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Ideal cardiovascular health associated with fatty liver: Results from a multi-ethnic survey

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HIGHLIGHTS

- To investigate the association between the cardiovascular health score (CVH) score, liver enzyme biomarkers and the risk of non-alcoholic fatty liver disease (NAFLD).
- Individuals with a higher CVH score had a more favorable profile of liver biomarkers.
- Individuals with a higher CVH score had 12% less likelihood of NAFLD compared with those with a lower score.
- Each CVH component separately was associated with the risk of NAFLD.

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ABSTRACT

Background and aims: Little is known about the role of liver enzymes as predictors of non-liver-related morbidity and mortality. The ideal cardiovascular health (CVH) score proposed by the American Heart Association (AHA) can be used to predict mortality and morbidity. We investigated the association of the CVH score with liver enzymes and the risk of non-alcoholic fatty liver disease (NAFLD) among US adults.
Methods: By using the National Health and Nutrition Examination Survey database (cross-sectional), the CVH score was calculated as meeting ideal levels of the following components: 4 behaviors (smoking, body mass index, physical activity and diet adherence) and 3 factors (total cholesterol, blood pressure and fasting glucose).
Results: Individuals with a higher CVH score ("better CVH") had a more favorable profile of liver biomarkers. Adjusted (for age, gender, race, poverty to income ratio, education, marital status and alcohol intake) linear regression indicated significant and negative associations between liver biomarkers and CVH score: ($\beta = -0.069$, $p < 0.001$) for alanine aminotransferase, ($\beta = -0.095$, $p < 0.001$), aspartate aminotransferase, ($\beta = -0.067$, $p < 0.001$), alkaline phosphatase and ($\beta = -0.125$, $p < 0.001$) and fatty liver index. In the logistic regression, with the same confounders, individuals with a higher CVH score had 12% less likelihood of NAFLD compared with those with a lower score. Furthermore, each CVH metric separately was inversely linked to the risk of NAFLD.
Conclusions: For the first time among US adults, our findings shed light on the role CVH on liver biomarkers.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) has reached epidemic proportions; currently, it is the most common chronic liver disease in Western Countries [1,2]. NAFLD is characterized by the increased accumulation of lipids (mainly triglycerides) in the liver among individuals without excessive consumption of alcohol, use of steatogenic drugs or hereditary diseases [3,4]. Accumulation of fatty acids in hepatic cells can be caused by several factors [3,4]. Important pathological mechanisms in hepatic steatosis involve increased visceral adipose tissue secretion of pro-inflammatory cytokines, higher oxidative stress and release of free fatty acids into the portal system and systemic

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circulation, causing dyslipidemia and systemic insulin resistance (IR) [5]. Of note, NAFLD has been associated with several cardiovascular (CV) risk factors including dyslipidemia, obesity, IR and diabetes [6–9]. The role of NAFLD as a potential independent risk factor for non-communicable diseases (NCDs) has recently gained considerable attention [6–9].

Mortality and morbidity due to CV disease (CVD) is increasing in the US and currently it is the first leading cause of death [10], accounting for 864,000 deaths annually. In response to the increasing burden of NCDs and CVD mortality, in 2010 the American Heart Association (AHA) suggested the use of the ideal CV health (CVH) index [11]. The aim was to improve CVH by 20% by 2020 and beyond [11]. These recommendations include 4 health behaviors and 3 health factors. The behavior-related criteria were: non-smoking, being physically active, having normal body mass index (BMI) and eating a healthy diet. The health factors included were: normal blood pressure (BP), plasma total cholesterol and fasting glucose. Achieving a greater number of ideal CVH metrics is associated with a lower risk for CVD events and mortality [12]. Therefore, the CVH index could represent a useful epidemiological tool to assess the CV profile in a general population.

Regarding the link between liver tests and NCDs, a high alanine aminotransferase (ALT) activity, as well as the fatty liver index (FLI) have been associated with the presence of high CVD risk factors and their clustering in adults [13–16]. In a previous epidemiological prospective cohort survey [17], elevated ALT activity was related to all-cause/cause-specific (including CVD and liver disease) mortality in long-term follow-up. Furthermore, ALT may also be a good indicator of overall health [18], particularly in the context of obesity, the metabolic syndrome, and the presence of CVD [19,20], as several patients affected by these conditions also are at risk of having NAFLD [21].

Studies have supported the link between CVH score and cardiometabolic factors [22–24]. For example, a study of 543 adolescents reported that a higher ideal CVH index was associated with a lower inflammatory score [22]. Another cross-sectional study among Chinese adults reported a reverse link between C-reactive protein and CVH score [25]. Another 2 studies in a Chinese population reported significant links between the plasma atherogenic index (AIP) and CVH score [23,24].

Given that liver enzymes are associated with cardiometabolic risk factors and that the CVH score is associated with a higher CVD risk, we hypothesized that individuals with a lower CVH score have a less favorable profile of liver tests and a greater likelihood of NAFLD. In this context, a study that included 1023 men and 1449 women, from the Chilean National Health Survey 2009–2010, demonstrated an association between CVH score and liver tests [26].

Given the paucity of studies and the importance of a link between NCD and NAFLD, we aimed to evaluate the link between ideal CVH score and liver tests [ALT, FLI, alkaline phosphatase (ALP) and aspartate aminotransferase (AST). Furthermore, we estimated the likelihood of NAFLD in relation to CVH metrics. The reason for choosing liver tests is that there is a cross-talk between cardiometabolic risk factors and liver tests; in this regard they might play a role as important components in CVH metrics.

2. Materials and methods

2.1. Population characteristics

The National Health and Nutrition Examination Survey (NHANES, cross-sectional) is an ongoing program which is conducted by the US National Center for Health Statistics (NCHS) [27]. NHANES uses a complex, multistage and stratified sampling design to select a representative sample of the civilian and non-institutionalized resident population of the USA [27]. The NCHS Research Ethics Review Board approved the NHANES protocol and informed consent was obtained from all participants [27]. Data collection on demographics occurred through in-home administered questionnaires, while anthropometric and biochemistry data were collected by trained personnel using mobile exam centers. More detailed information is available elsewhere [28]. Poverty to income variable is an index for the ratio of family income to poverty. The Department of Health and Human Services' (HHS) poverty guidelines were used as the poverty measure to calculate this index [28]. For the assessment of height and weight during the physical examination, participants were dressed in underwear, disposable paper gowns and foam slippers. A digital scale was used to measure weight to the nearest 100 g; a fixed stadiometer was used to measure height to the nearest mm. Body mass index (BMI) was calculated as weight (kg) divided by the square of height in (m).

A blood specimen was drawn from an antecubital vein. Fasting blood glucose (FBG) was measured by a hexokinase method using a Roche/Hitachi 911 Analyzer. Other laboratory-test details are available in the NHANES Laboratory/Medical Technologists Procedures Manual [29]. The activities of serum ALP, ALT, AST and gamma-glutamyl transferase (GGT) were measured spectrophotometrically using their respective kinetic enzymatic methods. To obtain the participants' BP, the average of all available measures after a total of 4 attempts was used. BP was measured in the right arm unless otherwise specified. Smoking status was self-reported. Levels of total serum cholesterol (TC) were measured enzymatically. Diabetes mellitus (DM) was defined as a self-reported history of DM or fasting plasma glucose $\geq$126 mg/dL [30]. Hypertension (HTN) was diagnosed in individuals with systolic blood pressure $\geq$140 mmHg and/or diastolic blood pressure $\geq$90 mmHg, and in persons on anti-hypertension medications [31].

Details on recording dietary intake have been previously described [32,33]. Briefly, dietary intake was assessed via 24 h recall obtained by a trained interviewer, with the use of a computer-assisted dietary interview system with standardized probes, i.e. the United States Department of Agriculture Automated Multiple-Pass Method (AMPM) [32,33]. The AMPM is designed to enhance complete and accurate data collection while reducing respondent burden [33,34]. The United States Department of Agriculture (USDA) Food and Nutrient Database for Dietary Studies was used to determine the nutrient content of foods during the NHANES survey.

The current study was based on the analysis of data from the 1999 to 2010 NHANES cycles. Analyses were restricted to participants aged $\geq$18 years.

2.2. Fatty liver index (FLI)

FLI was calculated according to the United States FLI [35]. The FLI included age, race/ethnicity, waist circumference, GGT activity, insulin and glucose. The FLI has been validated and shown to correlate well with the presence of NAFLD diagnosed by ultrasound [Receiver Operating Characteristic (ROC) curve of 0.80; 95%CI = 0.77–0.83] [35]. Using the recommended values, a score of FLI $\geq$30 was selected to rule in NAFLD. Furthermore, we performed a sensitivity analysis to rule out NAFLD based on FLI $\geq$60.

2.3. CVH score

CVH was assessed based on 7 metrics: smoking status, physical activity, diet, BMI, total cholesterol, FBG and BP. Each metric was categorized into 3 levels i.e. "poor", "intermediate" or "ideal" and scores of 0, 1 and 2 were assigned, respectively, according to the AHA definitions (as outlined in Supplementary Table 1) [11]. A total CVH score was calculated by summing scores for each of the 7 CVH metrics, ranging from 0 to 14, with the highest score indicating a better CVH. Total CVH score was then categorized into poor (0–7), intermediate [8–10] or ideal [11,11–14].

Smoking status was categorized as ideal (never smokers, those who reported never having smoked 100 cigarettes during their lifetime), intermediate (former smokers, those who reported smoking at least 100

Table 1
Characteristics of study participants according to CVH categories.

Characteristic		Total sample	Poor (Score 0–8) (n = 7638)	Intermediate (Score 9–10) (n = 10,496)	Ideal (Score 11–14) (n = 5093)	*p* value
Age (years)		47.3 ± 0.1	48.9 ± 0.1	42.8 ± 0.3	38.2 ± 0.2	<0.001
Gender	Men (%)	46.4	56.3	58.9	41.0	<0.001
	Women (%)	53.6	43.7	41.1	59.1	
Race/Ethnicity	Non-Hispanic White (%)	48.3	32.9	44.2	22.9	<0.001
	Non-Hispanic Black (%)	21.2	39.4	46.3	14.3	
	Mexican-American (%)	31.0	26.4	51.3	22.3	
Education	Less than high school (%)	29.6	46.3	42.1	11.6	<0.001
	Completed high school (%)	21.3	38.5	41.2	20.3	
	More than high school (%)	34.6	25.3	44.1	30.6	
Poverty income ratio		2.71 ± 0.08	3.41 ± 0.08	3.29 ± 0.07	2.32 ± 0.09	<0.001
ALT (U/L)		25.0 ± 0.1	29.2 ± 0.1	27.6 ± 0.1	25.4 ± 0.1	<0.001
AST (U/L)		26.1 ± 0.1	28.4 ± 0.1	26.9 ± 0.1	25.1 ± 0.1	<0.001
ALP (U/L)		70.3 ± 0.1	65.2 ± 0.2	60.8 ± 0.2	58.1 ± 0.1	<0.001
FLI		52.6 ± 0.2	78.2 ± 0.2	46.8 ± 0.4	19.1 ± 0.2	<0.001

Value presented as % or mean ± standard error of mean.
CVH: cardiovascular health, ALT: alanine aminotransferase, AST: aspartate aminotransferase, ALP: alkaline phosphatase, FLI: fatty liver index.

cigarettes during their lifetime but currently did not smoke), and poor (current smokers, those who smoked 100 cigarettes during their lifetime and were currently smoking).

Physical activity was assessed based on the frequency and duration of moderate and vigorous intensity of leisure, transportation, and household activities and classified as ideal (≥150 min/week moderate intensity, ≥75 min/week vigorous intensity, or equivalent combination), intermediate (1–149 min/week moderate intensity, 1–74 min/week vigorous intensity, or equivalent combination), and poor (no moderate and vigorous activity). BMI was classified as ideal (<25 kg/m^2), intermediate (25 to <30 kg/m^2) and poor (≥30 kg/m^2).

The healthy dietary score was assessed based on the Healthy Eating Index-2005 (HEI-2005). The HEI-2005 is a measure of diet quality that evaluates the extent to which an individual's diet conforms to the 2005 US Dietary Guidelines [36]. It is composed of 12 nutrients- and food-based components collected by 24-h dietary recalls. The first 6 components, including total fruit, whole fruit, total vegetables, dark green and orange vegetables and legumes, and total grains and whole grains, are each given a score of 0–5 points. The next 5 components, including milk, meat and beans, oils, saturated fat (SFA), and sugar, are each given 0 to 10 points. The last component that reflects calories from solid fat, alcohol and added sugars is given 0 to 20 points. The total HEI-2005 score of the 12 components range from 0 to 100. In the present analysis, participants with an HEI-2005 score <50 were categorized as having a poor diet quality, those with a score of >50 to <81 were assigned to intermediate diet quality and those with a score of ≥81 were assigned to ideal diet quality as previously defined [37].

Total cholesterol status was classified as ideal (untreated and <200 mg/dL), intermediate (treated to <200 or 200–239 mg/dL) and poor (≥240 mg/dL). FBG was classified as ideal (untreated and <100 mg/dL), intermediate (treated to <100 or 100–125 mg/dL), and poor (≥126 mg/dL). BP was classified as ideal (untreated and <120/<80 mmHg), intermediate (treated to <120/<80 mmHg or 120–139/80-89 mmHg) and poor (≥140/90 mmHg).

2.5. Statistical analysis

Analyses were conducted using the SPSS software (version 22, Chicago, IL, USA) according to the guidelines set by the Center for Disease and Prevention (CDC) for analysis of complex NHANES datasets, accounting for the masked variance and using the proposed weighting methodology [29]. We used means and standard error mean (SEM) for continuous measures (analysis of variance) and percentages for categorical variables (Chi-square). Adjusted [for age (continuous), gender (dichotomized), race (dichotomized), poverty to income ratio (continuous), education (dichotomized) and marital status (dichotomized) and alcohol consumption(continuous)] linear regression was applied to evaluate the link between CVH score and liver function tests [ALT (continuous), AST (continuous), FLI (continuous) and ALP (continuous)]. In linear regression, CVH score was used as the dependent factor, whereas the liver tests were independent variables in each model. The results of the linear regression were expressed as standardized beta-coefficients (β). Adjusted [for age (continuous), gender (dichotomized), race (dichotomized), poverty to income ratio (continuous), education (dichotomized) and marital status (dichotomized) and alcohol consumption (continuous)] logistic regression was performed to determine the likelihood of NAFLD according to the total CVH score as well as each CVH metric, including smoking, BMI, physical activity, diet score, total cholesterol, BP and FBG (poor considered as reference). In logistic regression, NAFLD (dichotomized) was used as dependent factors, whereas the CVH metric (dichotomized) was used as an independent variable in each model. The results of the logistic regression were expressed as odds ratio (OR) and 95% confidence interval (95%CI). Differences in liver biomarkers (ALT, AST, ALP and FLI) between presenting or non-presenting at least 4 CVH metrics were also examined by analysis of co-variance (ANCOVA) adjusting for [for age (continuous), gender (dichotomized), race (dichotomized), poverty to income ratio (continuous), education (dichotomized) and marital status (dichotomized) and alcohol consumption(continuous)] [26]. A two-sided $p \leq 0.05$ was considered as significant.

3. Results

Our study included 23,227 individuals with a mean age of 47.3 years (males: 47.8 *vs.* females: 46.7 years, $p = 0.076$). Males compromised 46.6% of our population. The characteristics of the population according to CVH categories are shown in Table 1. Individuals with an ideal level of CVH were significantly younger than those with an intermediate or poor CVH level (38.2 *vs.* 42.8 vs 48.9 years, respectively; $p < 0.001$, Table 1). The majority of individuals in poor and intermediate level of CVH were males, whereas females were the majority in the ideal category (female: 59.1 *vs.* male: 41.0%, $p < 0.001$, Table 1). With regard to race/ethnicity, non-Hispanic White (22.9%) and non-Hispanic Black (39.4%) consisted the majority of individuals with ideal and poor level of CVH ($p < 0.001$). Individuals with poor CVH level had the highest poverty to income ratio, followed by intermediate and ideal level (3.42 *vs.* 3.29 *vs.* 2.32, respectively; $p < 0.001$). Furthermore, compared with those with poor CVH score, individuals with ideal CVH score had lower levels of ALT (29.2 *vs.* 25.4 U/L, $p < 0.001$), AST (28.4 *vs.* 25.1 U/L, $p < 0.001$), ALP (65.2 *vs.* 58.1 U/L, $p < 0.001$) and FLI (78.2 *vs.* 19.1, $p < 0.001$) (Table 1). Within NAFLD participants, 54.1, 12.9 and 16.9% were obese, had DM and HTN, respectively.

Table 2
Gender stratified and total adjusted linear regression between liver tests and CVH score.

		ALT		AST		ALP		FLI	
		β	*p*-value	β	*p*-value	β	*p*-value	β	*p*-value
CVH Score	Total	−0.069	<0.001	−0.095	<0.001	−0.067	<0.001	−0.125	<0.001
	Female	−0.066	<0.001	−0.089	<0.001	−0.072	<0.001	−0.121	<0.001
	Male	−0.071	<0.001	−0.101	<0.001	−0.061	<0.001	−0.132	<0.001

CVH: cardiovascular health, β: standardized beta-coefficient, ALT: alanine aminotransferase, AST: aspartate aminotransferase, ALP: alkaline phosphatase, FLI: fatty liver index.
Model adjusted for age, gender (for total model), and race, poverty to income ratio, education, marital status and alcohol intake.

In adjusted (for age, gender, race, poverty to income ratio, education, marital status and alcohol intake) linear regression, significant and negative associations were found between all liver tests and CVH score ($\beta = -0.069$ for ALT, $\beta = -0.095$ for AST, $\beta = -0.067$ for ALP and $\beta = -0.125$ for FLI, all $p < 0.001$, Table 2). Results of gender stratified adjusted (for age, race, poverty to income ratio, education, marital status and alcohol intake) linear regression are presented in Table 2. Compared with those non-meeting at least 4 ideal components, individuals having at least 4 components of the CVH had a more favorable level of ALT (21.1 ± 0.1 *vs.* 20.3 ± 0.2 U/L, respectively; $p < 0.001$), AST (22.3 ± 0.2 U/L *vs.* 20.9 ± 0.3 U/L, respectively; $p < 0.001$) and FLI (51.6 ± 0.6 *vs.* 31.1 ± 0.4, respectively; $p < 0.001$).

After adjusting for age, gender, race, poverty to income ratio, education, marital status and alcohol consumption, the association between likelihood of NAFLD and each CVH metric (health behaviors and health factors was evaluated (Table 3). Compared with the group with a poor level of each CVH metric, individuals in the ideal group of each CVH metric had significantly lower odds of NAFLD. Furthermore, in adjusted (for age, gender, race, poverty to income ratio, education, marital status and alcohol consumption) logistic regression, a reverse link was observed between odds of NAFLD and total CVH score, i.e. individuals with ideal CVH level had 12% lower chance of NAFLD compared with the poor group [odds ratio (OR): 0.88, 95% Confidence Interval (CI): 0.79–0.97], whereas those with intermediate CVH levels had 7% lower chance of NAFLD (OR: 0.93, 95%CI: 0.86–0.98; poor group was considered as reference in the model).

With regard to the sensitivity analysis using FLI ≥60 to rule out NAFLD, it was shown in adjusted (age, gender, race, poverty to income ratio, education, marital status and alcohol consumption) logistic regression that participants with ideal CVH score had 22% lower risk of NAFLD (ideal = OR: 0.78, 95%CI: 0.67–0.89, intermediate = 0.85, 95%CI: 0.79–0.91; the poor CVH score group was considered as the reference in the model).

Table 3
Association between risk of NAFLD and each CVH component.

Components		Prevalence ratio	95% confidence interval
Smoking	Ideal	0.91	(0.88–0.94)
	Intermediate	0.99	(0.96–1.02)
Body Mass Index	Ideal	0.61	(0.54–0.68)
	Intermediate	0.84	(0.80–0.89)
Physical activity	Ideal	0.92	(0.88–0.96)
	Intermediate	0.96	(0.93–0.98)
Diet score	Ideal	0.73	(0.73–0.78)
	Intermediate	0.83	(0.79–0.86)
Total cholesterol	Ideal	0.64	(0.58–0.70)
	Intermediate	0.84	(0.78–0.90)
Blood pressure	Ideal	0.86	(0.80–0.93)
	Intermediate	0.94	(0.87–0.99)
Fasting plasma glucose	Ideal	0.53	(0.39–0.67)
	Intermediate	0.83	(0.77–0.90)

CVH: cardiovascular health. NAFLD: non-alcoholic fatty liver disease.
Poor level of CVH was considered as reference in models. Adjusted (age, gender, race, poverty to income ratio, education, marital status and alcohol consumption) logistic regression applied.

4. Discussion

For the first time among US adults, we report that the CVH score was associated with a more favorable profile of liver biomarkers. Interestingly, the relationships between liver biomarkers and CVH index were consistent across CVH behaviors and factors. These results were robust even after adjustment for a wide range of confounders. Our findings could be extrapolated to the US population given the random sampling and nationally representative selected population.

The link between CVH and liver tests which was assessed among Chilean adults (1023 men and 1449 women, age ≥15 years) and reported a negative association between liver enzyme levels and the ideal CVH score [26], in agreement with our findings. Previous observational studies evaluated the relationships of liver tests, as surrogate indicators of liver fibrosis and NAFLD, with cardiometabolic risk factors in adults [39,40]. This was further supported by a study carried out among European male and female adolescents (n = 1084) in which a lower AST to ALT ratio was associated with a less favorable profile of cardiometabolic risk factors [41].

Biologically, elevated FBG results from hepatic IR, whereas increased plasma free fatty acids concentrations are the expression of peripheral IR [42]. Additionally, NAFLD has been proposed as the hepatic manifestation of the metabolic syndrome which includes high BP, hyperglycaemia, central adiposity and dyslipidaemia [42]. High GGT, ALT and FLI values have been associated with cardiometabolic risk factors (i.e. elevated levels of total and low density lipoprotein (LDL) cholesterol, triglycerides, insulin, early carotid plaques and endothelial dysfunction) [13,43,44]. These findings are, in a way, in line with our results.

One of the most interesting findings of the current study is the significant association of the ideal CVH metrics (behaviors/risk factors) with liver tests. In a study performed among 637 European adolescents, there was a positive association between a higher number of CVH metrics (behaviors/factors) with lower GGT and ALT [45]. Similarly, we have found a reverse association between the likelihood of NAFLD and CVH score (i.e. individuals with a better CVH had a lower chance of NAFLD). To our knowledge, no other study examined the link between odds of NAFLD and CVH score. Furthermore, the relationship of FLI with cardiometabolic risk factors has been rarely evaluated. For example, others performed a cross-sectional study among 1012 individuals reporting that those with a FLI ≥60 had a higher risk of atherosclerotic lesions and lower plasma adiponectin levels (representing a higher inflammation level) compared with those with FLI <60 [13]. This is further supported by the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam study (nested case-cohort, n = 1922) that investigated the association between FLI and the risk of type 2 diabetes (T2DM) [29]. They evaluated to what extent single FLI components may contribute to T2DM risk. A strong positive association between FLI and incident T2DM was demonstrated, independently of potential confounding variables such as

socioeconomic and lifestyle risk factors [46].

Another study examined the link between CVH and liver biomarkers in adults aged ≥15 years [26], while previous studies reported a link between some of the selected health behavior and health factors considered in the CVH calculation with liver surrogate markers, which are in accordance with our findings [47–49]. Of note, most of these studies are among young and non-Latin adult populations [47–49]. For example, a study of 15,586 Japanese workers showed a positive correlation between higher GGT levels in smokers compared with in non-smokers in adults between 40 and 54 years of age [47]. This is further supported by Nakanishi et al. [48] and Kim et al. [49], who showed raised GGT and ALT activity in smokers compared with non-smoker peers. Cigarette smoking may affect all phases of carotid artery intimal hyperplasia from endothelial dysfunction [50], and one of the mechanisms that may participate in NAFLD development in smokers is the effect of nicotine on liver injury (confirmed in animal models) [51]. Additionally, circulating cigarette smoke constituents seem to play an important role in the underlying molecular mechanisms of muscle damage, such as reduced oxygen delivery and impaired mitochondrial function [52]. We previously reported on the detrimental impact of smoking on BP, glucose, lipids, arterial stiffness and hemostasis [53,54].

It is known that vigorous to regular physical activity is associated with a healthier metabolic profile [55], insulin sensitivity [56] as well as lower total and central adiposity [57] in adults. Increases in ideal CVH are directly associated with muscular fitness [58] and healthier levels of cardiorespiratory fitness in adolescents [59]. In fact, several epidemiological cross-sectional and retrospective studies revealed a significant association between higher levels of physical activity and a lower prevalence of NAFLD [49,60]. Recent evidence also suggests that physical activity may play a key role on hepatic fat content by directly altering hepatic β-oxidation and/or lipogenesis [61]. The activation of AMP-kinase increases ATP production through fatty acid oxidation and glucose transport, and AMP-activated protein kinase is activated by depletion of ATP such as in the case of exercise training. Our results supported that individuals with a higher level of physical activity have a lower risk of NAFLD.

The AHA includes BMI as 1 of the 4 health behaviors to track for the 2020 Strategic Impact Goals [11]. In line with our findings, individuals with a lower level of adiposity also have a lower risk of NAFLD [62] Similarly, previous studies observed higher ALT and GGT levels in obese compared with normal weight adults [63]. Indeed, a strong association between BMI and liver enzyme levels is consistent across several studies [43]. In the present study, the observed associations of liver tests with CV health factors and behaviors may be the consequence of a link between excess adiposity and hepatic IR, mediated by increased hepatic free fatty acid flux from adipocytes, leading to enhanced hepatic lipogenesis and triglyceride-rich lipoprotein secretion [64]. Furthermore, excess adiposity [41], free fatty acids, low physical activity level [65] or poor dietary habits [66] enhance the expression of pro-inflammatory cytokines, thus resulting in increased IR. High ALT [67] and GGT [68] and/or low AST/ALT ratio [41] have been associated with elevated levels of total and LDL cholesterol, triglycerides, insulin and BP. In this context, metabolic syndrome and its components have been related to hepatic steatosis [69].

There is evidence for the association of nutritional profile with CVD [70]. Especially, the influence of healthy dietary patterns on liver surrogate markers has been previously reported in adults [71]. In the present study, we found that individuals with a better diet score (as defined by the AHA) had a lower likelihood of NAFLD. However, these results did not agree with those reported among Chilean individuals which failed to find any link between healthy dietary behaviors and liver tests or FLI [26]. It has been shown that a higher adherence to a Mediterranean diet was linked to lower levels of ALT and GGT in adults [71,72]. Furthermore, a population-based study in Germany reported that dietary patterns associated with NAFLD was characterized by lower intakes of tea, confectionary, fats, bread, breakfast cereals and cheese, as well as with higher consumption of soups, beer, wine, juice, poultry and eggs [73]. Among 999 Chinese adults, the highest quarter of grains-vegetables dietary pattern (high intakes of coarse grains, tubers, vegetables, mushroom and kelp/seaweed, cooked meat and beans) was associated with the lowest prevalence of NAFLD [74].

We found that individuals with at least 4 AHA components of CVH had a significantly lower risk of NAFLD and a more favorable profile of liver biomarkers. Similarly, a study performed among Chilean adults reported a more favorable profile of liver biomarkers for individuals with at least 4 components of CVH metrics [26]. These findings have some significant clinical and public health implications. In this context, surveillance of ideal CVH (by health education and promotion and lifestyle interventions) is particularly important in the USA, where most of the CVD burden is due to unhealthy behaviors and related to NCDs [75]; 20–46% of the adults in Western countries have NAFLD [76,77]. It is estimated that nearly 80% of NCDs are preventable by maintaining healthy behaviors [78].

Some limitations of the current study should be considered. Diet and physical activity levels were measured by a self-administered questionnaire, so some of the questions may have been misinterpreted deliberately or unintentionally by some participants. However, the assessment of a relatively large sample of individuals not selected for our outcome should be considered as a counter-balancing strength of this study. Furthermore, although we cannot confirm that the enzymes analyzed were totally of hepatic origin. We are not able to exclude that liver enzyme concentrations could have been affected by viral hepatitis, drugs or alcohol-ingestion. Liver fat can be measured non-invasively by using imaging techniques (e.g. magnetic resonance imaging or computed tomography). However, this is time consuming and expensive and not feasible in large observational studies. For the future studies it would also be good to take into account the menopausal status. Finally, due to the cross-sectional design of the NHANES, the associations between liver enzymes and CVH components cannot prove causality. Although we have adjusted for important potential confounders and mediators, residual confounding correlated with both CVH and independent variables may still exist, including other chronic diseases (e.g. cancer), menopausal status, sex-hormones, level of lipid profile (TG could be an important factor when it comes to fatty liver as subjects with fatty liver might have insulin resistance which results in elevated TG levels [79]) and medication, as well as genetic, behavioral, psychosocial and environmental factors [80]. Given the design of our study, there is also a chance of residual bias and thus findings need to be confirmed in randomized trials. Furthermore, physical activity and diet were evaluated based on self-reports, so misclassification attributed to recall bias and measurement errors may occur. Additionally, only one 24 h was utilized to calculate part of CVH scores. Estimates of dietary intake are subject to day-to-day variability; so, a single day of information would provide a relatively imprecise estimate of usual intake that adds to overall variability and, thereby, imprecision [81,82]. Finally, NAFLD was not evaluated by biopsy.

Despite these limitations, our study is unique as, to our knowledge, we are the first to report the association between liver biomarkers and CVH metrics among US adults. Currently, this is the largest study to evaluate the associations of liver tests and CVH score with the risk of NAFLD. In addition, the present study was conducted in an ethnically diverse (multi-ethnic) and representative sample of US adults, suggesting that our findings are generalizable and can be extrapolated to the whole US population. There are several indices of NAFLD – we selected the FLI because it has been evaluated in a US population (i.e. NHANES) [35]. Finally, the use of reliable and standardized measures of CVH and other variables were also an important strength of this study.

In conclusion, a better CVH score was associated with a lower likelihood of NAFLD in the present study. This finding was consistent across CVH behaviors and factors, as well as independent of several

cardiometabolic confounders. The present results highlight the use of CVH metrics (as proposed by the AHA) to link with liver biomarkers and the risk of NAFLD. This is particularly interesting due to the increasing prevalence of NAFLD and its burden in Western countries. Therefore, a link between NCDs and NAFLD could be an important message for policy makers.

Conflicts of interest

NK has given talks, attended conferences and participated in trials sponsored by Amgen, Angelini, Astra Zeneca, Boehringer Ingelheim, MSD, Novartis, NovoNordisk, Sanofi and WinMedica. DPM has given talks and attended conferences sponsored by MSD, AstraZeneca and Libytec. The other authors have no conflict of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2018.11.012.

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