ACS Partner Journal

ENVIRONMENT & HEALTH

Open Access

pubs.acs.org/EnvHealth

Article

Methyl *tert*-Butyl Ether May Be a Potential Environmental Pathogenic Factor for Nonalcoholic Fatty Liver Disease: Results from NHANES 2017−2020

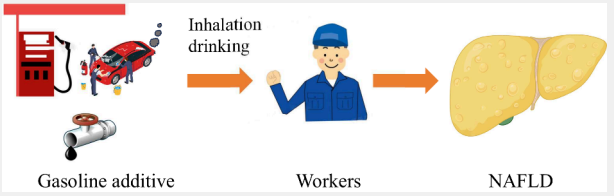
Fengtao Cui,[†] Hanyun Wang,[†] Mingxiao Guo, Yucheng Sun, Ye Xin, Wei Gao, Xingqiang Fang, Li Chen, Piye Niu,* and Junxiang Ma*

Cite This: *Environ. Health* 2025, 3, 190−198

Read Online

ACCESS | Metrics & More | Article Recommendations

ABSTRACT: Previous studies have shown that methyl *tert*-butyl ether (MTBE) could interfere with lipid metabolism. However, there is still a lack of epidemiological reports on the association between MTBE exposure and the risk of nonalcoholic fatty liver disease (NAFLD). In this study, a cross-sectional study was performed with data from the 2017−2020 cycles of the National Health and Nutrition Examination Survey (NHANES). The target population consisted of adults with reliable vibration controlled Transient elastography (VCTE) and blood MTBE concentration results. The hepatic steatosis and fibrosis were assessed by the values of the controlled attenuation parameter (CAP) and liver stiffness measurement (LSM), respectively. Generalized linear mixed model analysis was performed to evaluate the association between MTBE exposure and both steatosis and early liver fibrosis after adjustment for potential confounders. A total of 1303 subjects were enrolled and divided into NAFLD groups (CAP ≥ 248) and non-NAFLD groups (CAP < 248) based on the values of CAP in this study. Generalized linear mixed analysis suggested that blood MTBE concentration was positively associated with NAFLD risk in whole populations (OR: 2.153, 95% confidence interval [CI], 1.176−3.940) and female populations (OR: 11.019, 95% CI: 2.069−58.676). Blood MTBE concentration still showed an obvious positive correlation with the NAFLD risk after excluding factors such as diet and exercise in whole populations. Similarly, a positive correlation between blood MTBE concentration and liver fibrosis was also observed, although the results did not show significant statistical differences. In conclusion, our results indicate that MTBE exposure might be a potential important environmental pathogenic factor for NAFLD.



KEYWORDS: *Methyl tert-butyl ether (MTBE), nonalcoholic fatty liver disease (NAFLD), liver fibrosis, NHANES*

1. INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a prevalent chronic liver disease characterized by steatosis of the liver without excessive alcohol consumption and other causes of fatty liver.[1−4] A growing body of studies have suggested that many environmental pollutants contribute to the development of NAFLD.[5−7] Methyl *tert*-butyl ether (MTBE) is a widely used gasoline additive and a common environmental pollutant. It enters the environment mainly through pipeline leaks, transportation accidents, refueling or vehicle exhaust emissions.[8−10] Due to its high solubility in water and difficult degradation, MTBE can pass quickly through soil layers and potentially contaminate aquifers by gasoline released from leaking tanks, ultimately leading to severe groundwater population and posing a threat to human health.[11] Multiple studies have shown that MTBE can induce insulin resistance, glycolipid metabolism disorders,[12] and other diseases related to lipid metabolism disturbance.[13,14]

In previous studies,[14,15] we found that MTBE exposure could interfere with lipid metabolism and increase the risk of insulin resistance, which are two main pathophysiologic risk factors for NAFLD. Therefore, we speculated that MTBE exposure might be associated with NAFLD risk, and chose the National Health and Nutrition Examination Survey (NHANES) database to verify our hypothesis in the general U.S. population after excluding the common confounding factors, such as diet, physical activity, college education, and so on.

The NHANES is a cross-sectional study conducted by the National Center for Health Statistics to assess the nutritional status and emerging public health conditions of the U.S.

Received: July 21, 2024
Revised: October 15, 2024
Accepted: October 16, 2024
Published: November 7, 2024

https://doi.org/10.1021/envhealth.4c00140
Environ. Health 2025, 3, 190−198

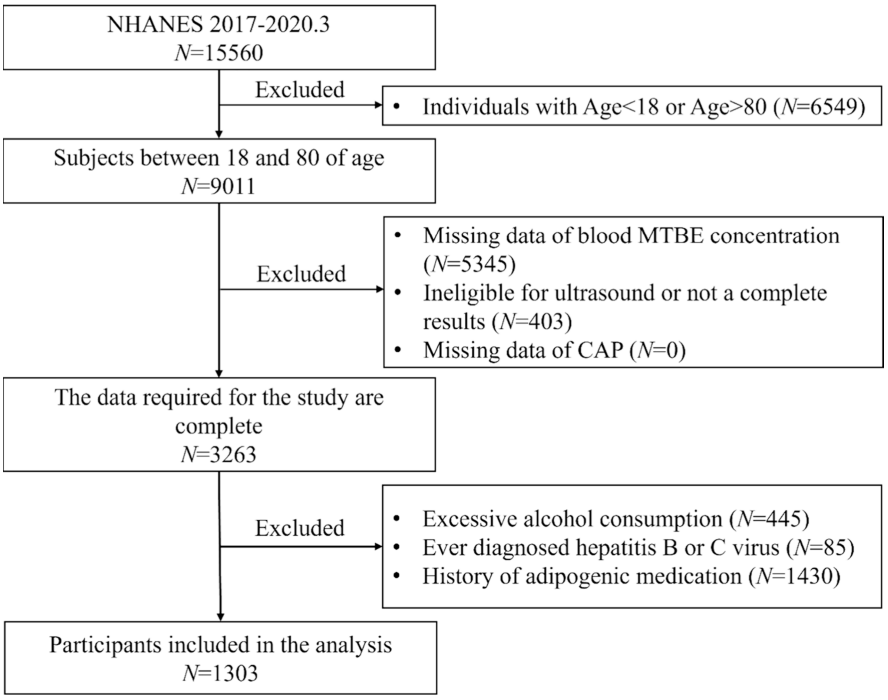


Figure 1. Flowchart for participant recruitment of this study, NHANES 2017−2020.3.

population. As such, the NHANES can provide high-quality, large-sample, and nationally representative data on the general population to assess the association of MTBE exposure with NAFLD risk.[16]

In the current study, we comprehensively assessed the relationship between MTBE exposure and NAFLD in the context of a large observational study in NHANES 2017−2020.3.

2. METHODS

2.1. Study Design and Population

The data used in this study are publicly available through the NHANES database (https://www.cdc.gov/nchs/nhanes/index.htm). NHANES is a complex, multiphase study conducted every two years[17,18] by the National Center for Health Statistics to assess the nutritional and physical health status of the American public.[19,20] Demographic, dietary, and health-related information was collected through interviews and related tests. The survey was approved by the Research Ethics Review Board of the Centers for Disease Control and Prevention, and informed consent was obtained from all survey participants.[21]

In the present study, the 2017−2020 precoronavirus-19 pandemic data from the NHANES database were used and about 15,560 participants were enrolled. Then 6549 participants were excluded who were younger than 18 years or older than 80 years, 5748 participants were excluded due to incomplete blood MTBE concentration data, ultrasound examination results or controlled attenuation parameter (CAP) data, and 1960 participants were excluded due to excessive alcohol consumption, infection with hepatitis B or C or taking adipogenic medications for more than 90 days.[16,22] Finally, this study consisted of 1303 participants. The detailed flowchart for participant recruitment is showed in Figure 1.

2.2. Definitions of NAFLD and Liver Fibrosis

In the NHANES survey, vibration-controlled transient elastography (VCTE) was used for the first time at 2017 to estimate hepatic fibrosis by measuring liver stiffness (LSM) and quantifying hepatic steatosis using CAP. The accuracy of elastography in assessing liver steatosis and fibrosis has been widely evaluated.[23] In this study, CAP 248 dB/m was used as the critical value for diagnosing hepatic steatosis with a sensitivity of 68.8% and a specificity of 82.2%, maximizing the Uden index.[24] Liver Fibrosis: An optimal LSM cutoff value of ≥6.3 kPa (sensitivity ≥90%) indicates clinical liver fibrosis.[25,26]

2.3. Covariate

Several factors were scrutinized as potential confounders and duly incorporated as adjustments within the analytical framework. The questionnaire reported demographic information, health status, and lifestyles, including age, sex, race/ethnicity, education level, house income, physical activity, and smoking and drinking history. Race/ethnicity were categorized as Mexican American, Non-Hispanic White, Non-Hispanic Black, other Hispanic, Non-Hispanic Asian and Other. Education levels were grouped into Some college or AA degree and below and College graduate or above. House income levels were defined by the poverty income ratio (PIR), which was low level (PIR < 1), middle level (1 ≤ PIR < 3), and high level (PIR ≥ 3).[27,28] We used the levels of proteins, fats and carbohydrate intake to evaluate nutritional intake. Physical activity (PA) was classified into low (<600 min/week), moderate (600 min/week−8000 min/week), and high levels (≥8000 min/week) using the metabolic equivalent of task (MET) (MET min/week).[26,29] Overweight was defined as a body mass index (BMI) of ≥25 kg/m^2, and obesity was defined as a BMI of ≥30 kg/m^2. History of alcohol consumption was defined as at least 12 drinks per year (including liquor, beer, wine, and any other type of alcoholic beverage). Smoking was defined as at least 100 lifetime cigarettes.

2.4. Statistical Analysis

Participants in this study were divided into with or without NAFLD groups according to the values of CAP, and with or without liver fibrosis groups according to the values of LSM.

Continuous variables were expressed as mean ± SD or medians (interquartile ranges), and categorical variables were presented as numbers (percentages). The "mice" package utilized the random forest algorithm for multiple interpolations of the missing data. All of the analyses took the complex design factors and sampling weights into account. All statistical analyses in this study were performed using R software (version 4.3.3) and SPSS (version 27.0). The significance level of the reported statistical results for all analyses was two-tailed, and $p < 0.05$ was considered statistically significant.

The connections between MTBE exposure and NAFLD or liver fibrosis were investigated by using two generalized linear mixed models.

https://doi.org/10.1021/envhealth.4c00140
Environ. Health 2025, 3, 190−198

Table 1. Statistical Descriptive Results for the Total Population, 2017−2020.3, NHANES

Variables	Non-NAFLD[a] N = 476	NAFLD N = 827	P
Race			0.116
Mexican American	36 (2.8%)	95 (7.3%)	
Other Hispanic	52 (4.0%)	78 (6.0%)	
Non-Hispanic White	184 (14.1%)	326 (25.0%)	
Non-Hispanic Black	137 (10.5%)	211 (16.2%)	
Non-Hispanic Asian	39 (3.0%)	81 (6.2%)	
Other Race	28 (2.1%)	36 (2.8%)	
Gender			0.002**
Male	177 (13.6%)	380 (29.2%)	
Female	299 (22.9%)	447 (34.3%)	
Age (years)	49.84 (34.00,65.00)	55.83 (47.00,66.00)	<0.001**
Weight (kg)	73.05 ± 16.75	92.37 ± 22.49	<0.001**
Blood MTBE concentration (ng/mL)	0.0073 (0.0070,0.0070)	0.0074 (0.0070,0.0070)	0.578
Waist circumference (cm)	91.81 ± 13.53	109.12 ± 14.96	<0.001**
Median stiffness (kPa)	5.18 (3.70,5.30)	6.34 (4.40,6.80)	<0.001**
Median CAP (dB/m)	206.18 ± 31.54	306.86 ± 40.29	<0.001**
HDL-cholesterol (mmol/L)	1.55 (1.29,1.76)	1.31 (1.06,1.50)	<0.001**
Total cholesterol (mmol/L)	4.75 ± 1.06	4.80 ± 1.10	0.467
ALT[b] (U/L)	18.41 (12.00,21.00)	23.79 (15.00,28.00)	<0.001**
AST[c] (U/L)	20.53 (16.00,22.00)	21.51 (16.00,24.00)	0.103
Triglycerides (mmol/L)	0.94 (0.59,1.15)	1.53 (0.88,1.77)	<0.001**
LDL-cholesterol (mmol/L)	2.69 (2.07,3.26)	2.80 (2.12,3.31)	0.135
BMI[d]			<0.001**
18.5 ≤ BMI < 25	195 (15.0%)	76 (5.8%)	
25 ≤ BMI < 30	173 (13.3%)	232 (17.8%)	
BMI ≥ 30	107 (8.2%)	517 (39.8%)	
Energy (kcal)	2005.75 (1400.50,2413.00)	2082.97 (1421.50,2602.50)	0.157
Nutrients			
Protein (g)	75.15 (49.24,92.77)	76.87 (50.38,98.14)	0.441
Fats (g)	82.83 (53.85,103.78)	88.16 (56.65,113.07)	0.052
Carbohydrate (g)	231.03 (155.85,283.14)	238.29 (158.57,299.07)	0.300
Physical Activity			0.009**
MET[e] < 600	155 (11.9%)	338 (25.9%)	
600 ≤ MET < 8000	245 (18.8%)	363 (27.9%)	
MET ≥ 8000	76 (5.8%)	126 (9.7%)	
Education level			
Some college or AA[f] degree and below	148 (11.4%)	304 (23.3%)	<0.001**
College graduate or above	303 (23.3%)	518 (39.8%)	
NA	25 (1.9%)	5 (0.4%)	
Ratio of family income to poverty			0.143
≤1	74 (6.5%)	102 (8.9%)	
1−3	146 (12.7%)	287 (25.0%)	
≥3	200 (17.5%)	337 (29.4%)	
Hypertension			<0.001**
Yes	171 (14.1%)	410 (33.7%)	
No	276 (22.7%)	359 (29.5%)	
Alcohol use			0.638
Yes	290 (22.3%)	493 (37.9%)	
No	185 (14.2%)	334 (25.7%)	
Smoking			0.019*
Yes	169 (13.0%)	348 (26.7%)	
No	307 (23.6%)	478 (36.7%)	

*P < 0.05. **P < 0.01. [a]Grouping based on CAP threshold of 248 dB/m. [b]ALT: Alanine aminotransferase. [c]AST: Aspartate Transaminase. [d]BMI: Body Mass Index. [e]MET: Metabolic equivalent of task. [f]Associate of Arts.

Model 1 was adjusted for race/ethnicity (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, or other race), blood pressure, BMI, drinking, smoking, education level, and family income-poverty ratio. Considering that exercise and dietary factors can impact the onset of NAFLD, we added physical activity and intake of the three major nutrients as covariates in Model 2.

3. RESULTS

3.1. Characteristics of the Study Participants

As Table 1 shows, the 1303 participants were divided into with NAFLD groups (CAP ≥ 248 dB/m) and without NAFLD

https://doi.org/10.1021/envhealth.4c00140
Environ. Health 2025, 3, 190−198

Table 2. Influencing Factors of MAFLD in NHANES 2017−2020.3 Population after Deleting Outliers

Variables	Total OR (95% CI)	P	Male OR (95% CI)	P	Female OR (95% CI)	P
Race						
Other Hispanic	0.478 (0.233, 0.980)	0.044*	1.330 (0.440, 4.023)	0.614	0.316 (0.114, 0.874)	0.026*
Non-Hispanic White	0.576 (0.366, 0.908)	0.017*	0.723 (0.246, 2.125)	0.555	0.502 (0.222, 1.137)	0.098
Non-Hispanic Black	0.365 (0.224, 0.593)	<0.001**	0.349 (0.135, 0.899)	0.029*	0.379 (0.176, 0.816)	0.013*
Non-Hispanic Asian	2.136 (1.361, 3.350)	0.001**	3.222 (0.925, 11.223)	0.066	1.556 (0.572, 4.233)	0.387
Other Race	0.773 (0.352, 1.699)	0.522	0.719 (0.122, 4.233)	0.715	0.819 (0.262, 2.557)	0.731
Mexican American	ref	ref	ref	ref	ref	ref
BMI						
Overweight	9.043 (5.150, 15.879)	<0.001**	12.330 (5.302, 28.674)	<0.001**	8.440 (4.572, 15.580)	<0.001**
Obesity	1.254 (0.986, 1.594)	0.065	1.334 (0.900, 1.976)	0.151	1.204 (0.849, 1.711)	0.297
Normal weight	ref	ref	ref	ref	ref	ref
Blood Pressure						
Hypertension	1.452 (0.975, 2.160)	0.066	2.158 (1.055, 4.406)	0.035*	1.303 (0.782, 2.173)	0.309
Standard blood pressure	ref	ref	ref	ref	ref	ref
Alcohol Use						
Yes	0.922 (0.686, 1.241)	0.593	1.061 (0.551, 2.042)	0.860	1.047 (0.690, 1.589)	0.830
No	ref	ref	ref	ref	ref	ref
Smoking						
Yes	1.145 (0.641, 2.044)	0.649	1.084 (0.498, 2.361)	0.839	1.259 (0.599, 2.649)	0.544
No	ref	ref	ref	ref	ref	ref
Blood MTBE concentration/0.01 ppb	2.153 (1.176, 3.940)	0.013*	1.332 (0.831, 2.135)	0.233	11.019 (2.069, 58.676)	0.005**
Education level						
College graduate or above	0.754 (0.467, 1.217)	0.248	0.357 (0.162, 0.787)	0.011*	0.854 (0.393, 1.855)	0.690
Some college or AA degree and below	ref	ref	ref	ref	ref	ref
Ratio of family income to poverty						
1 ≤ PIR < 3	1.582 (0.701, 3.572)	0.269	4.302 (0.777, 23.784)	0.095	1.293 (0.646, 2.588)	0.468
PIR ≥ 3	1.576 (0.695, 3.579)	0.276	5.900 (0.958, 36.307)	0.056	0.868 (0.360, 2.090)	0.751
<1	ref	ref	ref	ref	ref	ref

*$P < 0.05$. **$P < 0.01$.

groups (CAP < 248 dB/m) according to the values of CAP. The prevalence of NAFLD (early steatosis) in the general population was 63.5%, and the average ages of the with and without-NAFLD groups were 49.84 and 55.83. Waist circumference, body weight, triglyceride, and total cholesterol levels were higher in the NAFLD group than those in the non-NAFLD groups. Although the levels of blood MTBE in the NAFLD group were higher than those in the non-NAFLD group, unfortunately, the difference was not statistically significant. Those participants with higher BMI (BMI ≥ 25 kg/m^2), lower education level, higher household income, and higher total energy and the three major nutrients were more likely to suffer from NAFLD.

3.2. Associations between MTBE Exposure and NAFLD

After adjustment for several covariates, a significant positive correlation between blood MTBE concentration and NAFLD risk was observed in a generalized linear mixed model (OR: 2.153, 95% CI: 1.176−3.940). Similarly, further stratified analysis also showed an obvious positive association between blood MTBE concentration and the NAFLD risk female populations (OR: 11.019, 95% CI: 2.069−58.676). A positive association was also found in male populations (OR: 1.332, 95% CI: 0.831−2.135) although no statistical difference was observed ($P = 0.233$).

Consistent with a previous study, BMI also played an important role during the development of NAFLD induced by MTBE (overweight, OR: 9.043, 95% CI: 5.150−15.879). However, no significant difference was observed in obese people (OR: 1.254, 95% CI: 0.986−1.594, $P = 0.065$), which might be associated with the high lipid solubility of MTBE (Table 2).

3.3. Associations between MTBE Exposure and Liver Fibrosis

After adjusting for several covariates, blood MTBE concentration was positively associated with the liver fibrosis risk in the whole population (OR: 1.457, 95% CI: 0.986−2.154), male (OR: 1.188, 95% CI: 0.735−1.919) and female (OR: 1.730, 95% CI: 0.970−3.087) population; unfortunately, the difference was not statistically significant. Similarly, significant positive correlations between MTBE exposure and liver fibrosis were detected among overweight and obese people in the total (OR: 1.701, 95% CI: 1.067−2.707, $P = 0.026$) and female populations (OR: 2.208, 95% CI: 1.172−4.158, $P = 0.014$) (Table 3).

3.4. The Impact of Physical Activity and Intake of the Three Major Nutrients on MTBE and NAFLD

Subsequently, physical activity and dietary energy intake were included as covariates to reduce their impact on the development of NAFLD and liver fibrosis. In the adjusted analysis models, regardless of whether the two covariates (physical activity and nutritional intake) were included in the model, MTBE exposure was always significantly positively associated with the NAFLD risk in whole and female populations (Table 2 and Table 4), which indicated that exposure to MTBE increases the risk of developing NAFLD with or without adjustment for physical activity and dietary energy intake. In addition, we also found that high carbohydrate might increase the risk of NAFLD in whole (OR: 1.003, 95% CI: 1.001−1.005, $P = 0.013$) and female populations (OR: 1.003, 95% CI: 1.000−1.006, $P = 0.041$), while more physical activity (MET ≥ 8000) might

https://doi.org/10.1021/envhealth.4c00140
Environ. Health 2025, 3, 190−198

Table 3. Multivariate ORs of Liver Fibrosis in NHANES 2017−2020.3 Population after Deleting Outliers

Variables	Total OR (95% CI)	P	Male OR (95% CI)	P	Female OR (95% CI)	P
Race						
Other Hispanic	1.334 (0.742, 2.394)	0.336	1.194 (0.577, 2.469)	0.633	1.042 (0.486, 2.232)	0.917
Non-Hispanic White	1.218 (0.652, 2.273)	0.536	0.791 (0.377, 1.664)	0.538	1.300 (0.536, 3.152)	0.562
Non-Hispanic Black	1.763 (0.938, 3.317)	0.078	1.206 (0.508, 2.863)	0.671	1.855 (0.872, 3.951)	0.109
Non-Hispanic Asian	2.119 (0.902, 4.973)	0.085	1.861 (0.508, 6.828)	0.349	2.119 (0.766, 5.865)	0.148
Other Race	2.433 (0.665, 8.900)	0.179	3.193 (0.914, 11.145)	0.069	0.879 (0.110, 7.036)	0.903
Mexican American	ref	ref	ref	ref	ref	ref
BMI						
Overweight	2.686 (1.387, 5.197)	0.003**	4.175 (1.921, 9.079)	<0.001**	2.201 (1.110, 4.362)	0.024*
Obesity	1.701 (1.067, 2.707)	0.026*	1.089 (0.621, 1.910)	0.766	2.208 (1.172, 4.158)	0.014*
Normal weight	ref	ref	ref	ref	ref	ref
Blood Pressure						
Hypertension	0.979 (0.587, 1.636)	0.937	1.354 (0.675, 2.716)	0.393	0.736 (0.372, 1.458)	0.380
Standard blood pressure	ref	ref	ref	ref	ref	ref
Alcohol Use						
Yes	0.904 (0.668, 1.224)	0.514	0.885 (0.507, 1.548)	0.669	1.005 (0.631, 1.602)	0.984
No	ref	ref	ref	ref	ref	ref
Smoking						
Yes	0.972 (0.679, 1.392)	0.879	1.083 (0.675, 1.738)	0.741	0.778 (0.519, 1.165)	0.224
No	ref	ref	ref	ref	ref	ref
Blood MTBE concentration/0.01 ppb	1.457 (0.986, 2.154)	0.059	1.188 (0.735, 1.919)	0.481	1.730 (0.970, 3.087)	0.064
Education level						
College graduate or above	0.845 (0.493, 1.449)	0.540	1.294 (0.512, 3.274)	0.586	0.652 (0.303, 1.404)	0.274
Some college or AA degree and below	ref	ref	ref	ref	ref	ref
Ratio of family income to poverty						
1 ≤ PIR < 3	1.689 (0.907, 3.149)	0.099	1.259 (0.404, 3.927)	0.692	2.277 (1.241, 4.175)	0.008**
PIR ≥ 3	1.319 (0.732, 2.375)	0.357	1.010 (0.404, 2.524)	0.983	1.357 (0.657, 2.801)	0.409
<1	ref	ref	ref	ref	ref	ref

*$P < 0.05$. **$P < 0.01$.

contribute to reducing the risk of NAFLD in the female population (OR: 0.457, 95% CI: 0.219−0.955, $P = 0.037$).

Similarly, the positive association between MTBE exposure and liver fibrosis risk was also observed before and after physical activity and dietary energy intake including in the model (Table 3 and Table 5); unfortunately, no significant difference was observed. The protective effect of physical activity on liver fibrosis was also observed in the female population (OR: 0.552, 95% CI: 0.328−0.929, $P = 0.025$).

4. DISCUSSION

In this cross-sectional study with a nationally representative sample of US adults, the blood MTBE concentration was positively associated with NAFLD. In addition, after adjusting for potential confounders, there was still a significant positive correlation between the blood MTBE concentration and the risk of NAFLD. This was the first study to investigate the relationship between MTBE exposure and the NAFLD risk in the general population.

MTBE is a widely used unleaded gasoline additive and has brought great threat to the environment and human health.[13] Therefore, since 1999, various U.S. states began to enact laws prohibiting extensive use of MTBE as an oxygenated gasoline additive beginning in 2002, leading to a nationwide phaseout in 2006,[30] but a large amount of MTBE was still produced annually and exported to other countries where MTBE was not banned. And MTBE concentration could still be detected in the blood of the general population after gradually discontinuing its use as a fuel additive.[31] MTBE has certain endocrine disruptor-like effects,[32] which can alter the structure and insulin aggregated deposition of insulin and other proteins,[33,34] thereby affecting the balance of zinc ions and causing oxidative damage to the rat liver via generating large quantities of reactive oxygen species.[35,36] MTBE has been shown to interfere with energy and glucose metabolism by accumulating in adipose tissue, so prolonged and high levels of MTBE exposure might be a potential risk factor for disorders of glucose metabolism, type 2 diabetes mellitus, hyperglycemia, hypercholesterolemia, and other diseases.[37] Therefore, this study aimed to investigate the effect of MTBE on NAFLD after a total ban on MTBE use.

This study found that MTBE was positively associated with the development of NAFLD after the inclusion of relevant covariates, although the trend was not significant in the male population. Our findings also suggested that being overweight might play an important role in the development of NAFLD and liver fibrosis, which is consistent with previous studies.[38,39] Weight loss is an effective treatment for NAFLD: weight loss of about 10% can significantly improve steatosis in almost all patients and fibrosis in 80% of patients.[40−42] A case-control study based on a Swedish population also found that a mother's BMI in early pregnancy was an independent risk factor for the diagnosis of NAFLD and its severity in her offspring. With the increase of obesity, BMI will impact on the incidence of NAFLD.[43] Previous studies have shown that high BMI in early life[44,45] is associated with the development of severe liver disease. High BMI in late adolescence also predicted a higher risk of developing severe liver disease in later life, and overweight men have a 64% higher risk of developing severe liver disease than normal weight men.[45] Similarly, significant association between MTBE exposure and NAFLD risk was observed in

https://doi.org/10.1021/envhealth.4c00140
Environ. Health 2025, 3, 190−198

Table 4. Multivariate ORs for NAFLD in the NHANES 2017−2020.3 Population after Inclusion of Exercise and Diet and Removal of Outliers

Variables	Total OR (95% CI)	*P*	Male OR (95% CI)	*P*	Female OR (95% CI)	*P*
Race						
Other Hispanic	0.472 (0.203, 1.096)	0.081	1.501 (0.401, 5.624)	0.547	0.271 (0.084, 0.871)	0.028*
Non-Hispanic White	0.609 (0.342, 1.084)	0.092	0.887 (0.312, 2.517)	0.821	0.474 (0.198, 1.134)	0.093
Non-Hispanic Black	0.380 (0.219, 0.660)	0.001**	0.383 (0.143, 1.027)	0.057	0.337 (0.151, 0.752)	0.008**
Non-Hispanic Asian	2.010 (1.146, 3.525)	0.015*	3.155 (0.803, 12.391)	0.100	1.433 (0.474, 4.329)	0.524
Other Race	0.690 (0.286, 1.669)	0.410	0.730 (0.117, 4.559)	0.736	0.802 (0.248, 2.594)	0.713
Mexican American	ref	ref	ref	ref	ref	ref
BMI						
Overweight	8.793 (4.958, 15.611)	<0.001**	14.571 (7.591, 27.994)	<0.001**	8.109 (4.265, 15.417)	<0.001**
Obesity	1.306 (1.016, 1.679)	0.037*	1.328 (0.895, 1.970)	0.159	1.303 (0.900, 1.888)	0.161
Normal weight	ref	ref	ref	ref	ref	ref
Blood Pressure						
Hypertension	1.369 (0.905, 2.069)	0.137	2.307 (1.081, 4.923)	0.031*	1.244 (0.725, 2.132)	0.428
Standard blood pressure	ref	ref	ref	ref	ref	ref
Alcohol Use						
Yes	0.885 (0.649, 1.208)	0.442	1.047 (0.550, 1.994)	0.888	0.991 (0.628, 1.563)	0.969
No	ref	ref	ref	ref	ref	ref
Smoking						
Yes	1.204 (0.660, 2.195)	0.545	1.094 (0.462, 2.591)	0.839	1.385 (0.679, 2.824)	0.370
No	ref	ref	ref	ref	ref	ref
Blood MTBE concentration/0.01 ppb	2.070 (1.197, 3.577)	0.009**	1.441 (0.889, 2.336)	0.138	8.727 (1.812, 42.020)	0.007**
Nutrients						
Protein	1.002 (0.996, 1.008)	0.503	0.999 (0.987, 1.011)	0.890	0.997 (0.985, 1.008)	0.587
Fats	1 (0.993, 1.008)	0.953	0.991 (0.979, 1.003)	0.160	1.004 (0.995, 1.015)	0.379
Carbohydrate	1.003 (1.001, 1.005)	0.013*	1.004 (1.000, 1.007)	0.063	1.003 (1.000, 1.006)	0.041*
Physical Activity						
600 ≤ MET < 8000	0.772 (0.492, 1.212)	0.260	0.476 (0.193, 1.175)	0.107	0.699 (0.403, 1.212)	0.202
MET ≥ 8000	0.777 (0.511, 1.182)	0.239	0.470 (0.198, 1.114)	0.086	0.457 (0.219, 0.955)	0.037*
MET < 600	ref	ref	ref	ref	ref	ref
Education level						
College graduate or above	0.715 (0.436, 1.172)	0.184	0.349 (0.151, 0.803)	0.013*	0.844 (0.366, 1.951)	0.692
Some college or AA degree and below	ref	ref	ref	ref	ref	ref
Ratio of family income to poverty						
1 ≤ PIR < 3	1.610 (0.706, 3.673)	0.257	5.063 (0.893, 28.703)	0.067	1.367 (0.658, 2.824)	0.402
PIR ≥ 3	1.640 (0.691, 3.896)	0.262	9.300 (1.454, 59.561)	0.019*	0.911 (0.353, 2.350)	0.847
<1	ref	ref	ref	ref	ref	ref

whole, male and female populations that are overweight ($P < 0.001$). Unfortunately, we did not find a significant difference in obese people and speculate that the effect of MTBE on NAFLD might be weakened by the high lipid solubility of MTBE (Table 2).

In addition, we also incorporated educational attainment and household income poverty rates into the model, and we found that the higher the level of education, the lower the prevalence of NAFLD, and the higher the household income poverty rate, the higher the prevalence of NAFLD. The possible reason for this might be that people with higher education levels paid more attention to dietary intake, but people with higher household income poverty rate were less concerned about dietary balance and often consume more meat and fat in their diet, thereby leading to a higher risk of NAFLD. Similar results were observed in a study on American adolescents, which also showed that low household income and low education levels increased the risk of metabolic dysfunction associated fatty liver disease.[46]

In addition to educational attainment and household income, poor lifestyle, such as lack of exercise and an unhealthy diet, also were important factors affecting NAFLD.[40] It was reported that the incidence of sedentary behavior was higher among people with metabolic syndrome, excessive obesity, and type 2 diabetes.[47] Another study also showed that both aerobic and resistance exercise improved hepatic steatosis, resulting in a relative reduction of about 20−30% in intrahepatic lipids without weight loss.[48] Accumulated evidence also supported an association between healthy dietary patterns and a decreased risk of NAFLD.[49,50] Consistent with these previous findings, our results also showed that physical activity and high carbohydrate concentrations were negatively and positively associated with NAFLD and liver fibrosis, respectively (Table 4 and Table 5). Surprisingly, regardless of whether exercise and diet were included in the model, MTBE exposure was still significantly positively associated with NAFLD risk in the whole and female populations, which suggested that MTBE exposure might be a potential independent risk factor for increasing NAFLD risk. Unfortunately, we did not observe a significant effect of MTBE exposure on NAFLD risk in the male population, which indicated that the female population might be more sensitive at the same level of MTBE exposure.

The strength of this study was the inclusion of nationally representative data. The included large nationally representative sample of the US general population allowed us to estimate the

https://doi.org/10.1021/envhealth.4c00140
Environ. Health 2025, 3, 190−198

Table 5. Multivariate ORs of Liver Fibrosis in NHANES 2017−2020.3 Population after Inclusion of Exercise and Diet and Removal of outliers

	Total OR (95% CI)	P	Male OR (95% CI)	P	Female OR (95% CI)	P
Race						
Other Hispanic	1.376 (0.771, 2.452)	0.281	1.125 (0.536, 2.363)	0.754	1.266 (0.605, 2.649)	0.532
Non-Hispanic White	1.292 (0.674, 2.474)	0.440	0.676 (0.316, 1.448)	0.314	1.606 (0.670, 3.850)	0.288
Non-Hispanic Black	1.889 (0.997, 3.582)	0.051	1.003 (0.397, 2.537)	0.994	2.356 (1.127, 4.918)	0.023*
Non-Hispanic Asian	2.128 (0.876, 5.160)	0.095	1.513 (0.366, 6.259)	0.568	2.770 (1.051, 7.301)	0.039*
Other Race	2.435 (0.666, 8.917)	0.179	2.779(0.793, 9.738)	0.110	0.875(0.100, 7.675)	0.904
Mexican American	ref	ref	ref	ref	ref	ref
BMI						
Overweight	2.563 (1.344, 4.889)	0.004**	4.272 (1.895, 9.621)	<0.001**	2.175 (1.140, 4.145)	0.018*
Obesity	1.747 (1.049, 2.907)	0.032*	1.090 (0.640, 1.853)	0.752	2.134 (1.082, 4.212)	0.029*
Normal weight	ref	ref	ref	ref	ref	ref
Blood Pressure						
Hypertension	0.971 (0.577, 1.636)	0.912	1.339 (0.668, 2.933)	0.373	0.725 (0.370, 1.418)	0.347
Standard blood pressure	ref	ref	ref	ref	ref	ref
Alcohol Use						
Yes	0.885 (0.633, 1.239)	0.476	0.913 (0.485, 1.716)	0.777	0.918 (0.567, 1.484)	0.725
No	ref	ref	ref	ref	ref	ref
Smoking						
Yes	0.950 (0.667, 1.355)	0.779	1.017 (0.626, 1.652)	0.945	0.786 (0.534, 1.157)	0.222
No	ref	ref	ref	ref	ref	ref
Blood MTBE concentration/0.01 ppb	1.298 (0.824, 2.044)	0.260	1.159 (0.705, 1.904)	0.561	1.473 (0.637, 3.406)	0.365
Nutrients						
Protein	1.002 (0.996, 1.007)	0.528	0.992 (0.985, 1)	0.041*	1.007 (0.996, 1.017)	0.231
Fats	0.999 (0.994, 1.004)	0.696	1.004 (0.996, 1.012)	0.326	0.993 (0.983, 1.002)	0.135
Carbohydrate	1 (0.998, 1.002)	0.913	1 (0.996, 1.004)	0.889	1 (0.997, 1.003)	0.868
Physical Activity						
600 ≤ MET < 8000	0.700 (0.471, 1.039)	0.077	0.762 (0.432, 1.342)	0.346	0.552 (0.328, 0.929)	0.025*
MET ≥ 8000	1.096 (0.569, 2.111)	0.783	1.045 (0.586, 1.863)	0.883	0.991 (0.321, 3.056)	0.987
MET < 600	ref	ref	ref	ref	ref	ref
Education level						
College graduate or above	0.854 (0.495, 1.474)	0.570	1.363 (0.534, 3.487)	0.517	0.668 (0.327, 1.362)	0.267
Some college or AA degree and below	ref	ref	ref	ref	ref	ref
Ratio of family income to poverty						
1 ≤ PIR < 3	1.685 (0.929, 3.062)	0.086	1.127 (0.351, 3.629)	0.840	2.418 (1.354, 4.319)	0.003**
PIR ≥ 3	1.406 (0.809, 2.445)	0.226	0.950 (0.413, 2.184)	0.904	1.543 (0.774, 3.080)	0.218
<1	ref	ref	ref	ref	ref	ref

*$P < 0.05$. **$P < 0.01$.

nationwide prevalence of NAFLD directly and generalize the findings to the general U.S. adult population without being limited to specific populations, such as occupational groups. Furthermore, we applied VCTE, an objective, accurate, and reproducible technology, to simultaneously assess hepatic steatosis and fibrosis. However, our study had some limitations. First, the cross-sectional design limited the validation of causality; second, there needed to be a consensus on the thresholds for CAP and LSM; third, we only controlled for some simple physical activity data and did not delve into some of the more detailed exercise components. Fourth, there might be choice bias due to the lack of MTBE result; our conclusion still needs further validation in other larger sample sizes and more comprehensive databases.

5. CONCLUSIONS

In conclusion, this study showed a significant positive correlation between blood MTBE levels and NAFLD diagnosed by VCTE in the U.S. population. The higher the blood MTBE levels, the higher the incidence of early liver fibrosis, and MTBE exposure was more likely to induce NAFLD and liver fibrosis. Our study found for the first time that MTBE might be an environmental factor leading to NAFLD, and it provided new insights into the pathogenesis of NAFLD and early liver fibrosis.

AUTHOR INFORMATION

Corresponding Authors

Piye Niu − *Department of Occupational Health and Environmental Health, School of Public Health, Capital Medical University, Beijing 100069, China; Beijing Key Laboratory of Environmental Toxicology, School of Public Health, Capital Medical University, Beijing 100069, China;* orcid.org/0000-0002-0155-3438; Email: niupiye@ccmu.edu.cn

Junxiang Ma − *Department of Occupational Health and Environmental Health, School of Public Health, Capital Medical University, Beijing 100069, China; Beijing Key Laboratory of Environmental Toxicology, School of Public Health, Capital Medical University, Beijing 100069, China;* Email: majxiang83@ccmu.edu.cn

https://doi.org/10.1021/envhealth.4c00140
Environ. Health 2025, 3, 190−198

Authors

Fengtao Cui − *Department of Occupational Health and Environmental Health, School of Public Health, Capital Medical University, Beijing 100069, China; Beijing Key Laboratory of Environmental Toxicology, School of Public Health, Capital Medical University, Beijing 100069, China; Occupational Disease Prevention and Control Hospital of Huaibei Mining Co., Ltd, Huaibei, Anhui Province 235000, China*

Hanyun Wang − *Department of Occupational Health and Environmental Health, School of Public Health, Capital Medical University, Beijing 100069, China; Beijing Key Laboratory of Environmental Toxicology, School of Public Health, Capital Medical University, Beijing 100069, China;* orcid.org/0009-0007-4890-4083

Mingxiao Guo − *Department of Occupational Health and Environmental Health, School of Public Health, Capital Medical University, Beijing 100069, China; Beijing Key Laboratory of Environmental Toxicology, School of Public Health, Capital Medical University, Beijing 100069, China*

Yucheng Sun − *Department of Occupational Health and Environmental Health, School of Public Health, Capital Medical University, Beijing 100069, China; Beijing Key Laboratory of Environmental Toxicology, School of Public Health, Capital Medical University, Beijing 100069, China*

Ye Xin − *Department of Occupational Health and Environmental Health, School of Public Health, Capital Medical University, Beijing 100069, China; Beijing Key Laboratory of Environmental Toxicology, School of Public Health, Capital Medical University, Beijing 100069, China*

Wei Gao − *Occupational Disease Prevention and Control Hospital of Huaibei Mining Co., Ltd, Huaibei, Anhui Province 235000, China*

Xingqiang Fang − *Occupational Disease Prevention and Control Hospital of Huaibei Mining Co., Ltd, Huaibei, Anhui Province 235000, China*

Li Chen − *Department of Occupational Health and Environmental Health, School of Public Health, Capital Medical University, Beijing 100069, China; Beijing Key Laboratory of Environmental Toxicology, School of Public Health, Capital Medical University, Beijing 100069, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/envhealth.4c00140

Author Contributions

†F.C. and H.W. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This study was supported by the Natural Science Foundation (No. 7242184 and No.81973009). Thanks are extended to the cooperation of all volunteers in this study.

■ REFERENCES

(1) Matteoni, C. A.; Younossi, Z. M.; Gramlich, T.; Boparai, N.; Liu, Y. C.; McCullough, A. J. Nonalcoholic fatty liver disease: A spectrum of clinical and pathological severity. *Gastroenterology.* **1999**, *116* (6), 1413−1419.

(2) Younossi, Z. M.; Stepanova, M.; Younossi, Y.; Golabi, P.; Mishra, A.; Rafiq, N.; Henry, L. Epidemiology of chronic liver diseases in the USA in the past three decades. *Gut.* **2020**, *69* (3), 564−568.

(3) Younossi, Z.; Anstee, Q. M.; Marietti, M.; Hardy, T.; Henry, L.; Eslam, M.; George, J.; Bugianesi, E. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. *Nat. Rev. Gastro Hepat.* **2018**, *15* (1), 11−20.

(4) Pedrosa, M.; Balp, M.; Janssens, N.; Lopez, P.; Mckenna, S.; Chatterjee, S.; Kalra, M.; Jain, A.; Sonaxi, S. Global Prevalence of Nonalcoholic Steatohepatitis (Nash): Findings from a Targeted Literature Review. *Value Health.* **2018**, *21*, S82−S82.

(5) Li, W.; Xiao, H. T.; Wu, H.; Pan, C.; Deng, K.; Xu, X. W.; Zhang, Y. E. Analysis of environmental chemical mixtures and nonalcoholic fatty liver disease: NHANES 1999−2014. *Environ. Pollut.* **2022**, *311*, 119915.

(6) Guo, B.; Guo, Y. M.; Nima, Q. C.; Feng, Y. M.; Wang, Z. Y.; Lu, R.; Baimayangji; Ma, Y.; Zhou, J. M.; Xu, H.; Chen, L.; Chen, G. B.; Li, S. S.; Tong, H.; Ding, X. B.; Zhao, X. Exposure to air pollution is associated with an increased risk of metabolic dysfunction-associated fatty liver disease. *J. Hepatol.* **2022**, *76* (3), 518−525.

(7) Chen, Y.; Ngan, H. L.; Song, Y.; Qi, Z.; Zhao, L.; Dong, C.; Li, R.; Li, Y.; Yang, Z.; Cai, Z. Chronic Real-Ambient PM2.5 Exposure Exacerbates Cardiovascular Risk via Amplifying Liver Injury in Mice Fed with a High-Fat and High-Cholesterol Diet. *Environment & Health.* **2024**, *2* (4), 221−232.

(8) Shashkin, P.; Dragulev, B.; Ley, K. Macrophage differentiation to foam cells. *Curr. Pharm. Design.* **2005**, *11* (23), 3061−3072.

(9) Kim, D.; Andersen, M. E.; Pleil, J. D.; Nylander-French, L. A.; Prah, J. D. Refined PBPK model of aggregate exposure to methyl tertiary-butyl ether. *Toxicol. Lett.* **2007**, *169* (3), 222−235.

(10) Prah, J.; Ashley, D.; Blount, B.; Case, M.; Leavens, T.; Pleil, J.; Cardinali, F. Dermal, oral, and inhalation pharmacokinetics of methyl tertiary butyl ether (MTBE) in human volunteers. *Toxicol. Sci.* **2004**, *77* (2), 195−205.

(11) Johnson, R.; Pankow, J.; Bender, D.; Price, C.; Zogorski, J. MTBE - To what extent will past releases contaminate community water supply wells? *Environ. Sci. Technol.* **2000**, *34* (9), 210a−7a.

(12) Zhang, D.; Liu, X.; Tu, J.; Xiao, Q.; Han, L.; Fu, J.; Bian, J.; Zhang, R.; Chen, J.; Shao, Y.; Lu, S. Mediating Role of Glucose-Lipid Metabolism in the Association between the Increased Risk of Coronary Heart Disease and Exposure to Organophosphate Esters, Phthalates, and Polycyclic Aromatic Hydrocarbons. *Environment & Health.* **2024**, *2* (3), 170−179.

(13) Rais, Y.; Drabovich, A. P. Gasoline-derived methyl tert-butyl ether as a potential obesogen linked to metabolic syndrome. *J. Environ. Sci.* **2020**, *91*, 209−211.

(14) Guo, M. X.; Li, M. D.; Cui, F. T.; Ding, X. P.; Gao, W.; Fang, X. Q.; Chen, L.; Wang, H. Y.; Niu, P. Y.; Ma, J. X. MTBE exposure may increase the risk of insulin resistance in male gas station workers. *Environ. Sci-Proc. Imp.* **2024**, *26* (2), 334−343.

(15) Guo, M. X.; Li, M.; Chen, L.; Wang, H. Y.; Wang, J. J.; Niu, P. Y.; Ma, J. X. Glutaminase 1 isoform up-regulation associated with lipid metabolism disorder induced by methyl tertiary-butyl ether in male rats. *Ecotox Environ. Safe.* **2023**, *255*, 114763.

(16) Yuan, M. Q.; He, J.; Hu, X.; Yao, L. C.; Chen, P.; Wang, Z.; Liu, P. J.; Xiong, Z. Y.; Jiang, Y. A.; Li, L. J. Hypertension and NAFLD risk: Insights from the NHANES 2017−2018 and Mendelian randomization analyses. *Chinese Med. J-Peking.* **2024**, *137* (4), 457−464.

(17) Geng, R. L.; Zhang, Y.; Liu, M.; Deng, S. F.; Ding, J. W.; Zhong, H. F.; Tu, Q. Y. Elevated serum uric acid is associated with cognitive improvement in older American adults: A large, population-based-analysis of the NHANES database. *Front Aging Neurosci.* **2022**, *14*, 1024415.

(18) Xie, R. J.; Liu, Y. L.; Wang, J. S.; Zhang, C. H.; Xiao, M. M.; Liu, M. J.; Zhang, Y. Race and Gender Differences in the Associations Between Cadmium Exposure and Bone Mineral Density in US Adults. *Biol. Trace Elem Res.* **2023**, *201* (9), 4254−4261.

(19) Tan, L.; Zhou, Q. Y.; Liu, J.; Liu, Z. Y.; Shi, R. Z. Association of iron status with non-alcoholic fatty liver disease and liver fibrosis in US adults: a cross-sectional study from NHANES 2017−2018. *Food Funct.* **2023**, *14* (12), 5653−5662.

(20) Gong, R. P.; Pu, X. L.; Cheng, Z. Q.; Ding, J.; Chen, Z. H.; Wang, Y. J. The association between serum cadmium and diabetes in the general population: A cross-sectional study from NHANES (1999−2020). *Front Nutr.* **2022**, *9*, 966500.
(21) Chen, X. Y.; Tian, F.; Wu, J. F.; Liu, L.; Li, Y.; Yu, G. F.; Duan, H. L.; Jiang, Y. Q.; Liu, S. Y.; He, Y. J.; Luo, Y. S.; Song, C.; Li, H. Z.; Liang, Y. Q.; Wan, H.; Shen, J. Associations of phthalates with NAFLD and liver fibrosis: A nationally representative cross-sectional study from NHANES 2017 to 2018. *Front Nutr.* **2022**, *9*, 1059675.
(22) Chalasani, N.; Younossi, Z.; Lavine, J. E.; Charlton, M.; Cusi, K.; Rinella, M.; Harrison, S. A.; Brunt, E. M.; Sanyal, A. J. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. *Hepatology.* **2018**, *67* (1), 328−357.
(23) Shen, Y.; Wu, Y. H.; Fu, M. H.; Zhu, K.; Wang, J. S. Association between weight-adjusted-waist index with hepatic steatosis and liver fibrosis: a nationally representative cross-sectional study from NHANES 2017 to 2020. *Front Endocrinol.* **2023**, *14*, 1159055.
(24) Karlas, T.; Petroff, D.; Sasso, M.; Fan, J.-G.; Mi, Y.-Q.; de Ledinghen, V.; Kumar, M.; Lupsor-Platon, M.; Han, K.-H.; Cardoso, A. C.; Ferraioli, G.; Chan, W.-K.; Wong, V. W.-S.; Myers, R. P.; Chayama, K.; Friedrich-Rust, M.; Beaugrand, M.; Shen, F.; Hiriart, J.-B.; Sarin, S. K.; Badea, R.; Jung, K. S.; Marcellin, P.; Filice, C.; Mahadeva, S.; Wong, G. L.-H.; Crotty, P.; Masaki, K.; Bojunga, J.; Bedossa, P.; Keim, V.; Wiegand, J. Individual patient data meta-analysis of controlled attenuation parameter (CAP) technology for assessing steatosis. *J. Hepatol.* **2017**, *66* (5), 1022−1030.
(25) Cassinotto, C.; Boursier, J.; de Ledinghen, V.; Lebigot, J.; Lapuyade, B.; Cales, P.; Hiriart, J.-B.; Michalak, S.; Bail, B. L.; Cartier, V.; Mouries, A.; Oberti, F.; Fouchard-Hubert, I.; Vergniol, J.; Aube, C. Liver, Stiffness in Nonalcoholic Fatty Liver Disease: A Comparison of Supersonic Shear Imaging, FibroScan, and ARFI With Liver Biopsy. *Hepatology.* **2016**, *63* (6), 1817−1827.
(26) Tian, T.; Zhang, J. X.; Xie, W.; Ni, Y. L.; Fang, X. Y.; Liu, M.; Peng, X. Z.; Wang, J.; Dai, Y.; Zhou, Y. L. Dietary Quality and Relationships with Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD) among United States Adults, Results from NHANES 2017−2018. *Nutrients.* **2022**, *14* (21), 4505.
(27) Yang, Z.; Gong, D. Q.; He, X. X.; Huang, F.; Sun, Y.; Hu, Q. M. Association between daidzein intake and metabolic associated fatty liver disease: A cross-sectional study from NHANES 2017−2018. *Front Nutr.* **2023**, *10*, 1113789.
(28) Hou, W. Y.; Chen, S. Q.; Zhu, C. Y.; Gu, Y. F.; Zhu, L.; Zhou, Z. X. Associations between smoke exposure and osteoporosis or osteopenia in a US NHANES population of elderly individuals. *Front Endocrinol.* **2023**, *14*, 1074574.
(29) Kyu, H. H.; Bachman, V. F.; Alexander, L. T.; Mumford, J. E.; Afshin, A.; Estep, K.; Veerman, J. L.; Delwiche, K.; Iannarone, M. L.; Moyer, M. L.; Cercy, K.; Vos, T.; Murray, C. J. L.; Forouzanfar, M. H. Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013. *Bmj-Brit Med. J.* **2016**, *354*, i3857.
(30) Bogen, K. T.; Heilman, J. M. Reassessment of MTBE cancer potency considering modes of action for MTBE and its metabolites. *Crit Rev. Toxicol.* **2015**, *45*, 1−56.
(31) Silva, L. K.; Espenship, M. F.; Pine, B. N.; Ashley, D. L.; De Jesus, V. R.; Blount, B. C. Methyl Tertiary-Butyl Ether Exposure from Gasoline in the U.S. Population, NHANES 2001−2012. *Environ. Health Perspect.* **2019**, *127* (12), 127003.
(32) de Peyster, A.; Stanard, B.; Westover, C. Effect of ETBE on reproductive steroids in male rats and rat Leydig cell cultures. *Toxicol. Lett.* **2009**, *190* (1), 74−80.
(33) Najdegerami, I. H.; Maghami, P.; Sheikh-Hasani, V.; Hosseinzadeh, G.; Sheibani, N.; Moosavi-Movahedi, A. A. Antichaperone activity and heme degradation effect of methyl tert-butyl ether (MTBE) on normal and diabetic hemoglobins. *J. Mol. Recognit.* **2017**, *30* (5), DOI: 10.1002/jmr.2596.
(34) Valipour, M.; Maghami, P.; Habibi-Rezaei, M.; Sadeghpour, M.; Khademian, M. A.; Mosavi, K.; Sheibani, N.; Moosavi-Movahedi, A. A. Interaction of insulin with methyl tert-butyl ether promotes molten globule-like state and production of reactive oxygen species. *Int. J. Biol. Macromol.* **2015**, *80*, 610−614.
(35) Saeedi, A.; Fardid, R.; Khoshnoud, M. J.; Kazemi, E.; Omidi, M.; Mohammadi-Bardbori, A. Disturbance of zinc and glucose homeostasis by methyl tert-butyl ether (MTBE); evidence for type 2 diabetes. *Xenobiotica.* **2017**, *47* (6), 547−552.
(36) Xie, G. S.; Hong, W. X.; Zhou, L.; Yang, X. F.; Huang, H. Y.; Wu, D. S.; Huang, X. F.; Zhu, W. G.; Liu, J. J. An investigation of methyl tert-butyl ether-induced cytotoxicity and protein profile in Chinese hamster ovary cells. *Mol. Med. Rep.* **2017**, *16* (6), 8595−8604.
(37) Tang, Y.; Ren, Q. D.; Wen, Q.; Yu, C. X.; Xie, X. N.; Hu, Q.; Du, Y. G. Effect of methyl tert-butyl ether on adipogenesis and glucose metabolism and. *J. Environ. Sci.* **2019**, *85*, 208−219.
(38) Fan, Y.; Pedersen, O. Gut microbiota in human metabolic health and disease. *Nat. Rev. Microbiol.* **2021**, *19* (1), 55−71.
(39) Li, H. Y.; Huang, S. Y.; Zhou, D. D.; Xiong, R. G.; Luo, M.; Saimaiti, A.; Han, M. K.; Gan, R. Y.; Zhu, H. L.; Li, H. B. Theabrownin inhibits obesity and non-alcoholic fatty liver disease in mice via serotonin-related signaling pathways and gut-liver axis. *J. Adv. Res.* **2023**, *52*, 59−72.
(40) Romero-Gómez, M.; Zelber-Sagi, S.; Trenell, M. Treatment of NAFLD with diet, physical activity and exercise. *J. Hepatol.* **2017**, *67* (4), 829−846.
(41) Jarvis, H.; Craig, D.; Barker, R.; Spiers, G.; Stow, D.; Anstee, Q. M.; Hanratty, B. Metabolic risk factors and incident advanced liver disease in non-alcoholic fatty liver disease (NAFLD): A systematic review and meta-analysis of population-based observational studies. *Plos Med.* **2020**, *17* (4), e1003100.
(42) Wang, X.; Sun, Z.; Liu, Q. S.; Zhou, Q.; Jiang, G. Environmental Obesogens and Their Perturbations in Lipid Metabolism. *Environment & Health.* **2024**, *2* (5), 253−268.
(43) Hagström, H.; Simon, T. G.; Roelstraete, B.; Stephansson, O.; Söderling, J.; Ludvigsson, J. F. Maternal obesity increases the risk and severity of NAFLD in offspring. *J. Hepatol.* **2021**, *75* (5), 1042−1048.
(44) Hagström, H.; Tynelius, P.; Rasmussen, F. High BMI in late adolescence predicts future severe liver disease and hepatocellular carcinoma: a national, population-based cohort study in 1.2 million men. *Gut.* **2018**, *67* (8), 1536−1542.
(45) Hagström, H.; Stål, P.; Hultcrantz, R.; Hemmingsson, T.; Andreasson, A. Overweight in late adolescence predicts development of severe liver disease later in life: A 39 years follow-up study. *J. Hepatol.* **2016**, *65* (2), 363−368.
(46) Paik, J. M.; Duong, S.; Zelber-Sagi, S.; Lazarus, J. V.; Henry, L.; Younossi, Z. M. Food Insecurity, Low Household Income, and Low Education Level Increase the Risk of Having Metabolic Dysfunction-Associated Fatty Liver Disease Among Adolescents in the United States. *Am. J. Gastroenterol.* **2024**, *119* (6), 1089−1101.
(47) Dunstan, D. W.; Salmon, J.; Healy, G. N.; Shaw, J. E.; Jolley, D.; Zimmet, P. Z.; Owen, N. Association of television viewing with fasting and 2-h postchallenge plasma glucose levels in adults without diagnosed diabetes. *Diabetes Care.* **2007**, *30* (3), 516−522.
(48) Hashida, R.; Kawaguchi, T.; Bekki, M.; Omoto, M.; Matsuse, H.; Nago, T.; Takano, Y.; Ueno, T.; Koga, H.; George, J.; Shiba, N.; Torimura, T. Aerobic. resistance exercise in non-alcoholic fatty liver disease: A systematic review. *J. Hepatol.* **2017**, *66* (1), 142−152.
(49) Zelber-Sagi, S.; Ivancovsky-Wajcman, D.; Isakov, N. F.; Webb, M.; Orenstein, D.; Shibolet, O.; Kariv, R. High red and processed meat consumption is associated with non-alcoholic fatty liver disease and insulin resistance. *J. Hepatol.* **2018**, *68* (6), 1239−1246.
(50) Hassani Zadeh, S.; Mansoori, A.; Hosseinzadeh, M. Relationship between dietary patterns and non-alcoholic fatty liver disease: A systematic review and meta-analysis. *J. Gastroen Hepatol.* **2021**, *36* (6), 1470−1478.