Received: 22 June 2023 | Accepted: 1 July 2023

DOI: 10.1097/HC9.0000000000000240

ORIGINAL ARTICLE

OPEN

Higher ultra-processed food intake was positively associated with odds of NAFLD in both US adolescents and adults: A national survey

Longgang Zhao[1] | **Xinyuan Zhang**[1] | **Euridice Martinez Steele**[2] | **Chun-Han Lo**[3] | **Fang Fang Zhang**[4] | **Xuehong Zhang**[1]

[1]Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA

[2]Center for Epidemiological Studies in Health and Nutrition, University of São Paulo, São Paulo, Brazil

[3]Internal Medicine and Kirk Kerkorian School of Medicine, University of Nevada, Las Vegas, Nevada, USA

[4]Friedman School of Nutrition Science and Policy, Tufts University, Boston, Massachusetts, USA

Correspondence
Xuehong Zhang, Brigham and Women's Hospital and Harvard Medical School, Room 453, 181 Longwood Ave, Boston, MA 02115, USA.
Email: xuehong.zhang@channing.harvard.edu

Abstract

Background: The effect of ultra-processed foods (UPF) on NAFLD remains unclear. Related evidence for adult NAFLD is limited and no study has yet evaluated UPF's impact on NAFLD in adolescence.

Methods: We used data from the National Health and Nutrition Examination Survey (2017-2018) with 806 adolescents and 2734 adults. UPF intake was estimated using dietary data from two 24-hour dietary recalls. NAFLD was defined by transient elastography. Logistic regression was used to estimate the multivariable OR and 95% CI for associations between UPF and NAFLD with survey weight adjustments.

Results: The mean UPF intake was 812 g/d in adolescents and 823 g/d in adults. A total of 12.4% of the adolescents and 35.6% of the adults had NAFLD. Higher UPF intake was associated with higher odds of NAFLD in both adolescents ($OR_{\text{Quintile 5 vs. Quartile 1}} = 2.34$, 95% CI, 1.01, 5.41; $p_{trend} = 0.15$) and adults ($OR_{\text{Quintile 5 vs. Quintile 1}} = 1.72$, 95% CI, 1.01, 2.93; $p_{trend} = 0.002$). In adults, ~68% and 71% of the association between UPF intake and NAFLD was mediated by body mass index and waist circumference (all p-values < 0.001), respectively. The results were similar for adolescents but not statistically significant. A higher UPF intake was associated with lower levels of serum albumin and higher levels of C-reactive protein in adults.

Conclusions: Higher UPF intake was linked to higher NAFLD odds in both adolescents and adults, mainly because of elevated body fatness. If confirmed, reducing UPF intake may help prevent NAFLD in both adolescents and adults.

Abbreviations: ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; CDC, Centers for Disease Control and Prevention; CSF, clinically significant fibrosis; GGT, gamma-glutamyl transpeptidase; hs-CRP, high-sensitivity C-reactive protein; MET, metabolic equivalent of task; NHANES, National Health and Nutrition Examination Survey; UPF, ultra-processed foods; VCTE, vibration-controlled transient elastography

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.hepcommjournal.com.

INTRODUCTION

NAFLD is a multisystem disease, viewed as a hepatic manifestation of metabolic syndrome.[1] Along with obesity, diabetes, and other metabolic diseases, the prevalence of NAFLD is increasing in both adolescents and adults. NAFLD affects over one in 10 children and adolescents and 1 in 3 adults.[2,3] Additionally, NAFLD is the most common cause of hepatitis among adolescents with a prevalence of 17% for boys and girls aged 15–19 years.[4] Emerging evidence supports the role of diet in the prevention of NAFLD. For example, a recent review paper summarized epidemiological studies and concluded that healthy dietary patterns and total vegetable intake were associated with a lower risk of NAFLD while dietary inflammatory patterns and red or processed meat were associated with a higher risk of NAFLD.[5] However, evidence is still limited to draw conclusions for other dietary factors in both adolescents and adults.

Recent years have witnessed a significant rise of ultra-processed foods (UPF) in the food market, which contributed 67% of the total calories for US adolescents and 57% for US adults in 2017-2018.[6] Studies have shown positive associations of UPF with obesity, type 2 diabetes, heart disease, certain cancers, and mortality risk among older adults.[7] Of note, consistent evidence has shown that higher intake of UPF is associated with a higher risk of obesity in adolescents.[8,9] These chronic diseases, especially obesity and type 2 diabetes, share common pathophysiological pathways with NAFLD including the inflammation and insulin resistance. However, evidence regarding the association between UPF consumption and NAFLD is limited and inconsistent. One study, based on a prospective cohort of 16,168 Chinese men, reported a positive association between UPF and NAFLD risk.[10] Another study, including 789 participants from a hospital-based cross-sectional study in Israel, reported that UPF intake was not associated with NAFLD.[11] To date, evidence is still lacking in western populations, where the consumption of UPF is high.[12] In addition, although several studies suggested detrimental effects of UPF intake on obesity among adolescents, the association between UPF intake and NAFLD among adolescent has not yet been evaluated.

Therefore, we aimed to examine the association between UPF intake and NAFLD among adolescents and adults based on a nationally representative sample of the US population who participated in the US National Health and Nutrition Examination Surveys (NHANES). We further evaluated to what extent the association between UPF intake and NAFLD is mediated by obesity and diabetes. Moreover, we investigated the relationships between UPF intake and serum biomarkers related to liver diseases.

METHODS

Study design and participants

We used data from a national representative survey, the NHANES, which was conducted by the US Centers for Disease Control and Prevention and approved by the National Center for Health Statistics Research Ethics Review Board. All participants provided informed consent. Since 1999, the survey has been conducted on a continuous basis, with ~6000 subjects each year, and data are reported for 2-year cycles. All data from the NHANES are available for public download (http://www.cdc.gov/nchs/nhanes.htm). This analysis used data from 2017 to 2018 cycle on all participants with two valid days of 24-hour dietary recalls and valid results (participants aged 12 y and over) from liver vibration-controlled transient elastography (VCTE).[13] Of the 9254 participants in the NHANES 2017-2018, a total of 8704 participated in health examinations at the Mobile Examination Center. We excluded those meeting the following criteria: (1) heavy alcohol drinkers (for women >2 standard drinks per day and for men >3 standard drinks per day) ($n = 846$); (2) serologic positivity for chronic hepatitis B or C infection ($n = 428$); (3) steatogenic medications ($n = 47$); (4) without 2 days of 24-hour dietary recalls ($n = 1781$); (5) no valid results for VCTE examinations ($n = 1814$); and (6) missing values in education, smoking, alcohol drinking, diabetes, body mass index (BMI), or waist circumference ($n = 248$). As a result, we included 3540 participants (806 adolescents and 2734 adults) in the current analyses. A flowchart of the analytical sample-creation process is presented in Figure 1.

Dietary assessment

Dietary data were collected using 2 days of 24-hour dietary recalls. Using the NOVA classification, food items from the 24-hour dietary recalls were classified into 4 mutually exclusive food groups according to the extent and purpose of food processing: unprocessed/minimally processed foods, processed culinary ingredients, processed foods, or UPF. For food items deemed to be handmade recipes, the classification was applied to underlying ingredient codes obtained from the US Department of Agriculture Food and Nutrient Database for Dietary Studies 2017-2018.[14] We used the UPF group based on the average of two 24-hour dietary recalls as the main exposure, defined by NOVA as industrial formulations of food-derived substances (such as oils, fats, sugars, starch, and protein isolates) that contain little or no whole food and often include flavorings, colorings, emulsifiers, and other additives with cosmetic functions.[15] UPFs included beverages, frozen or shelf-stable ready-to-eat/heat meals, ultra-processed bread and breakfast

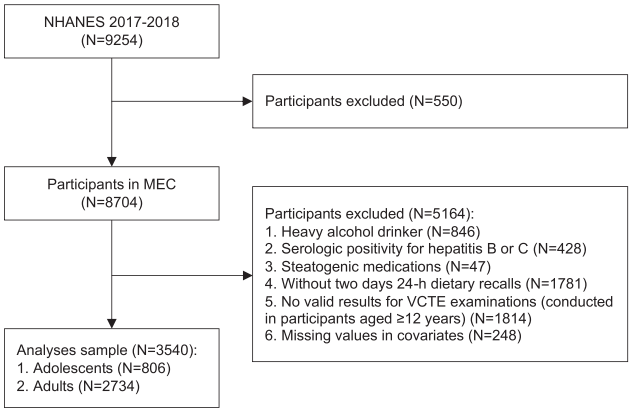

FIGURE 1 A flow chart of the study. Abbreviations: MEC, mobile examination center; VCTE, vibration-controlled transient elastography.

foods, packaged sweet snacks and desserts, meat and meat-substitute-based products, sauces/cheese spreads/gravies, dairy-based desserts, packaged savory snacks, and others. Details about the labeling process were reported elsewhere.[16] In the main analyses, we used the energy-adjusted absolute food weight in grams from the UPF daily as the exposure. In the sensitivity analyses, we used percentage of energy from the UPF daily.

NAFLD definition

NAFLD was determined based on the VCTE-measured controlled attenuation parameter (CAP). Details about the VCTE measures are provided in Supplemental Table S1, http://links.lww.com/HC9/A455. An optimal CAP cutoff of ≥285 dB/m was indicative of hepatic steatosis, with a sensitivity of 80% and specificity of 77%.[17] Therefore, consistent with previous studies,[18] we defined an individual having NAFLD if levels of CAP ≥285 dB/m and having non-NAFLD if levels of CAP < 285 dB/m. We further categorized the NAFLD into 2 groups based on the liver stiffness measurement: NAFLD without clinically significant fibrosis (CSF, liver stiffness measurement < 8.6 kPa) and NAFLD with CSF (liver stiffness measurement ≥8.6 kPa).[17] Same classification criteria were used for adolescents and adults.

Serum biomarkers assessment

We *a priori* selected biomarkers related to liver diseases based on the availability in the NHANES and literature including alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), total bilirubin, high-sensitivity C-reactive protein (hs-CRP), and albumin. We further calculated the ratio of ALT and AST (ALT/AST),[19] a maker of liver damage linked to hepatocyte injury. Laboratory methods for these serum biomarkers were described in detail on the NHANES website.[13]

Covariate assessment

Demographic, lifestyle, and health history information were collected during the NHANES interviewer-administered questionnaire in the participants' homes. Demographic covariates included age, sex, race/ethnicity, and educational attainment. We defined age groups as 20–39, 40–59, and ≥60 years for adults. We defined the self-reported race/ethnicity groups as non-Hispanic White, Hispanic, non-Hispanic Black, and others. For adolescents, education level was grouped into less than fifth grade, fifth to ninth grade, and higher than ninth grade. For adults, education level was categorized as below college, college, and above college. Height and weight were measured to calculate BMI in kilogram square meter and then classified into 4 groups: underweight (<18.5), normal weight (18.5– <25.0), overweight (25.0– <30.0), and obese (≥30.0). Waist circumference was measured at the level of the iliac crest in cm. Total physical activity was defined as the sum of minutes weekly of work-related activity, transportation activity, and leisure time activity. Alcohol consumption was measured by asking participants about the drink of any kind of alcohol (liquor, beer, wine, wine coolers, and any other type of alcohol-associated beverage) per week. Pack-years were used to define smoking status and were classified into 3 groups: never smoker, pack-years <15, and pack-years ≥15. History of diabetes was self-reported by asking participants whether they had ever been diagnosed with diabetes by a doctor. For adolescents, we did not adjust for physical activity because the physical activity questionnaire was administered to participants aged above 18 years only.

Statistical analyses

Due to the complex survey design of the NHANES, we used appropriate sample weights, stratification, and clustering to ensure representative population-level data for the entire United States. UPF consumption in grams per day was adjusted for total energy intake using residual methods and then categorized into quintile categories based on the distribution of participants without NAFLD. We also categorized UPF intake based on the distribution of all participants in the sensitivity analyses to evaluate the robustness of research findings. We provided percentage for categorical variables and means (SDs) for continuous variables. The *p*-value for difference between UPF quintiles was calculated by ANOVA for continuous variables and Chi-squared test for categorical variables. Logistic regression with adjustment for potential confounders was performed to estimate the ORs and 95% CIs for

NAFLD, comparing quintiles of UPF consumption. Considering the fibrosis, we used ordinal logistic regressions to estimate the OR and 95% CIs across NAFLD phenotypes categories (non-NAFLD, NAFLD without CSF, and NAFLD with CSF). The test for trend was performed by assigning the median value of UPF consumption to each quintile and modeling it as a continuous variable. We also calculated the OR for per 100-g increase in the UPF intake. In adults, we conducted *a priori* subgroup analyses stratified by age (<60, $\geq$ 60 y), sex (male, female), race/ethnicity (non-Hispanic Whites, others), education level (below college, college or above), smoking status (never smoker, ever smoker), alcohol drinking (never drinker, ever drinker), physical activity (<150, ≥ 150 min/wk), BMI (<30, ≥ 30 kg/m^2), and self-reported diabetes (no, yes). *P*-value for interaction was calculated based on the model with a product of UPF intake and stratified factor in the multiadjusted model. We conducted analyses separately for adults and adolescents. However, we did not run ordinal logistic regression and subgroup analyses for adolescents due to the limited sample size. We also estimated UPF consumption using the percentage of energy from UPF and assessed the association between percentage of energy from UPF and NAFLD in the sensitivity analysis.

We further evaluated to what extent of the association between UPF and NAFLD was mediated by BMI, waist circumference, diabetes, or hs-CRP using the causal mediation models (SAS PROC Causalmed). We adjusted for the same confounding factors in the mediation analyses as in the main analyses. Under a counterfactual framework, the total effect can be decomposed into 2 components: the natural direct effect and the natural indirect effect. The percentage mediated was computed as the proportion of natural indirect effect divided by total effect based on the OR scale.

In a secondary analysis, we further examined the association between subgroup UPF (in grams) and NAFLD based on previous literature.[20] The 9 subgroups included ultra-processed bread and breakfast foods, frozen or shelf-stable ready-to-eat/heat meals, packaged sweet snacks and desserts, sauces/cheese spreads/gravies, dairy-based desserts, beverages, meat and meat-substitute-based products, packaged savory snacks, and others (Supplemental Table S2, http://links.lww.com/HC9/A455). We further explored different cutoffs of CAP to define NAFLD to test the robustness of our main findings. We also performed multiple linear regression models to evaluate the relationship between UPF consumption and liver function biomarkers.

All statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC). The statistical significance was evaluated using a 2-sided test at 0.05.

RESULTS

Study population characteristics

We included 806 adolescents and 2734 adults in current analyses. The weighted mean (SE) consumption of UPF was 812 (15.9) g/d for adolescents and 823 (23.6) g/d for adults. The weighted prevalence of NAFLD based on the CAP is 12.4% (n = 111) in adolescents and 35.6% (n = 1053) in adults. Among adolescent with NAFLD, there are only 12 with clinically significant fibrosis (weighted prevalence among adolescents with NAFLD: 8.5%). Among adults with NAFLD, 191 (weighted prevalence among adults with NAFLD: 16.1%) were with clinically significant fibrosis. Characteristics of participants according to the quintiles of energy-adjusted UPF gram intake are shown in Table 1. We did not observe significant difference in the characteristics between quintiles of UPF intake among adolescents. Among adults, participants with higher UPF intake were more likely to be female and non-Hispanic Whites and Blacks, had a higher BMI and waist circumference, had lower levels of education, and had a diagnosis of diabetes.

Associations between UPF and NAFLD

For adolescents, we observed a positive association between higher UPF intake and NAFLD, with a non-significant *p*-value for trend (OR $_{\text{Quintile 5 vs. Quintile 1}}$ = 2.34, 95% CI, 1.01, 5.41; p_{trend} = 0.15) (Table 2). We observed similar, albeit slightly stronger, positive association if using percentage of energy from UPF to estimate the UPF intake (OR $_{\text{Q5 vs. Q1}}$ = 2.83, 95% CI, 1.08, 7.43; p_{trend} = 0.04) (Supplemental Table S3, http://links.lww.com/HC9/A455).

For adults, multivariable analyses showed a significant positive association across quintile categories of energy-adjusted UPF intake with NAFLD among adults (OR $_{\text{Q5 vs. Q1}}$ = 1.72, 95% CI, 1.01, 2.93; p_{trend} = 0.002) (Table 2). We observed similar results if using percentage of energy from UPF (OR $_{\text{Q5 vs. Q1}}$ = 1.55, 95% CI, 1.09, 2.21) (Supplemental Table S3, http://links.lww.com/HC9/A455). Categorical analyses based on the quintiles of UPF intake for all participants yielded similar results (Supplemental Table S4, http://links.lww.com/HC9/A455). Since the proportional odds assumption met, we further treated the outcome as ordinal variable (non-NAFLD, NAFLD without CSF, NAFLD with CSF). Higher UPF consumption was associated with higher odds of NAFLD with CSF (OR $_{\text{Q5 vs. Q1}}$ = 1.74, 95% CI, 1.06, 2.85; p_{trend} = 0.001) (Supplemental Table S5, http://links.lww.com/HC9/A455).

We further evaluated the associations between UPF subgroups (in grams) and NAFLD. For adolescents (Figure 2A and Supplemental Table S2, http://links.lww.

TABLE 1 Characteristics of adolescents and adults according to the quintile of energy-adjusted ultra-processed foods intake (gram) in the NHANES 2017-2018

	Quintile of energy-adjusted UPF intake (grams/day)[a]							
	Adolescents				Adults			
	Quintile 1	Quintile 3	Quintile 5	*p*	Quintile 1	Quintile 3	Quintile 5	*p*
N	154	160	161	—	520	547	588	—
Age, year	15.4 (0.3)	15.3 (0.3)	15.5 (0.2)	0.93	48.6 (1.3)	50.0 (1.2)	47.7 (1.6)	0.17
Body mass index, kg/m^2	23.1 (0.8)	24.0 (0.9)	25.1 (0.6)	0.06	28.6 (0.4)	28.9 (0.3)	31.3 (0.4)	< 0.001
Waist circumference, cm	79.9 (1.7)	82.2 (2.5)	84.3 (1.7)	0.07	98.3 (1.3)	98.6 (0.8)	104.4 (1.1)	< 0.001
Total physical activity, minutes/week	206 (51)	202 (65)	308 (84)	0.21	857 (84)	869 (102)	1049 (86)	0.13
Total energy intake, kcal/day	2227 (63)	1895 (71)	2025 (57)	0.13	2491 (91)	1852 (39)	2150 (30)	0.02
Female (%)	52.5	44.0	38.8	0.36	41.7	62.7	48.9	<0.001
Race/ethnicity (%)	—	—	—	0.27	—	—	—	<0.001
Non-Hispanic White	39.6	53.7	55.9	—	64.8	62.3	69.4	—
Non-Hispanic Black	14.6	10.5	12.9	—	8.0	13.1	13.8	—
Hispanic	24.2	25.6	23.7	—	11.3	17.0	9.2	—
Other	21.5	10.1	7.5	—	15.8	7.5	7.6	—
Education (%)[b]	—	—	—	0.62	—	—	—	< 0.001
Low	4.7	1.5	4.7	—	27.5	39.4	39.6	—
Middle	48.4	55.0	49.1	—	25.9	24.8	36.5	—
High	47.0	43.4	46.2	—	46.6	35.7	23.9	—
Smoking (%)[c]				NA				0.07
Never smoker	99.8	100	98.0	—	62.3	71.0	55.6	—
Pack-years < 15	0.2	0	2.0	—	25.2	17.0	23.6	—
Pack-years ≥ 15	0	0	0	—	12.5	12.0	20.8	—
Alcohol drinker (%)	16.2	17.4	14.9	0.27	92.0	91.0	92.3	0.86
Self-reported diabetes (%)	0.5	0.4	1.3	0.44	8.5	10.2	16.4	0.009

Values are weighted mean (SD) for continuous variables and weighted percentage for categorical variables; the *p*-value was derived from the Student *t* test for continuous variables and χ^2 test for categorical variables.
[a]Ultra-processed food intake was adjusted total energy intake using residual methods. The cutoffs for quintile were adolescents: 442.8, 625.1, 784.4, and 976.9 g/d; Adults: 367.8, 525.1, 707.5, and 961.8 g/d.
[b]Education for adolescents: less than fifth grade, fifth to ninth grade, higher than ninth grade; education for adults: below college, college, and above college.
[c]*p*-value for adolescents cannot be calculated due to the cells with zero.
Abbreviation: UPF, ultra-processed food.

com/HC9/A455), the main weight contributor of UPF was beverages (41.7%), followed by frozen or shelf-stable ready-to-eat/heat meals (15.0%) and ultra-processed bread and breakfast foods (14.8%). We found that packaged savory snacks were negatively associated with NAFLD (OR $_{\text{Tertile 3 vs. Tertile 1}}$ = 0.38, 95% CI, 0.18, 0.82; p_{trend} = 0.03) (Supplemental Table S6, http://links.lww.com/HC9/A455). For adults, the main weight contributor to UPF was beverages (38.9%), followed by ultra-processed bread and breakfast foods (17.7%) and frozen or shelf-stable ready-to-eat/heat meals (13.2%) (Figure 2B and Supplemental Table S2, http://links.lww.com/HC9/A455). Among adults, we found positive associations with ultra-processed bread and breakfast foods (OR $_{\text{T3 vs. T1}}$ = 1.66, 95% CI, 1.17, 2.35; p_{trend} = 0.003), and meat and meat-substitute-based products (OR $_{\text{T3 vs. T1}}$ = 1.47, 95% CI, 1.11, 1.96; p_{trend} = 0.02) (Supplemental Table S6, http://links.lww.com/HC9/A455). Results were similar after mutual adjustment for the significant subcomponents (data not shown). We further explored different cutoffs of CAP to define NAFLD and our main findings did not materially change (data not shown).

In the stratification analyses among adults (Supplemental Table S7, http://links.lww.com/HC9/A455), we found similar associations between subgroups except education level, and alcohol intake with *p*-values for interaction as 0.02, and 0.03, respectively.

Mediation analyses

In adolescents, 90% (95% CI, −63, 242) and 65% (95% CI, −29, 158) of the association of UPF intake with

TABLE 2 Associations between energy-adjusted ultra-processed food intake (gram) and NAFLD in the NHANES 2017-2018

	Quintiles of energy-adjusted UPF intake (grams/day)[a]						
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*p* trend	Per 100 g
Adolescents (12− < 20 y old)							
Median UPF level, grams (NAFLD/no NAFLD)	326/315	545/545	694/696	884/878	1196/1185	—	—
NAFLD/no NAFLD cases	15/139	24/139	21/139	29/139	22/139	—	—
Age and energy-adjusted OR (95% CI)	1 (ref)	2.54 (0.99, 6.52)	1.60 (0.54, 4.79)	2.86 (0.95, 8.61)	2.25 (0.87, 5.80)	0.18	1.06 (0.99, 1.13)
Multivariable-adjusted OR (95% CI)[b]	1 (ref)	2.34 (1.02, 5.34)	1.59 (0.57, 4.40)	2.97 (1.11, 7.99)	2.34 (1.01, 5.41)	0.15	1.08 (1.00, 1.16)
Adults (≥ 20 y old)							
Median UPF level, grams (NAFLD/no NAFLD)	235/236	450/443	620/620	809/813	1238/1244	—	—
NAFLD/no NAFLD cases	184/336	179/336	211/336	228/336	251/337	—	—
Age and energy-adjusted OR (95% CI)	1 (ref)	0.97 (0.52, 1.82)	1.38 (0.93, 2.06)	1.44 (0.94, 2.22)	1.76 (1.10, 2.83)	<0.001	1.03 (0.99, 1.06)
Multivariable-adjusted OR (95% CI)[b]	1 (ref)	0.94 (0.49, 1.82)	1.43 (0.92, 2.23)	1.38 (0.83, 2.29)	1.72 (1.01, 2.93)	0.002	1.02 (0.99, 1.07)

[a]The quintile was calculated based on the distribution of energy-adjusted ultra-processed food intake among no NAFLD using the residual method.
[b]Multivariable-adjusted model adjusted for age, sex, race/ethnicity, education, smoking pack-years, alcohol drinking, physical activity (adults only), and total energy intake
Abbreviation: UPF, ultra-processed foods.

NAFLD were mediated by BMI and waist circumference, with insignificant *p*-values as 0.25 and 0.18, respectively (Table 3). In adults, 68% (95% CI, 31, 105) and 71% (95% CI, 33, 109) of the association between UPF intake and NAFLD among adults was mediated by BMI and waist circumference, respectively ($p < 0.001$, Table 3). We also found 25% (95% CI, 8, 43) of the association between UPF intake and NAFLD was mediated by diabetes ($p = 0.005$). The serum hs-CRP mediated 25% (95% CI, 4, 45) of the association between UPF intake and NAFLD ($p = 0.02$) among adults.

Associations between UPF and liver function biomarkers

We further evaluated the association between UPF gram intake and liver function biomarker levels (Table 4). Among adolescents, we observed inverse associations between UPF intake and AST (β change per 100 g/d = −0.17, $p = 0.004$) and ALP (β change per 100 g/d = −2.26, $p = 0.003$). Among adults, higher UPF intake was associated with a lower level of albumin (β changes per 100 g/d = −0.01, $p = 0.002$) but a higher level of hs-CRP (β changes per 100 g/d = 0.18, $p = 0.02$) after controlling for potential confounders. We did not find any significant associations between UPF and AST, ALT, ALT/AST, GGT, ALP, or total bilirubin levels among adults.

DISCUSSION

In this cross-sectional study with a nationally representative sample of the US population, we found positive associations between UPF intake and NAFLD among both adolescents and adults. Over two-thirds of the association was mediated by BMI or waist circumference and approximately one-quarter by diabetes among adults. Our findings also indicated that UPF intake was positively associated with serum hs-CRP levels and inversely associated with serum albumin among adults.

This is the first study to report a positive association between UPF intake and NAFLD in adolescents. The prevalence of NAFLD in children and adolescents worldwide has increased over the last three decades, with an annual increase of 1.35% between 1990 and 2017.[21] Although dietary habits of youth may track into adulthood, evidence on adverse impact of UPF on adolescent health is still in the early stage of investigation. UPF component like sugar-sweetened beverages is a main source of fructose and most UPFs are characterized by high amounts of fat.[22] Emerging evidence suggests that diet high in fructose and saturated fat may promote the development of adolescent NAFLD by affecting gut microbiota.[23]

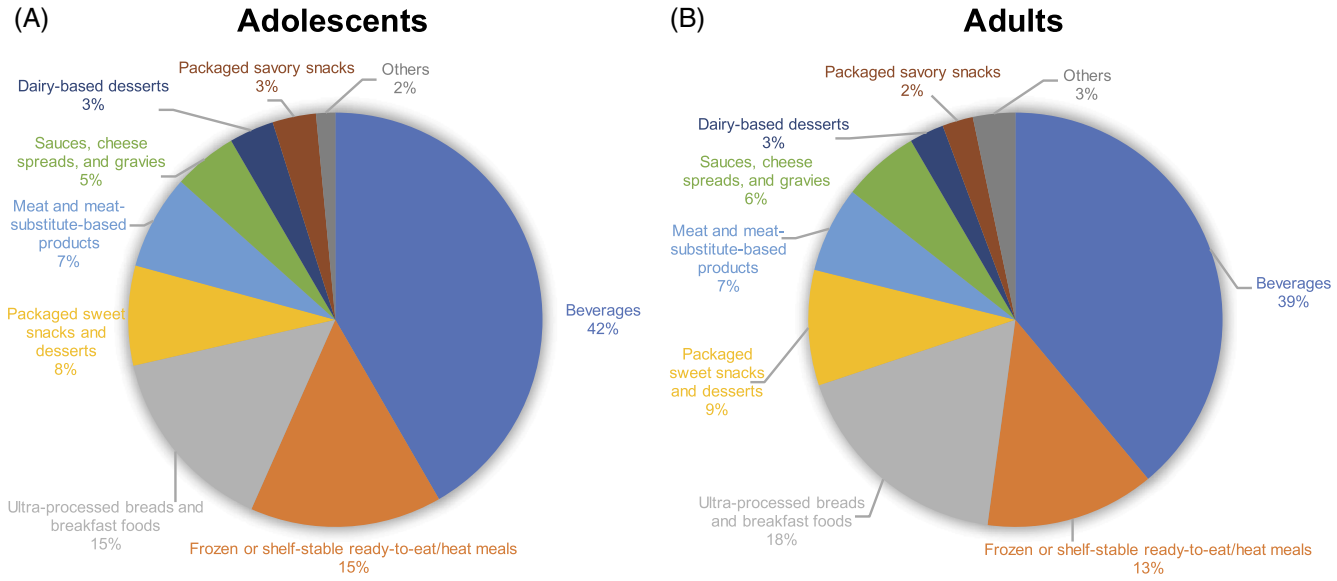

FIGURE 2 Relative contribution of each food group (gram) to ultra-processed food consumption. A, adolescents; B, adults.

In addition, a study using data from seven countries suggested that UPF intake is a potential determinant of obesity in children and adolescents.[8] A study using data from the NHANES found that greater consumption of UPF was associated with lower cardiovascular health scores among adolescents.[24] Taking together, our findings call attention to high UPF consumption in adolescents and its detrimental impact on obesity and NAFLD.

The potential detrimental impact of UPF on health among adults has also been identified. A Chinese prospective cohort study with 16,168 participants reported a positive linear association between UPF intake and the risk of NAFLD (HR $_{\text{Quartile 4 vs. quartile 1}}$ = 1.18, 95% CI, 1.07, 1.30; $P_{\text{trend}} < 0.001$).[10] Another study with a hospital-based cross-sectional design reported no association with NAFLD. However, they found positive associations of UPF intake with presumed NASH among participants with NAFLD (OR $_{\text{High vs. low}}$ = 1.89, 95% CI, 1.07, 3.38).[11] Data from the PREDIMED-Plus trial with one-year follow-up reported that per 10% daily increment in UPF intake was associated with greater fatty liver index (FLI) and hepatic steatosis index (HIS).[25] A recent study using the NHANES data evaluated the UPF intake and NAFLD defined by fatty liver index among adults, which reported a positive association between UPF intake (% of weight) and NAFLD (OR $_{\text{Quartile 4 vs. quartile 1}}$ = 1.83, 95% CI, 1.33, 2.53).[26] Our study, the first time using the Fibro-Scan to define NAFLD, strengthened the conclusion that higher UPF was associated with greater risk of NAFLD.

Studies evaluating associations between UPF intake and the liver function-related biomarkers are limited. Our study suggests an inverse association of UPF intake with serum albumin and a positive association with CRP. A previous study indicated that a decline in the serum albumin level is a predictor of worse liver health and is associated with the risk of cirrhosis.[27] Therefore, the inverse relationship between UPF intake and serum albumin level may partly explain the positive association between UPF and NAFLD. Additionally, the observed positive association between UPF and serum CRP level was consistent with a previous study.[28] The findings indicated that a higher intake of UPF may affect the risk of NAFLD partially by means of the serum CRP level.

We found that a substantial proportion (68%–71%) of the detrimental effect of UPF on NAFLD risk is potentially mediated by BMI or waist circumference among adults. Recently, a study evaluated the association between dietary quality and NAFLD risk using NHANES data, which reported that 85% to 98% of the beneficial effects were mediated by BMI or waist circumference.[18] These findings were consistent with evidence from clinical trials that weight loss induced by lifestyle changes (interventions on diet and physical activity) was associated with resolution of steatohepatitis and improvement in fibrosis and portal inflammation.[29] Additionally, in a study using data from the PREDIMED-Plus trial, changes in BMI were responsible for 69% of the association between concurrent changes in UPF consumption and NAFLD measured by both FLI and HIS.[25]

The positive association between UPF intake and NAFLD risk can be attributed to several underlying mechanisms. First, studies have shown that UPF intake is characterized by a poor nutritional profile with higher energy density, added sugar, and saturated fatty acids [30,31] which are potential risk factors

TABLE 3 Mediation analyses for associations between energy-adjusted ultra-processed food intake (gram) and NAFLD

	Effect[a]	Total effect[b]	Natural direct effect	Natural indirect effect	Percentage mediated (%)
Adolescents (12− < 20 y old)					
Body mass index	OR (95% CI) [c]	1.04 (0.97, 1.11)	1.00 (0.94, 1.07)	1.04 (1.01, 1.06)	90 (−63, 242)
	p	0.30	0.91	0.02	0.25
Waist circumference	OR (95% CI)	1.05 (0.97, 1.13)	1.02 (0.95, 1.09)	1.03 (1.00, 1.06)	65 (−29, 158)
	p	0.23	0.63	0.06	0.18
Diagnosed diabetes	OR (95% CI)	1.05 (0.99, 1.11)	1.05 (0.99, 1.11)	1.000 (0.997, 1.003)	0 (−6, 7)
	p	0.12	0.12	0.97	0.97
Serum C-reactive protein	OR (95% CI)	1.04 (0.98, 1.11)	1.04 (0.97, 1.10)	1.01 (0.99, 1.02)	19 (−22, 60)
	p	0.20	0.28	0.33	0.37
Adults (≥ 20 y old)					
Body mass index	OR (95% CI) [c]	1.04 (1.01, 1.06)	1.01 (0.99, 1.03)	1.02 (1.01, 1.03)	68 (31, 105)
	p	0.001	0.24	< 0.001	< 0.001
Waist circumference	OR (95% CI)	1.04 (1.02, 1.06)	1.01 (0.99, 1.03)	1.03 (1.02, 1.04)	71 (33, 109)
	p	0.001	0.28	< 0.001	< 0.001
Diagnosed diabetes	OR (95% CI)	1.03 (1.01, 1.05)	1.02 (1.01, 1.04)	1.007 (1.003, 1.011)	25 (8, 43)
	p	< 0.001	< 0.001	< 0.001	0.005
Serum C-reactive protein	OR (95% CI)	1.03 (1.01, 1.05)	1.02 (1.00, 1.04)	1.007 (1.002, 1.011)	25 (4, 45)
	p	0.004	0.02	0.007	0.02

[a]Model adjusted for: adolescent: age, sex, and race/ethnicity; adults: age, sex, race/ethnicity, education, smoking pack-years, alcohol drinking, physical activity (adults only), and total energy intake.
[b]Natural direct effect measures the effect of exposure on the outcome while the mediator value is held constant. Natural indirect effect measures the effect of exposure on the outcome when the mediator changed 1 U and the exposure is held constant. The percentage mediated was computed as the proportion of natural indirect effect divided by total effect based on the OR scale.
[c]OR was presented for 100 g of food intake from ultra-processed foods. Mediation analyses did not consider the complex survey design.

for obesity and type 2 diabetes, two conditions closely related to NAFLD.[32,33] It is plausible that the higher UPF intake is associated with NAFLD risk by affecting the obesity and type 2 diabetes status. Our mediation analyses showed that over two-thirds of the harmful effects of UPF on NAFLD were mediated by obesity indicators and one-quarter by diabetes. Second, inflammation is another potential pathway linking the UPF intake and NAFLD. We found that higher UPF intake was positively associated with serum CRP, which is a potential risk factor for the NAFLD.[34] Our analyses showed that serum CRP level mediated 25% of the association between dietary UPF and NAFLD. This is aligned with our previous systematic review indicating that higher inflammatory potential of diet was associated with greater risk of NAFLD.[5] Third, UPF could affect NAFLD risk by influencing the gut microbiota diversity and functionality. Dysbiosis further induces hepatic exposure to toxic substances that lead to hepatic inflammation and fibrosis.[35] In addition, additives commonly used in the UPF, such as sweeteners, is another potential mechanism. For example, sugar-sweetened beverages could affect NAFLD by promoting hepatic fat accumulation and insulin resistance.[36] Some experimental studies also indicated some additives like nanoparticles could induce gastrotoxicity, hepatotoxicity, and alterations in gut microbiota.[37]

The notable strength of this study is the use of ultrasound-diagnosed NAFLD. It could minimize the misclassification by providing higher accuracy in the diagnosis of NAFLD compared to other methods like the definition based on the hepatic steatosis index or fatty liver index. Our study is strengthened by a nationally representative of the US general population and our findings are generalizable to the US population. The current study is the first to report a positive association between UPF intake and NAFLD in adolescents. However, there are several limitations. One major limitation of our study is that the cross-sectional study design limits our capacity to establish the temporal causality. Prospective studies are needed to confirm our findings. Moreover, the two 24-hour dietary recalls may not fully capture long-term dietary intake due to the effect of day-to-day variation in food intake.

In conclusion, dietary UPF intake is associated with a higher risk of NAFLD in both adolescents and adults. These associations were largely mediated by elevated body fatness. Further prospective studies are needed to confirm our findings. If confirmed, reducing UPF intake is a potential strategy for reducing the burden of NAFLD in both adolescents and adults.

TABLE 4 Associations between energy-adjusted ultra-processed food intake (gram) and liver function biomarkers

Biomarkers[a,b]	Unit	Changes in biomarkers for per 100 g/d of UPF intake, mean (SE)	*p* trend[c]
Adolescents (12– <20 y old)			
AST	U/L	−0.166 (0.073)	0.04
ALT	U/L	−0.088 (0.112)	0.44
Ratio of ALT/AST	1	0.002 (0.002)	0.40
GGT	U/L	0.081 (0.096)	0.41
ALP	IU/L	−2.257 (0.632)	0.003
Total bilirubin	mg/dL	0.091 (0.139)	0.52
Albumin	g/dL	−0.002 (0.005)	0.72
hs-CRP	mg/L	−0.008 (0.068)	0.91
Adults (≥20 y old)			
AST	U/L	−0.009 (0.051)	0.86
ALT	U/L	0.100 (0.066)	0.15
Ratio of ALT/AST	1	0.003 (0.002)	0.20
GGT	U/L	0.193 (0.129)	0.16
ALP	IU/L	0.251 (0.138)	0.09
Total bilirubin	mg/dL	−0.012 (0.034)	0.73
Albumin	g/dL	−0.007 (0.002)	0.002
hs-CRP	mg/L	0.175 (0.065)	0.02

[a]Model adjusted for age group, sex, race/ethnicity, smoking pack-years, alcohol drinking, physical activity (adults only), and total energy intake.
[b]Sample size varied from biomarkers: Adolescents: n = 722 for AST and AST/ALT, n = 727 for ALT, GGT, ALP, total bilirubin, albumin, n = 728 for hs-CRP. Adults: n = 2567 for AST and AST/ALT, n = 2574 for ALT, GGT, and ALP, n = 2575 for total bilirubin, n = 2576 for albumin, and n = 2573 for hs-CRP.
[c]*p*-trend was calculated from the multivariable-adjusted logistic model by treating UPF intake as a continuous variable.
Abbreviations: ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; hs-CRP, high-sensitivity C-reactive protein; UPF, ultra-processed foods.

DATA AVAILABILITY

All data are publicly available on the NHANES website, and the programs are available by contacting the corresponding author.

AUTHOR CONTRIBUTIONS

Study concept and design: Longgang Zhao and Xuehong Zhang. Statistical analysis: Longgang Zhao. Data analysis review: Xinyuan Zhang. Drafting of the manuscript: Longgang Zhao. Interpretation of results: All the authors. Critical revision of the manuscript for intellectual content: All authors. Supervision: Xuehong Zhang. All authors reviewed and edited the manuscript drafts, read, and agreed to the published version of the manuscript.

ACKNOWLEDGMENT

The authors thank the US National Center for Health Statistics for building and maintaining national data on important health issues. Data from NHANES are freely available on the Centers for Disease Control and Prevention website: https://www.cdc.gov/nchs/nhanes/

FUNDING INFORMATION

Dr Xuehong Zhang is supported by NIH/NCI R21 CA238651, R21 CA252962, R37 CA262299, U01 CA259208, U01 CA272452, American Cancer Society Research Scholar Grant (RSG-17-190-01-NEC), and American Cancer Society Interdisciplinary Team Award (PASD-22-1003396-01-PASD).

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

ORCID

Longgang Zhao https://orcid.org/0000–0001–9254–1952
Xinyuan Zhang https://orcid.org/0000–0002–2974–8392
Euridice Martinez Steele https://orcid.org/0000–0002–2907–3153
Chun-Han Lo https://orcid.org/0000–0001–8202–4513
Fang Fang Zhang https://orcid.org/0000–0002–3130–0087
Xuehong Zhang https://orcid.org/0000–0002–8260–8508

REFERENCES

1. Kim CH, Younossi ZM. Nonalcoholic fatty liver disease: a manifestation of the metabolic syndrome. Cleve Clin J Med. 2008;75:721–8.
2. Li J, Ha A, Rui F, Zou B, Yang H, Xue Q, et al. Meta-analysis: Global prevalence, trend and forecasting of non-alcoholic fatty liver disease in children and adolescents, 2000-2021. Aliment Pharmacol Ther. 2022;56:396–406.
3. Riazi K, Azhari H, Charette JH, Underwood FE, King JA, Afshar EE, et al. The prevalence and incidence of NAFLD worldwide: A systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2022;7:851–61.
4. Schwimmer JB, Deutsch R, Kahen T, Lavine JE, Stanley C, Behling C. Prevalence of fatty liver in children and adolescents. Pediatrics. 2006;118:1388–93.
5. Zheng J, Zhao L, Dong J, Chen H, Li D, Zhang X, et al. The role of dietary factors in nonalcoholic fatty liver disease to hepatocellular carcinoma progression: A systematic review. Clin Nutr. 2022;41:2295–307.
6. Baraldi LG, Martinez Steele E, Canella DS, Monteiro CA. Consumption of ultra-processed foods and associated sociodemographic factors in the USA between 2007 and 2012: evidence from a nationally representative cross-sectional study. BMJ Open. 2018;8:e020574.
7. Pagliai G, Dinu M, Madarena MP, Bonaccio M, Iacoviello L, Sofi F. Consumption of ultra-processed foods and health status: a systematic review and meta-analysis. Br J Nutr. 2021;125:308–18.
8. Neri D, Steele EM, Khandpur N, Cediel G, Zapata ME, Rauber F, et al. Ultraprocessed food consumption and dietary nutrient profiles associated with obesity: A multicountry study of children and adolescents. Obes Rev. 2022;23(Suppl 1):e13387.
9. De Amicis R, Mambrini SP, Pellizzari M, Foppiani A, Bertoli S, Battezzati A, et al. Ultra-processed foods and obesity and

adiposity parameters among children and adolescents: A systematic review. Eur J Nutr. 2022;61:2297–311.
10. Zhang S, Gan S, Zhang Q, Liu L, Meng G, Yao Z, et al. Ultra-processed food consumption and the risk of non-alcoholic fatty liver disease in the Tianjin Chronic Low-grade Systemic Inflammation and Health Cohort Study. Int J Epidemiol. 2022;51:237–49.
11. Ivancovsky-Wajcman D, Fliss-Isakov N, Webb M, Bentov I, Shibolet O, Kariv R, et al. Ultra-processed food is associated with features of metabolic syndrome and non-alcoholic fatty liver disease. Liver Int. 2021;41:2635–45.
12. Vandevijvere S, Jaacks LM, Monteiro CA, Moubarac JC, Girling-Butcher M, Lee AC, et al. Global trends in ultra-processed food and drink product sales and their association with adult body mass index trajectories. Obes Rev. 2019;20 (Suppl 2):10–9.
13. Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. 2022.
14. U.S. Department of Agriculture ARS. USDA food and nutrient database for dietary studies 2017-2018. 2018.
15. Monteiro CA, Cannon G, Levy RB, Moubarac JC, Louzada ML, Rauber F, et al. Ultra-processed foods: What they are and how to identify them. Public Health Nutr. 2019;22:936–41.
16. Martinez Steele E, Baraldi LG, Louzada ML, Moubarac JC, Mozaffarian D, Monteiro CA. Ultra-processed foods and added sugars in the US diet: Evidence from a nationally representative cross-sectional study. BMJ Open. 2016;6:e009892.
17. Siddiqui MS, Vuppalanchi R, Van Natta ML, Hallinan E, Kowdley KV, Abdelmalek M, et al. Vibration-controlled transient elastography to assess fibrosis and steatosis in patients with non-alcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2019;17: 156–163.e152.
18. Vilar-Gomez E, Nephew LD, Vuppalanchi R, Gawrieh S, Mladenovic A, Pike F, et al. High-quality diet, physical activity, and college education are associated with low risk of NAFLD among the US population. Hepatology. 2022;75: 1491–506.
19. Zou Y, Zhong L, Hu C, Sheng G. Association between the alanine aminotransferase/aspartate aminotransferase ratio and new-onset non-alcoholic fatty liver disease in a nonobese Chinese population: A population-based longitudinal study. Lipids Health Dis. 2020;19:245.
20. Lo CH, Khandpur N, Rossato SL, Lochhead P, Lopes EW, Burke KE, et al. Ultra-processed foods and risk of crohn's disease and ulcerative colitis: A prospective cohort study. Clin Gastroenterol Hepatol. 2022;20:e1323–37.
21. Zhang X, Wu M, Liu Z, Yuan H, Wu X, Shi T, et al. Increasing prevalence of NAFLD/NASH among children, adolescents and young adults from 1990 to 2017: A population-based observational study. BMJ Open. 2021;11:e042843.
22. Steele EM, Popkin BM, Swinburn B, Monteiro CA. The share of ultra-processed foods and the overall nutritional quality of diets in the US: Evidence from a nationally representative cross-sectional study. Population Health Metrics. 2017;15:6.
23. Bonsembiante L, Targher G, Maffeis C. Non-alcoholic fatty liver disease in obese children and adolescents: A role for nutrition? Eur J Clin Nutr. 2022;76:28–39.
24. Zhang Z, Jackson SL, Steele EM, Gillespie C, Yang Q. Relationship between ultra-processed food intake and cardiovascular health among U.S. adolescents: Results from the National Health and Nutrition Examination Survey 2007-2018. J Adolesc Health. 2022;70:249–57.
25. Konieczna J, Fiol M, Colom A, Martinez-Gonzalez MA, Salas-Salvado J, Corella D, et al. Does consumption of ultra-processed foods matter for liver health? Prospective analysis among older adults with metabolic syndrome. Nutrients. 2022;14:4142.
26. Liu Z, Huang H, Zeng Y, Chen Y, Xu C. Association between ultra-processed foods consumption and risk of non-alcoholic fatty liver disease: A population-based analysis of NHANES 2011-2018. Br J Nutr. 2022:1–9. doi:10.1017/S0007114522003956
27. Kawaguchi K, Sakai Y, Terashima T, Shimode T, Seki A, Orita N, et al. Decline in serum albumin concentration is a predictor of serious events in nonalcoholic fatty liver disease. Medicine (Baltimore). 2021;100:e26835.
28. Lane MM, Lotfaliany M, Forbes M, Loughman A, Rocks T, O'Neil A, et al. Higher ultra-processed food consumption is associated with greater high-sensitivity C-reactive protein concentration in adults: cross-sectional results from the Melbourne Collaborative Cohort Study. Nutrients. 2022;14:3309.
29. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. Gastroenterology. 2015;149:367–78.
30. Martinez Steele E, Popkin BM, Swinburn B, Monteiro CA. The share of ultra-processed foods and the overall nutritional quality of diets in the US: Evidence from a nationally representative cross-sectional study. Popul Health Metr. 2017;15:1–11.
31. Martinez Steele E, Marron Ponce JA, Cediel G, Louzada MLC, Khandpur N, Machado P, et al. Potential reductions in ultra-processed food consumption substantially improve population cardiometabolic-related dietary nutrient profiles in eight countries. Nutr Metab Cardiovasc Dis. 2022;32:2739–50.
32. Delpino FM, Figueiredo LM, Bielemann RM, da Silva BGC, Dos Santos FS, Mintem GC, et al. Ultra-processed food and risk of type 2 diabetes: A systematic review and meta-analysis of longitudinal studies. Int J Epidemiol. 2022;51:1120–41.
33. Rauber F, da Costa Louzada ML, Steele EM, Millett C, Monteiro CA, Levy RB. Ultra-processed food consumption and chronic non-communicable diseases-related dietary nutrient profile in the UK (2008-2014). Nutrients. 2018;10:587.
34. Lee J, Yoon K, Ryu S, Chang Y, Kim HR. High-normal levels of hs-CRP predict the development of non-alcoholic fatty liver in healthy men. PLoS One. 2017;12:e0172666.
35. Leung C, Rivera L, Furness JB, Angus PW. The role of the gut microbiota in NAFLD. Nat Rev Gastroenterol Hepatol. 2016;13:412–25.
36. Chhimwal J, Patial V, Padwad Y. Beverages and non-alcoholic fatty liver disease (NAFLD): Think before you drink. Clin Nutr. 2021;40:2508–19.
37. Kamm MA. Processed food affects the gut microbiota: The revolution has started. J Gastroenterol Hepatol. 2020;35:6–7.

How to cite this article: Zhao L, Zhang X, Martinez Steele E, Lo C-H, Zhang FF, Zhang X. Higher ultra-processed food intake was positively associated with odds of NAFLD in both US adolescents and adults: A national survey. Hepatol Commun. 2023;7:e0240. https://doi.org/10.1097/HC9.0000000000000240