometric variables capturing adiposity at baseline are presented in Table 2. BMI, BSI, BSA, RFM, WWI, WHtR, and WHR were positively associated with all four LFTs, ALP, AST, ALP and GGT (p-value < 0.001). These associations remained stable after adjusting for a broad range of potential confounders (Model 2).

Table 2: Associations between log-transformed liver function tests and anthropometric variables at baseline (2003-2006).

	Total Model 1		**Total Model 2**	
	Coefficient (95% CI)	**P-value**	**Coefficient (95% CI)**	**P-value**
	N = 5171		N = 5171	
Alanine aminotransferase (IU/L)				
BMI (kg/m2)	0.04 (0.03; 0.04)	<0.001	0.02 (0.02; 0.03)	<0.001
BSI (m11/6kg-2/3)	2.002 (1.81; 2.19)	<0.001	1.47 (1.28; 1.66)	<0.001
BSA (m0.725kg0.425)	1.83 (1.72; 1.93)	<0.001	1.52 (1.40; 1.64)	<0.001
RFM	0.74 (0.70; 0.78)	<0.001	0.67 (0.63; 0.72)	<0.001
WWI (m/kg2)	2.01 (1.83; 2.19)	<0.001	1.49 (1.30; 1.67)	<0.001
WHtR (ratio)	1.42 (1.32; 1.51)	<0.001	1.19 (1.08; 1.30)	<0.001
WHR (ratio)	2.26 (2.13; 2.40)	<0.001	1.02 (0.8; 1.20)	<0.001
Aspartate aminotransferase (IU/L)				
BMI (kg/m2)	0.015 (0.014; 0.019)	<0.001	0.009 (0.007; 0.01)	<0.001
BSI (m11/6kg-2/3)	1.03 (0.91; 1.15)	<0.001	0.80 (0.67; 0.92)	<0.001
BSA (m0.725kg0.425)	0.84 (0.78; 0.91)	<0.001	0.73 (0.65; 0.81)	<0.001
RFM	0.35 (0.33; 0.38)	<0.001	0.34 (0.32; 0.37)	<0.001
WWI (m/kg2)	0.91 (0.79; 1.02)	<0.001	0.69 (0.57; 0.81)	<0.001
WHtR (ratio)	0.58 (0.52; 0.65)	<0.001	0.50 (0.43; 0.58)	<0.001

WHR (ratio)	1.08 (0.99; 1.17)	<0.001	0.40 (0.28; 0.51)	<0.001
Alkaline phosphatase (IU/L)				
BMI (kg/m2)	0.013 (0.011; 0.016)	<0.001	0.006 (0.004; 0.009)	<0.001
BSI (m11/6kg-2/3)	0.59 (0.47; 0.70)	<0.001	0.50 (0.39; 0.62)	<0.001
BSA (m0.725kg0.425)	0.38 (0.31; 0.48)	<0.001	0.29 (0.22; 0.34)	<0.001
RFM	0.18 (0.16; 0.20)	<0.001	0.16 (0.13; 0.19)	<0.001
WWI (m/kg2)	0.75 (0.64; 0.86)	<0.001	0.52 (0.41; 0.64)	<0.001
WHtR (ratio)	0.48 (0.42; 0.54)	<0.001	0.33 (0.26; 0.40)	<0.001
WHR (ratio)	0.47 (0.39; 0.57)	<0.001	0.24 (0.13; 0.35)	<0.001
Gamma-glutamyl transpeptidase (IU/L)				
BMI (kg/m2)	0.043 (0.039; 0.048)	<0.001	0.02 (0.01; 0.03)	<0.001
BSI (m11/6kg-2/3)	2.96 (2.71; 3.21)	<0.001	2.02 (1.78; 2.26)	<0.001
BSA (m0.725kg0.425)	2.15 (2.01; 2.45)	<0.001	1.57 (1.41; 1.72)	<0.001
RFM	0.90 (0.85; 0.95)	<0.001	0.72 (0.66	

Results express variations in log-transformed LFTs per a 1-unit increase in log-transformed anthropometric measure. BMI, body mass index; BSI, body shape index; BSA, body surface area; RFM, relative fat mass; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; WWI, weight-adjusted-waist index. Model 1 was adjusted for age, sex. Model 2 was adjusted for age, sex, smoking, and alcohol use, education levels, prevalence of diabetes, SBP, DBP, LDL, TC, hs-CRP.

Table 3 presents the associations between LFTs and anthropometric variables (BMI, BSI, BSA, RFM, WWI, WHtR and WHR) at baseline, stratified by sex. Among males, ALT and GGT showed a positive association with all anthropometric variables. However, AST and ALP presented a few exceptions: AST was positively associated with all anthropometric variables except BSI, while GGT demonstrated a positive association only with BSI and WWI. In females, all LFTs were positively associated with all anthropometric variables.

Table 3: Associations between log-transformed liver function tests and anthropometric variables at baseline (2003-2006), stratified by sex.

	Males		**Females**	
	Coefficient (95% CI)	**P-value**	**Coefficient (95% CI)**	**P-value**
	N = 2393		N = 2778	
Alanine aminotransferase (IU/L)				
BMI (kg/m2)	0.04 (0.03; 0.04)	<0.001	0.02 (0.01; 0.02)	<0.001
BSI (m11/6kg-2/3)	0.59 (0.22; 0.96)	0.002	0.31 (0.08; 0.54)	<0.001
BSA (m0.725kg0.425)	0.89 (0.68; 1.11)	0.000	0.61 (0.43; 0.80)	<0.001
RFM	1.30 (1.13; 1.45)	<0.001	0.29 (0.21; 0.36)	<0.001
WWI (m/kg2)	1.49 (1.16; 1.82)	<0.001	0.63 (0.42; 0.84)	<0.001
WHtR (ratio)	1.28 (1.10; 1.46)	<0.001	0.64 (0.50; 0.75)	<0.001
WHR (ratio)	1.72 (1.42; 2.02)	<0.001	0.67 (0.47; 0.86)	<0.001
Aspartate aminotransferase (IU/L)				
BMI (kg/m2)	0.01 (0.009; 0.015)	<0.001	0.007 (0.004; 0.01)	<0.001
BSI (m11/6kg-2/3)	0.043 (-0.23; 0.28)	0.728	0.25 (0.10; 0.40)	<0.001
BSA (m0.725kg0.425)	0.35 (0.21; 0.50)	<0.001	0.12 (0.009; 0.24)	<0.001
RFM	0.38 (0.26; 0.50)	<0.001	0.11 (0.06; 0.15)	<0.001
WWI (m/kg2)	0.34 (0.11; 0.59)	<0.001	0.35 (0.22; 0.49)	<0.001
WHtR (ratio)	0.38 (0.26; 0.50)	<0.001	0.63 (0.50; 0.75)	<0.001
WHR (ratio)	0.54 (0.34; 0.74)	<0.001	0.31 (0.18; 0.44)	<0.001
Alkaline phosphatase (IU/L)				
BMI (kg/m2)	-0.001 (-0.004; 0.002)	0.231	0.01 (0.008; 0.01)	<0.001
BSI (m11/6kg-2/3)	0.46 (0.24; 0.68)	<0.001	0.35 (0.19; 0.51)	<0.001

BSA (m0.725kg0.425)	-0.04 (-0.17; 0.08)	0.532	0.38 (0.22; 0.48)	<0.001
RFM	0.08 (-0.02; 0.19)	0.139	0.20 (0.15; 0.25)	<0.001
WWI (m/kg2)	0.33 (0.13; 0.53)	0.002	0.47 (0.33; 0.62)	<0.001
WHtR (ratio)	0.06 (-0.4; 0.17)	0.231	0.38 (0.29; 0.47)	<0.001
WHR (ratio)	0.14 (-0.03; 0.32)	0.112	0.28 (0.14; 0.42)	<0.001
Gamma-glutamyl transpeptidase (IU/L)				
BMI (kg/m2)	0.03 (0.02; 0.03)	<0.001	0.01 (0.01; 0.02)	<0.001
BSI (m11/6kg-2/3)	0.95 (0.47; 1.43)	<0.001	0.87 (0.58; 1.16)	<0.001
BSA (m0.725kg0.425)	0.73 (0.45; 1.02)	<0.001	0.52 (0.28; 0.76)	<0.001
RFM	1.28 (1.04; 1.51)	<0.001	0.24 (0.15; 0.33)	<0.001
WWI (m/kg2)	1.73 (1.30; 2.16)	<0.001	0.90 (0.64; 1.17)	<0.001
WHtR (ratio)	1.27 (1.04; 1.50)	<0.001	0.26 (0.17; 0.34)	<0.001
WHR (ratio)	1.93 (1.51; 2.33)	<0.001	0.93 (0.68; 1.18)	<0.001

Results express variations in log-transformed LFTs per a 1-unit increase in log-transformed anthropometric measure. BMI, body mass index; BSI, body shape index; BSA, body surface area; RFM, relative fat mass; WWI, weight-adjusted-waist index; WHtR, waist-to-height ratio; WHR, waist-to-hip ratio.

Longitudinal association between liver tests and anthropometric variables

The longitudinal associations between LFTs and anthropometric variables (BMI, BSI, BSA, RFM, WWI, WHtR and WHR) are presented in Table 4. Model 1, adjusting for age and sex, showed a positive association between all LFTs and anthropometric variables. These associations remained significant even after further adjustment for additional factors (including smoking, alcohol use, education levels, diabetes, blood pressure, cholesterol, and hs-CRP), although the magnitude of the associations slightly decreased.

Table 4: Longitudinal associations between log-transformed liver function tests and anthropometric variables.

	Total Model 1		**Total Model 2**	
	Coefficient (95% CI)	**P-value**	**Coefficient (95% CI)**	**P-value**
	N = 5171		N = 5171	
Alanine aminotransferase (IU/L)				
BMI (kg/m2)	0.027 (0.025; 0.029)	<0.001	0.028 (0.024; 0.03)	<0.001
BSI (m11/6kg-2/3)	0.16 (0.07; 0.26)	0.001	0.19 (0.09; 0.29)	<0.001
BSA (m0.725kg0.425)	1.25 (1.15; 1.34)	<0.001	1.04 (0.94; 1.14)	<0.001
RFM	0.53 (0.49; 0.56)	<0.001	0.46 (0.42; 0.60)	<0.001
WWI (m/kg2)	0.62 (0.60; 0.83)	<0.001	0.57 (0.54; 0.60)	<0.001
WHtR (ratio)	0.88 (0.82; 0.95)	<0.001	0.79 (0.72; 0.88)	<0.001
WHR (ratio)	1.11 (1.01; 1.22)	<0.001	0.98 (0.87; 1.09)	<0.001
Aspartate aminotransferase (IU/L)				
BMI (kg/m2)	0.009 (0.007; 0.01)	<0.001	0.007 (0.005; 0.009)	<0.001
BSI (m11/6kg-2/3)	0.27 (0.20; 0.34)	<0.001	0.26 (0.19; 0.33)	<0.001
BSA (m0.725kg0.425)	0.24 (0.17; 0.31)	<0.001	0.16 (0.09; 0.23)	<0.001
RFM	0.19 (0.17; 0.22)	<0.001	0.15 (0.12; 0.18)	<0.001
WWI (m/kg2)	0.40 (0.33; 0.46)	<0.001	0.35 (0.28; 0.42)	<0.001
WHtR (ratio)	0.36 (0.31; 0.40)	<0.001	0.30 (0.25; 0.35)	<0.001
WHR (ratio)	0.31 (0.24; 0.49)	<0.001	0.27 (0.19; 0.35)	<0.001
Alkaline phosphatase (IU/L)				
BMI (kg/m2)	0.01 (0.009; 0.014)	<0.001	0.007 (0.006; 0.009)	<0.001
BSI (m11/6kg-2/3)	0.16 (0.10; 0.21)	<0.001	0.12 (0.06; 0.17)	<0.001

BSA (m0.725kg0.425)	0.44 (0.37; 0.51)	<0.001	0.31 (0.24; 0.38)	<0.001
RFM	0.24 (0.22; 0.27)	<0.001	0.15 (0.12; 0.18)	<0.001
WWI (m/kg2)	0.29 (0.24; 0.35)	<0.001	0.17 (0.12; 0.22)	<0.001
WHtR (ratio)	0.36 (0.32; 0.41)	<0.001	0.29 (0.23; 0.35)	<0.001
WHR (ratio)	0.17 (0.11; 0.23)	<0.001	0.06 (0.001; 0.12)	0.004
Gamma-glutamyl transpeptidase (IU/L)				
BMI (kg/m2)	0.03 (0.031; 0.037)	<0.001	0.025 (0.023; 0.029)	<0.001
BSI (m11/6kg-2/3)	0.39 (0.23; 0.50)	<0.001	0.36 (0.25; 0.47)	<0.001
BSA (m0.725kg0.425)	1.60 (1.46; 1.70)	<0.001	1.40 (1.001; 1.27)	<0.001
RFM	0.56 (0.50; 0.63)	<0.001	0.41 (0.36; 0.46)	<0.001
WWI (m/kg2)	0.78 (0.67; 0.89)	<0.001	0.63 (0.52; 0.73)	<0.001
WHtR (ratio)	1.07 (0.97; 1.25)	<0.001	0.86 (0.77; 0.94)	<0.001
WHR (ratio)	1.42 (1.22; 1.55)	<0.001	1.23 (1.10; 1.35)	<0.001

Results express variations in log-transformed LFTs per a 1-unit increase in log-transformed anthropometric measure. BMI, body mass index; BSI, body shape index; BSA, body surface area; RFM, relative fat mass; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; WWI, weight-adjusted-waist index. Model 1 was adjusted for age, sex. Model 2 was adjusted for age, sex, smoking, and alcohol use, education levels, prevalence of diabetes, SBP, DBP, LDL, TC, hs-CRP.

The same analyses stratified by sex are presented in Table 5. Among males, only AST showed a positive association with all anthropometric variables. ALT and GGT were positively associated with nearly all anthropometric variables, except for BSI. Lastly, ALP did not demonstrate a positive association with BMI, BSA or WHR. Among females, almost all LFTs showed a positive association with anthropometric variables, with the sole exception of the association between AST and BSI.

Table 5: Longitudinal associations between log-transformed liver function tests and anthropometric variables, stratified by sex.

	Males		**Females**	
	Coefficient (95% CI)	**P-value**	**Coefficient (95% CI)**	**P-value**
	N = 2393		N = 2778	
Alanine aminotransferase (IU/L)				
BMI (kg/m2)	0.034 (0.029; 0.037)	<0.001	0.018 (0.015; 0.020)	<0.001
BSI (m11/6kg-2/3)	0.05 (-0.13; 0.24)	0.565	0.204 (0.089; 0.320)	<0.001
BSA (m0.725kg0.425)	1.30 (1.14; 1.46)	<0.001	0.85 (0.73; 0.98)	<0.001
RFM	1.15 (1.03; 1.26)	<0.001	0.30 (0.26; 0.35)	<0.001
WWI (m/kg2)	0.74 (0.56; 0.92)	<0.001	0.45 (0.34; 0.56)	<0.001
WHtR (ratio)	1.13 (1.02; 1.25)	<0.001	0.56 (0.48; 0.64)	<0.001
WHR (ratio)	1.48 (1.29; 1.67)	<0.001	0.65 (0.52; 0.78)	<0.001
Aspartate aminotransferase (IU/L)				
BMI (kg/m2)	1.11 (1.03; 1.26)	<0.001	0.004 (0.002; 0.006)	<0.001
BSI (m11/6kg-2/3)	0.25 (0.11; 0.39)	<0.001	0.03 (-0.05; 0.11)	0.465
BSA (m0.725kg0.425)	0.32 (0.20; 0.43)	<0.001	0.08 (0.05; 0.11)	<0.001
RFM	0.42 (0.33; 0.50)	<0.001	0.27 (0.19; 0.35)	<0.001
WWI (m/kg2)	0.47 (0.33; 0.60)	<0.001	0.42 (0.35; 0.49)	<0.001
WHtR (ratio)	0.48 (0.37; 0.56)	<0.001	0.18 (0.12; 0.23)	<0.001
WHR (ratio)	0.46 (0.32; 0.51)	<0.001	0.12 (0.03; 0.21)	<0.001
Alkaline phosphatase (IU/L)				
BMI (kg/m2)	0.0001 (-0.002; 0.002)	0.921	0.01 (0.009; 0.016)	<0.001
BSI (m11/6kg-2/3)	0.22 (0.12; 0.31)	<0.001	0.04 (0.02; 0.11)	<0.001
BSA (m0.725kg0.425)	-0.05 (-0.15; 0.04)	0.271	0.54 (0.44; 0.60)	<0.001

RFM	0.11 (0.09; 0.18)	<0.001	0.15 (0.10; 0.18)	<0.001
WWI (m/kg2)	0.22 (0.13; 0.31)	<0.001	0.16 (0.11; 0.26)	<0.001
WHtR (ratio)	0.12 (0.05; 0.19)	<0.001	0.27 (0.23; 0.32)	<0.001
WHR (ratio)	-0.08 (-0.18; 0.01)	0.115	0.08 (0.007; 0.17)	0.003
Gamma-glutamyl transpeptidase (IU/L)				
BMI (kg/m2)	0.039 (0.033; 0.044)	<0.001	0.018 (0.014; 0.022)	<0.001
BSI (m11/6kg-2/3)	0.13 (-0.07; 0.34)	0.221	0.45 (0.32; 0.57)	<0.001
BSA (m0.725kg0.425)	1.48 (1.26; 1.71)	<0.001	0.92 (0.75; 1.09)	<0.001
RFM	1.11 (0.96; 1.25)	<0.001	0.31 (0.25; 0.36)	<0.001
WWI (m/kg2)	0.67 (0.47; 0.88)	<0.001	0.61 (0.48; 0.73)	<0.001
WHtR (ratio)	1.27 (1.17; 1.45)	<0.001	0.66 (0.55; 0.76)	<0.001
WHR (ratio)	1.84 (1.61; 2.07)	<0.001	0.93 (0.78; 1.08)	<0.001

Results express variations in log-transformed LFTs per a 1-unit increase in log-transformed anthropometric measure. BMI, body mass index; BSI, body shape index; BSA, body surface area; RFM, relative fat mass; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; WWI, weight-adjusted-waist index.

Factors influencing liver function tests longitudinally

Several factors (diabetes, smoking, blood pressure, cholesterol and alcohol) that can influence LFTs levels over time are presented in Supplementary Table 2. ALT was positively associated with all these factors. There were positive associations between AST and GGT with nearly all factors, except for smoking. ALP, on the other hand, demonstrated a positive association with all the factors, with the exception of diabetes.

Discussion

Based on a prospective and contemporaneous cohort of > 5000 middle-aged community-dwellers, our findings showed that LFTs progression varied by age. In general, ALT levels remained stable, while AST, ALP and GGT levels showed an increase with age. Whereas LFTs were higher in males at all age groups, patterns of changes over time were not exactly similar in both sexes, with ALP levels decreasing with age in males and increasing in females. Both at baseline and longitudinally, adiposity-related measures were strongly associated with LFTs, a relationship that remained robust after adjustment, though some sex-specific variations were observed. Additionally, LFTs changes correlated positively and independently with most traditional cardiovascular risk factors and markers of inflammation. However, smoking was associated only with changes in ALT and ALP, while diabetes showed no association with ALP changes.

We first analyzed the distribution of LFTs across different age groups in the total population, followed by a sex-specific analysis in males and females. A study by Leclerc et al, conducted on volunteer blood donors, aligns with our results, showing that ALT levels increased with age up to the fifth decade [5]. This study also reported an age-related increase in ALT levels in females, while in males, they rose until around 50 years old before declining [5]. Similarly, a study on 1673 community-dwelling males found a 30% decrease in ALT levels between those aged 70 to 74.9 years and those over 90 years [8]. Petroff et al also observed comparable trends with a moderate increase in AST values until around 60 followed by stabilization in females, and a continuous increase in GGT values up to the age of 60 in males, and throughout life in females [21]. However, their findings, suggesting a decline in ALT levels with age in males, differ from ours [21]. A cross-sectional study of 2364 participants [19] and data from the US National Health and Nutrition Examination Survey [5, 9, 12] also reported a decline in ALT levels with age. Similarly, a study by Chen et al found decreasing ALT levels with age in males but an increase in females [13]. Conversely, a cross-sectional study performed in 934 male blood donors showed a negative relation between ALT and AST, and age [20].

Further, we assessed how traditional cardiovascular factors and inflammation (such as diabetes, smoking, blood pressure, total cholesterol and LDL-cholesterol, hs-CRP, and alcohol consumption) associate with LFTs over time. Nearly all factors were associated with LFTs. A comparative study by Teshom et al reported a significant association between ALT, AST, ALP and various risk factors, including blood pressure, fasting blood sugar, triglycerides, total cholesterol and LDL-cholesterol, which aligns closely with our findings [2]. A cross-sectional study on 500 health-check examinees found that both cigarette smoking and alcohol consumption independently elevate GGT values but do not influence ALT or AST [24]. However, this is not enterily consistent with our findings, as smoking showed no association with GGT, while alcohol consumption was positively associated with all LFTs. Kim WR et al analyzed the available scientific data and concluded that cholesterol and triglycerides were positively associated with ALT, whereas smoking showed a negative association [6].

We investigated how several clinical anthropometric measures capturing adiposity, namely BMI, BSI, BSA, RFM, WWI, WHtR, and WHR, associated with LFTs changes. At baseline, our findings demonstrated that adiposity-related measures were consistently associated with LFTs, which was robust to adjustment. Most studies reported a strong positive association

between LFTs and BMI [3-6, 11-13, 18, 20]. However, only a few studies analyzed additional adiposity parameters over a prolonged period. One cross-sectional study, conducted on 5724 participants, found a positive association between ALT ant two measures of adiposity, that is BMI and WHR [12]. Similarly, a cross-sectional study, on 934 male blood donors aged 18 to 68 years, reported associations between ALT, AST, and GGT with BMI, central adiposity, as well as waist and hip circumference [20]. Expanding on this, a cross-sectional study of patients with type 2 diabetes highlighted waist circumference, BMI, AST levels, and educational background as key clinical predictors of significant and advanced fibrosis in primary care [25]. Physicians should take these factors into account and integrate this understanding into their clinical decision-making and patient management.

Strengths and limitations

The main strengths of the present study included a population-based prospective design using both cross-sectional and longitudinal data. With a large sample size of over 5000 participants, the study provided robust statistical power. It also accounted for a variety of confounders, such as cardiovascular risk factors, inflammation, and lifestyle factors. Furthermore, we were able to assess associations between LFTs and a wide range of anthropometric measures, with consistent findings. The inclusion of various adiposity indices offered for a more nuanced understanding of body composition's impact on LFTs. Some limitations should be acknowledged. First, a sizable portion of the baseline sample was excluded from the analyses. Participants who were excluded due to missing follow-up data or elevated hs-CRP levels had significantly different baseline characteristics, including higher BMI and LFTs. This exclusion may as well have favored the selection of the most motivated individuals (with complete data and follow-ups), potentially causing selection bias. Second, the study was conducted with a middle-aged population from the city of Lausanne, Switzerland, which may limit its generalizability to other populations. Finally, the observed elevation in LFTs could be influenced by various factors, including ethnicity, comorbidities, patient medications [7], dietary habits, physical activity, and genetic predispositions, among others, which were not accounted for.

Conclusion

Our study highlights the role of adiposity-related clinical markers that are independently associated with changes in LFTs. Temporal variations in LFTs should then be interpreted in the context of the clinical context, comprising age, sex, and cardiometabolic factors.

From a clinical perspective, the elevation of LFTs in individuals with overweight and obesity represents an indirect sign of potential MASH and, consequently, significant liver fibrosis development. Our study highlights the importance of LFTs monitoring in these individuals.

Data availability

The data of CoLaus|PsyCoLaus study used in this article cannot be fully shared as they contain potentially sensitive personal information on participants. According to the Ethics Committee for Research of the Canton of Vaud, sharing these data would be a violation of Swiss legislation with respect to privacy protection. However, coded individual-level data that do not allow researchers to identify participants are available upon request to researchers who meet the criteria for data sharing of the CoLaus|PsyCoLaus Datacenter (CHUV, Lausanne, Switzerland). Any researcher affiliated to a public or private research institution who complies with the CoLaus|PsyCoLaus standards can submit a research application to research.colaus@chuv.ch or research.psycolaus@chuv.ch. Proposals requiring baseline data only, will be evaluated by the baseline (local) Scientific Committee (SC) of the CoLaus and PsyCoLaus studies. Proposals requiring follow-up data will be evaluated by the follow-up (multicentric) SC of the CoLaus|PsyCoLaus cohort study. Detailed instructions for gaining access to the CoLaus|PsyCoLaus data used in this study are available at www.colaus-psycolaus.ch/professionals/ how-to-collaborate/.

Acknowledgements

The authors would like to thank all the people who participated in the recruitment of the participants, data collection and validation, particularly Nicole Bonvin, Yolande Barreau, Eva Pochon, Manuella Bonvin, Kimberley Meyer, Mathieu Firmann, François Bastardot, Panagiotis Antiochos, Cédric Gubelmann, Marylène Bay and Benoît Delabays.

Declaration of Conflict of interests

The authors of this article declare that they have no conflicts of interest related to the content of this manuscript.

Credit author statement

Noushin Ahanchi Sadat was responsible for the methodology, software development, and contributed to the supervision of the project. Professor Julien Vaucher conceived the project and provided supervisory oversight. Dr. Montserrat Fraga served as a reviewer and advisor, offering her expertise as a hepatologist. Manon Scyboz conducted the literature review and was the primary author of the introduction, results, discussion, conclusion, and abstract.

Use of AI

During the preparation of this article, ChatGPT was used as a language assistance tool to help refine the English phrasing of certain sections. This support was particularly helpful in improving sentence structure, ensuring the use of appropriate scientific vocabulary, and enhancing overall clarity and coherence.

Abbreviations

ALP, alkaline phosphatase. ALT, alanine aminotransferase.

AST, aspartate aminotransferase. BMI, body mass index. BRI, body roundness index. BSA, body surface area. BSI, body shape index. DBP, diastolic blood pressure. GGT, gamma-glutamyl transferase. HCC, hepatocellular carcinoma. Hs-CRP, high-sensitivity C-reactive protein. LDL, low-density lipoprotein cholesterol. LFT, liver function test. MAFL, metabolic dysfunction-associated fatty liver. MAFLD, metabolic dysfunction-associated fatty liver disease. Mash, metabolic dysfunction-associated steatohepatitis. RFM, relative fat mass. SBP, systolic blood pressure. TC, total cholesterol. WHR, waist-to-hip ratio. WHtR, waist-to-height ratio. WWI, weight-adjusted-waist index. WWR, waist-to-weight ratio.

Funding

The CoLaus|PsyCoLaus study was supported by unrestricted research grants from GlaxoSmithKline, the Faculty of Biology and Medicine of Lausanne, the Swiss National Science Foundation (grants 3200B0-105993, 3200B0-118308, 33CSCO-122661, 33CS30-139468, 33CS30-148401, 33CS30-177535 and 3247730-204523) and the Swiss Personalized Health Network (grant 2018DRI01).

References

1. Jaunin-Stalder N, Pasche O, Cornuz J. Patient avec des tests hépatiques perturbés : que faire ? Rev Med Suisse. 2009; 227(43): 2410–2414.
2. Teshome G, Ambachew S, Fasil A, Abebe M. Prevalence of Liver Function Test Abnormality and Associated Factors in Type 2 Diabetes Mellitus: A Comparative Cross-Sectional Study. EJIFCC. 2019; 30(3): 303–316.
3. Valenti L, Pelusi S, Bianco C, Ceriotti F, Berzuini A, Iogna Prat L et al. Definition of Healthy Ranges for Alanine Aminotransferase Levels: A 2021 Update. Hepatology Communications. 2021; 5(11): 1824–1832. DOI 10.1002/hep4.1794
4. Piton A, Poynard T, Imbert-Bismut F, Khalil L, Delattre J, Pelissier E et al. Factors associated with serum alanine transaminase activity in healthy subjects: Consequences for the definition of normal values, for selection of blood donors, and for patients with chronic hepatitis C. Hepatology. 1998; 27(5): 1213–1219. DOI 10.1002/hep.510270505
5. Leclercq I, Horsmans Y, De Bruyere M, Geubel AP. Influence of body mass index, sex and age on serum alanine aminotransferase (ALT) level in healthy blood donors. Acta Gastro-Enterologica Belgica. 1999; 62(1): 16-20.
6. Kim WR, Flamm SL, Di Bisceglie AM, Bodenheimer HC. Serum activity of alanine aminotransferase (ALT) as an indicator of health and disease. Hepatology. 2008 ; 47(4): 1363–1370. DOI 10.1002/hep.22109
7. Giannini EG, Testa R, Savarino V. Liver enzyme alteration: a guide for clinicians. Canadian Medical Association Journal. 2005; 172(3): 367-379. DOI 10.1503/cmaj.1040752
8. Le Couteur DG, Blyth FM, Creasey HM, Handelsman DJ, Naganathan V, Sambrook PN et al. The Association of Alanine Transaminase with Aging, Frailty, and Mortality. The Journal of Gerontology Series A: Biological Sciences and Medical Sciences. 2010; 65A (7): 712–717. DOI 10.1093/Gerona/glq082
9. Liangpunsakul S, Chalasani N. Unexplained Elevations in Alanine Aminotransferase in Individuals with the Metabolic Syndrome: Results from the Third National Health and Nutrition Survey (NHANES III). The American Journal of the Medical Sciences. 2005; 329(3): 111–116. DOI 10.1097/00000441-200503000-00001
10. Agrawal S, Dhiman RK, Limdi JK. Evaluation of abnormal liver function tests. Postgraduate Medical Journal. 2016; 92(1086): 223–234. DOI 10.1136/postgradmedj-2015-133715
11. El-Eshmawy MM. Impact of obesity on liver function tests: is nonalcoholic fatty liver disease the only player? A review article. Porto Biomedical Journal. 2023; 8(5): e228. DOI 10.1097/j.pbj.0000000000000228
12. Ruhl CE, Everhart JE. Determinants of the association of overweight with elevated serum alanine aminotransferase activity in the United States. Gastroenterology. 2003 ; 124(1): 71–79. DOI 10.1053/gast.2003.50004
13. Chen Z, Chen L, Dai H, Chen J, Fang L. Relationship between alanine aminotransferase levels and metabolic syndrome in nonalcoholic fatty liver disease. Journal of Zhejiang University Science B. 2008; 9(8): 616–622. DOI 10.1631/jzus. B0720016
14. Li W, Homer K, Hull S, Boomla K, Robson J, Alazawi W. Obesity Predicts Liver Function Testing and Abnormal Liver Results. Obesity. 2020; 28(1): 132–138. DOI 10.1002/oby.22669
15. Kim H, Kisseleva T, Brenner DA. Aging and liver disease. Current opinion in gastroenterology. 2015; 31(3): 184–191. DOI 10.1097/MOG.0000000000000176
16. Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. Journal of Hepatology. 2019; 70(1): 151-171. DOI 10.1016/j.jhep.2018.09.014
17. Hall KE, Proctor DD, Fisher L, Rose S. American Gastroenterological Association Future Trends Committee Report: Effects of Aging of the Population on Gastroenterology Practice, Education, and Research. Gastroenterology. 2005; 129(4): 1305–1338. DOI 10.1053/j.gastro.2005.06.013
18. Patt CH, Yoo HY, Dibadj K, Flynn J, Thuluvath PJ. Prevalence of Transaminase Abnormalities in Asymptomatic, Healthy Subjects Participating in an Executive Health-Screening Program. Digestive Diseases and Sciences. 2003; 48(4): 797-801.
19. Dong MH, Bettencourt R, Barrett-Connor E, Loomba R. Alanine Aminotransferase Decreases with Age: The Rancho Bernardo Study. PLoS One. 2010; 5(12): e14254.

DOI 10.1371/journal.pone.0014254
20. Khedmat H, Fallahian F, Abolghasemi H, Hajibeigi B, Attarchi Z, Alaeddini F et al. Serum γ-glutamyltransferase, alanine aminotransferase, and aspartate aminotransferase activity in Iranian healthy blood donor men. World Journal of Gastroenterology. 2007; 13(6): 889–894. DOI 10.3748/wjg.v13.i6.889
21. Petroff D, Bätz O, Jedrysiak K, Kramer J, Berg T, Wiegand J. Age Dependence of Liver Enzymes: An Analysis of Over 1,300,000 Consecutive Blood Samples. Clin Gastroenterol Hepatol. 2022; 20(3): 641-650. DOI 10.1016/j.cgh.2021.01.039
22. Dong MH, Bettencourt R, Brenner DA, Barrett-Connor E, Loomba R. Serum levels of alanine aminotransferase decrease with age in longitudinal analysis. Clin Gastroenterol Hepatol. 2012; 10(3): 285-290.e1. DOI 10.1016/j.cgh.2011.10.014
23. Firmann M, Mayor V, Vidal PM, Bochud M, Pécoud A, Hayoz D et al. The CoLaus study: a population-based study to investigate the epidemiology and genetic determinants of cardiovascular risk factors and metabolic syndrome. BMC Cardiovascular Disorders. 2008; 8(1): 1-11. DOI 10.1186/1471-2261-8-6
24. Jang ES, Jeong SH, Hwang SH, Kim HY, Ahn SY, Lee J et al. Effects of coffee, smoking, and alcohol on liver function tests: a comprehensive cross-sectional study. BMC Gastroenterology. 2012; 12: 145. DOI 10.1186/1471-230X-12-145
25. Forlano R, Stanic T, Jayawardana S, Mullish BH, Yee M, Mossialos E et al. A prospective study on the prevalence of MASLD in people with type-2 diabetes in the community. Cost effectiveness of screening strategies. Liver International. 2024; 44(1): 61–71. DOI 10.1111/liv.15730

Supplementary Tables

Table 1: Comparison between Included and Excluded.

Variable	Included	Excluded	P value*
Sample size	5171	1562	
Age (years)	52.1 (10.4)	54.3 (11.8)	0.004
Smoking status (n, %)			0.002
Never	2126 (41.1)	612 (38.4)	
Former	1729 (33.4)	454 (29.1)	
Current	1316 (25.4)	496 (31.8)	
Education level (n, %)			0.02
High	1102 (21.3)	218 (14.1)	
Middle	1321 (25.5)	304 (19.6)	
Low	2748 (53.1)	1040 (66.2)	
Alcohol drinker (units/week)	4 (0-10)	3 (0-10)	0.02
Excessive alcohol consumers (n, %)	1029 (19.9)	330 (21.1)	0.003
BMI (kg/m2)	24.4 (4.23)	26.8 (5.1)	0.04
BSI (m11/6kg-2/3)	0.078 (0.07; 0.082)	0.079 (0.07; 0.08)	0.04
BSA (m0.725kg0.425)	0.006 (0.005; 0.007)	0.006 (0.005; 0.006)	0.05
RFM	31.02 (22.9; 38.35)	34.11 (26.06; 40.25)	0.002
WWI (m/kg2)	10.34 (9.82; 10.87)	10.41 (9.8; 10.95)	0.01
WHtR (ratio)	0.51 (0.46; 0.56)	0.52 (0.47; 0.57)	0.04
WHR (ratio)	0.86 (0.80-0.92)	0.89 (0.83-0.95)	0.06
hs-CRP (mg/L)	1.18 (0.6-2.4)	1.92 (0.9-5.4)	0.02
Prevalence of diabetes	274 (5.3)	162 (10.4)	0.003
SBP (mm Hg)	126.8 (17.3)	131.5 (18.9)	0.006
DBP (mm Hg)	78.8 (10.7)	80.4 (11.1)	0.04
HDL-C (mmol/L)	1.6 (0.4)	1.5 (0.43)	0.03

TC (mmol/L)	5.5 (1.00)	5.6 (1.1)	0.06
LDL (mmol/L)	3.32 (0.9)	3.33 (0.9)	0.07
Liver tests (IU/L)			
Alanine aminotransferase	23 (17-32)	24 (17-35)	0.001
Aspartate aminotransferase	27 (23-33)	28 (23-35)	0.003
Alkaline phosphatase	61.9 (51-75)	68.2 (56-82)	0.002
Gamma-glutamyl transpeptidase	20 (14- 32)	24 (16-42)	0.005

BMI, body mass index; BSA, body surface area; BSI, body shape index; RFM, relative fat mass; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; WWI, weight-adjusted-waist index; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; CRP, C-reactive protein; HDL-C, High-Density Lipoprotein; TC, Total Cholesterol; LDL, Low-Density Lipoprotein Cholesterol. Continuous variables shown as mean (SD) with p according to t-test; categorical variables as % with p according to $\chi 2$, median (25th-75th percentile) with p according to Mann–Whitney U-test * Compare the characteristics of participants who were included versus those who were excluded.

Table 2: Factors longitudinally influencing liver function tests.

	Coefficient (95% CI)	**P-value**
	N = 5171	
Alanine aminotransferase (IU/L)		
Diabetes	0.09 (0.07; 0.12)	<0.001
Smoking status	-0.01 (-0.02; -0.003)	0.008
SBP	0.002 (0.001; 0.003)	<0.001
DBP	0.005 (0.003; 0.008)	<0.001
TC	0.05 (0.04; 0.06)	<0.001
hs-CRP	0.005 (0.002; 0.007)	<0.001
LDL	0.04 (0.02; 0.05)	<0.001
Alcohol use	0.004 (0.003; 0.005)	<0.001
Aspartate aminotransferase (IU/L)		
Diabetes	0.03 (0.01; 0.05)	<0.001
Smoking status	-0.005 (-0.01; 0.001)	0.13
SBP	0.002 (0.001; 0.003)	<0.001
DBP	0.003 (0.002; 0.004)	<0.001
TC	0.04 (0.03; 0.05)	<0.001
hs-CRP	0.003 (0.002; 0.40)	<0.001
LDL	0.02 (0.01; 0.03)	<0.001
Alcohol use	0.004 (0.003; 0.005)	<0.001
Alkaline phosphatase (IU/L)		
Diabetes	0.003 (-0.011; 0.018)	0.62
Smoking status	0.011 (0.009; 0.013)	<0.001
SBP	0.0008 (0.0006; 0.0021)	<0.001
DBP	0.001 (0.001; 0.27)	<0.001
TC	0.025 (0.021; 0.030)	<0.001
hs-CRP	0.013 (0.012; 0.014)	<0.001
LDL	0.017 (0.01; 0.02)	<0.001
Alcohol use	-0.002 (-0.003; -0.001)	<0.001
Gamma-glutamyl transpeptidase (IU/L)		
Diabetes	0.13 (0.10; 0.16)	<0.001
Smoking status	0.012 (-0.001 ; 0.02)	0.07

SBP	0.0025 (0.0023; 0.0028)	<0.001
DBP	0.006 (0.005; 0.007)	<0.001
TC	0.08 (0.06; 0.09)	<0.001
hs-CRP	0.02 (0.01; 0.03)	<0.001
LDL	0.03 (0.01; 0.04)	<0.001
Alcohol use	0.011 (0.010; 0.012)	<0.001

Results express variations in log-transformed LFTs per a 1-unit increase in log-transformed anthropometric measure. BMI, body mass index; BSI, body shape index; BSA, body surface area; RFM, relative fat mass; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; WWI, weight-adjusted-waist index; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; hs-CRP, high-sensitivity C-reactive protein; TC, Total Cholesterol; LDL, Low-Density Lipoprotein Cholesterol.