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Association between lipid accumulation products and gallstones: an analysis of the National Health and Nutrition Examination Survey 2017–2020

Huimin Wang¹, Xiaojia Feng², Qihui Huang³ and Xiaowei Zheng^{4*}

Abstract

Aims The aim of the research was to look into the connection between the occurrence of gallstones in adult US citizens and lipid accumulation products (LAP).

Methods We conducted a cross-sectional study of 3,582 U.S. adults with relevant indicators collected from the 2017–2020 National Health and Nutrition Examination Survey (NHANES) database. Multifactorial logistic regression was used to investigate the linear relationship between LAP and gallstone incidence, while smoothed curve fitting was used to describe the nonlinear relationship, and subgroup and interaction analyses were used to evaluate the potential differences between groups.

Results Among the 3582 participants aged ≥ 20 years included, there was a positive association between LAP and gallstones. Following adjustments for all covariates, the likelihood of getting gallstones rose by 29% for each unit rise in log₂-LAP (OR = 1.29, 95% CI: 1.13–1.49). Compared to those in the lowest tertile, those in the highest LAP tertile had a significantly higher risk of developing gallstones (OR = 1.97, 95% CI: 1.31–2.95). Subgroup analyses indicated that the association between LAP and gallstones was not affected by the stratification of the variables examined.

Conclusion Gallstones and LAP exhibited a positive association in our investigation, indicating that LAP may be utilized as a clinical indicator to determine the occurrence of gallstones.

Keywords NHANES, Gallstones, Cross-sectional study, Lipid accumulation products

Background

Gallstone disease is one of the most common digestive disorders in the world, affecting about 10 to 15% of adults in the United States and Europe [1]. It is characterized by the production of hardened stones in the gallbladder or bile ducts. Most people with gallstones may have no evident symptoms [2], but when the stones clog the bile ducts or induce inflammation, a series of clinical symptoms such as abdominal pain, nausea, and vomiting, as well as complications such as perforation of the gallbladder, are often observed [3–5], which adversely impact the patient's daily life and health state. Although the major

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risk factors for gallstones are known to include genetic predisposition, obesity, a high-fat diet, and certain gallbladder diseases [6, 7], reliable clinical indicators are still needed to predict the occurrence of gallstones.

In recent years, the number of people suffering from obesity has increased dramatically worldwide, posing a serious health threat [8]. Numerous metabolism-related diseases have a substantial correlation with obesity [9]. Currently, the body mass index (BMI) and waist circumference (WC) are the most widely used clinical markers for assessing obesity. However, when used, BMI is influenced by age and sex, fails to distinguish between variations in body composition, and may overestimate obesity in individuals with high levels of muscle mass. Several studies have highlighted the controversy surrounding BMI's use in determining the risk of certain diseases and mortality [10, 11]. In addition, a limitation of WC is the inability to separate visceral and subcutaneous adipose tissue. As a new obesity assessment metric, lipid accumulation product (LAP) has been shown to be superior

to traditional obesity metrics in predicting cardiovascular risk, and metabolic syndrome [12, 13]. Recent studies have also reported the association and unique predictive value of LAP with various diseases such as osteoarthritis, obstructive sleep apnea, psoriasis, and testosterone deficiency [14–17].

Therefore, this study used the National Health and Nutrition Examination Survey (NHANES) database, a survey database designed to assess the health and nutritional status of adults and children in the United States, to investigate the relationship between LAP and gallstones and examine the possible function of LAP in the prediction of gallstone risk by assessing the incidence of gallstones among individuals with varying levels of LAP.

Methods

Participants in the NHANES study

We selected 15,560 individuals from the 2017–2020 NHANES survey for the study. After screening, 3582 participants were ultimately included in this study (Fig. 1).

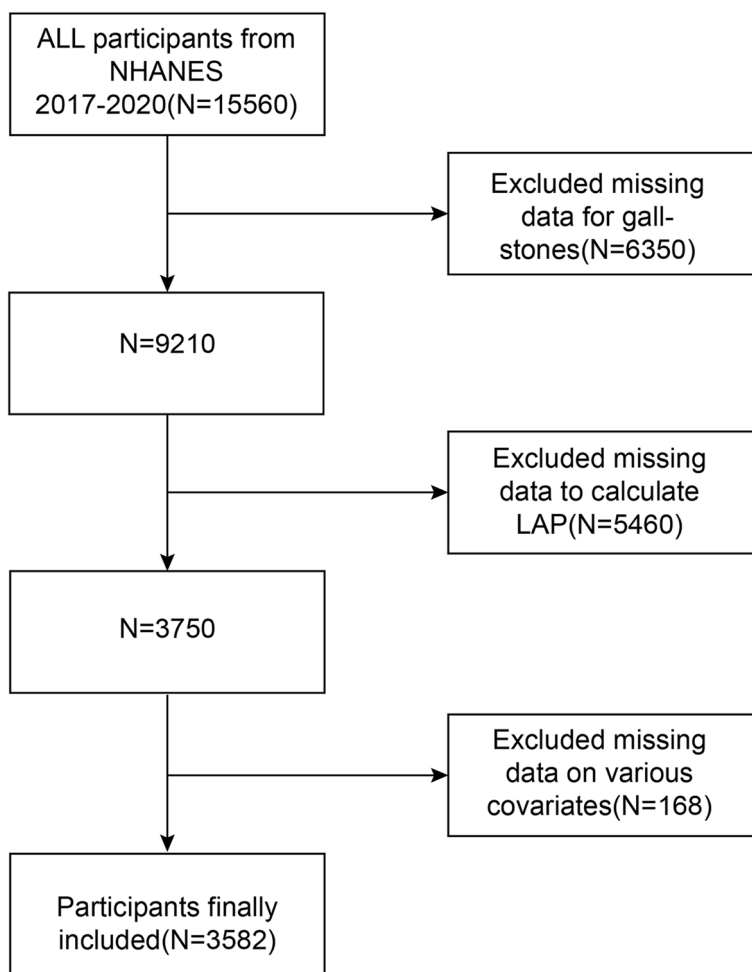


Fig. 1 Flow chart of participants selection

We omitted those who lacked data on gallstones (6350), those who lacked data on calculated LAP (5460), and those who were missing other covariates (168). The data originates from the publicly accessible NHANES official website, The National Research Ethics Board of the United States reviewed and approved.

Measurement of the LAP

LAP is calculated using WC and triglycerides (TG) as described in previous literature: for men, $LAP = (WC (cm) - 65) * TG (mmol/L)$; for women, $LAP = (WC (cm) - 58) * TG (mmol/L)$.

Assessment of gallstones

The outcome variable was the occurrence of gallstones. To assess gallbladder stones, questionnaires were used, including: "Has a doctor or other health professional ever told you that you had gallstone?"

Covariates

Based on previous studies, confounding factors that may be associated with LAP and gallstones were included in the final analysis [18, 19], including gender (male/female), age (years), race (Mexican American/Other Hispanic/Non-Hispanic White/Non-Hispanic Black/Other Race), educational status (less than high school/high school/more than high school), marital status (cohabitation/solitude), and poverty-to-income ratio (PIR) in demographic data. Ultrasound transient elastography of the liver in examination data. Also included in the questionnaire data are smoking, alcohol consumption, hypertension, diabetes, cancer and asthma. A history of smoking was defined as having smoked at least 100 cigarettes in a lifetime, a history of alcohol consumption was defined as having ever had any kind of alcohol, and asthma, diabetes, hypertension, and cancer were identified by whether or not they had ever been told in the questionnaire that they had these diseases. The use of the controlled attenuation parameter (CAP) reflects hepatic steatosis, which was diagnosed when the CAP was ≥ 285 dB/m in reference to previous studies [20].

Statistical analysis

EmpowerStats 4.0 (<http://www.empowerstats.com/>) was used, and $p < 0.05$ was considered statistically significant. Categorical data were expressed as proportions and continuous variables were expressed as mean \pm SD. To investigate the association between gallstones and LAP, multivariate logistic regression models were used. Three models were used for multivariate testing: model 2 included adjustments for sex, age, race, marital status, PIR, and education level; model 3 included adjustments for all covariates. Model 1 did not include any adjustments. The

variables were changed to fit the smoothing curves. Subgroup analyses and interaction tests were used to examine the heterogeneity of associations between subgroups of different ages, sex, hypertension, diabetes, and other conditions.

Results

Baseline characteristics of participants

A total of 3582 participants were included, with 49.25% being male and an average age of 50.75 years. The mean LAPs of all participants were 51.86 (54.37), of which 377 (10.52%) had gallstones. The clinical characteristics of the participants stratified according to the presence or absence of gallstones as a column variable are shown in Table 1. Age, gender, race, PIR, BMI, TG, WC, smoking, asthma, cancer, hypertension, and diabetes were significantly different between the two groups ($p < 0.05$). Compared to the non-gallstone group, the gallstone group had higher waist circumference, BMI, and age; they also had poorer income and more females than males. They were more likely to be concurrent smokers and to have asthma, cancer, hypertension, diabetes, and hepatic steatosis.

Association of LAP with gallstones

Table 2 shows the results of the multifactorial regression analysis of LAP and gallstones and we observe a positive correlation between LAP and gallstones, which remained stable (OR = 1.29, 95% CI: 1.13–1.49) in the fully adjusted model (Model 3), meaning that the likelihood of getting gallstones rose by 29% for each unit rises in log₂-LAP. The above associations remained statistically significant after dividing LAP into tertiles (P less than 0.01 for all trends). Participants in the highest tertile of LAP were significantly more likely to develop gallstones compared to those in the lowest tertile of LAP (OR = 1.97, 95% CI: 1.31–2.95). Furthermore, the nonlinear positive connection between LAP and gallstones was further supported by the findings of smoothed curve fitting (Fig. 2).

Subgroup analysis

We conducted interaction tests and subgroup analyses by sex, age, smoking status, alcohol use, asthma, cancer, hypertension, diabetes, and hepatic steatosis to determine if the relationship between LAP and gallstones is constant across groups. As shown in Fig. 3, our results indicate that the positive association between LAP and gallstones is similar across populations.

Discussion

A positive link was found between gallstones and LAP in this cross-sectional study with 3582 participants. Following adjustments for all covariates, the likelihood of getting gallstones rose by 35% for each unit rise in log₂-LAP

Table 1 Characteristics of the study population

Characteristics	Total N = 3582	Non-stone formers N = 3205	Stone formers N = 377	P-value
Age(years)	50.75 ± 17.25	49.95 ± 17.30	57.49 ± 15.28	< 0.001
Gender, n(%)				< 0.001
Male	49.25	51.73	28.12	
Female	50.75	48.27	71.88	
Race, n(%)				< 0.001
Mexican American	12.90	12.64	15.12	
Other Hispanic	10.11	9.77	13.00	
Non-Hispanic White	34.81	34.13	40.58	
Non-Hispanic Black	25.13	26.08	16.98	
Other race	17.06	17.38	14.32	
Education Level, n(%)				0.547
Less than high school	7.29	7.33	6.90	
High school	35.12	34.82	37.67	
More than high school	57.59	57.85	55.44	
Marital status, n(%)				0.904
Cohabitation	59.13	59.10	59.42	
Solitude	40.87	40.90	40.58	
Alcohol (%)				0.584
Yes	91.29	91.20	92.04	
No	8.71	8.80	7.96	
Smoked (%)				< 0.001
Yes	43.47	43.18	45.89	
No	56.53	56.82	54.11	
Asthma (%)				< 0.001
Yes	15.97	15.13	23.08	
No	84.03	84.87	76.92	
Cancers (%)				< 0.001
Yes	10.66	9.70	18.83	
No	89.34	90.30	81.17	
Hypertension (%)				< 0.001
Yes	38.50	36.63	54.38	
No	61.50	63.37	45.62	
Diabetes (%)				< 0.001
Yes	15.91	14.70	26.26	
No	84.09	85.30	73.74	
Hepatic steatosis(%)				< 0.001
Yes	36.07	34.54	49.07	
No	63.93	65.46	50.93	
BMI(kg/m ²)	29.91 ± 7.31	29.51 ± 7.06	33.34 ± 8.47	< 0.001
PIR	2.65 ± 1.51	2.66 ± 1.52	2.56 ± 1.43	0.229
TG(mmol/L)	1.24 ± 1.06	1.22 ± 1.06	1.37 ± 1.08	< 0.001
WC (cm)	100.98 ± 17.19	100.10 ± 16.97	108.44 ± 17.32	< 0.001
LAP	51.86 ± 54.37	49.80 ± 50.66	69.39 ± 77.10	< 0.001
log ₂ LAP	5.19 ± 1.27	5.12 ± 1.28	5.72 ± 1.05	< 0.001

Continuous variables are expressed as mean ± SEM and *p*-values were calculated by survey-weighted linear regression analysis. Categorical variables are expressed as percentages and *p*-values were calculated by survey-weighted chi-square tests

PIR poverty-to-income ratio, BMI body mass index, TG triglycerides, WC waist circumference, LAP lipid accumulation product, log₂ LAP logarithmic transformation of LAP

Table 2 Association between LAP and gallstones

Characteristic	Model 1 OR (95%CI)	Model 2 OR (95%CI)	Model 3 OR (95%CI)
Log2-transformed LAP	1.51 (1.37, 1.65) <0.0001	1.43 (1.29, 1.59) <0.0001	1.29 (1.13, 1.49) 0.0002
LAP Tertiles			
Tertile 1(0.42–4.74)	Reference	Reference	Reference
Tertile 2(4.74–5.80)	1.93 (1.41, 2.63) <0.0001	1.61 (1.17, 2.22) 0.0036	1.59 (1.09, 2.33) 0.0164
Tertile 3(5.80–10.40)	3.23 (2.41, 4.33) <0.0001	2.54 (1.87, 3.44) <0.0001	1.97 (1.31, 2.95) 0.0011
P for trend	<0.0001	<0.0001	0.0012

Model 1: not adjusted for covariates. Model 2: Adjusted for age, gender, race, marital status, household poverty-to-income ratio, and education level.c Model 3: Adjusted for age, gender, race, marital status, household poverty-to-income ratio, education level, alcohol use, smoking status, asthma, cancer, diabetes, hypertension and hepatic steatosis

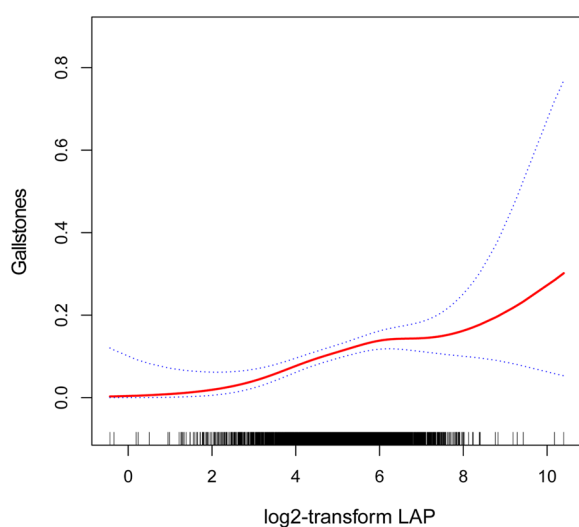


Fig. 2 The nonlinear associations between log₂-LAP and gallstones. The solid red line represents the smooth curve fit between variables. Blue bands represent the 95% of confidence interval from the fit

[1.35 (1.21, 1.50)]. This suggests that LAP may have potential clinical value in predicting gallstone risk.

As far as we know, this is the first research to assess the connection between LAP and gallstones. LAP values are a comprehensive assessment of obesity in combination with WC and TG levels, and current evidence has shown that obesity poses a significant risk for the development of gallstones [21]. BMI and WC are commonly used to assess obesity, and previous studies have shown that overweight and obese people have a significantly higher risk of having symptomatic gallstones [22, 23]. Additional studies have also found an 81% increase in gallstone prevalence for each standard deviation increase in WC [24]. However, since BMI cannot assess localized obesity and WC does not distinguish between visceral and subcutaneous fat, both have limitations in the prediction of disease. A previous prospective study showed that abdominal obesity was significantly associated with gallstones and independent of BMI

[25]. Additionally, the research by Radmard et al. demonstrated that there was no meaningful correlation between the development of gallstones and subcutaneous fat [26]. These results suggest that BMI and WC are somewhat controversial in independently predicting gallstone risk. LAP is a simple and non-invasive method for assessing visceral fat accumulation and metabolic abnormalities. It has been linked to a variety of disorders and has been shown to be a more accurate predictor of cardiovascular disease [27, 28]. therefore, the present study used the composite index, LAP, to investigate the relationship with gallstones.

According to this study, there is a positive correlation between LAP and gallstones, and there may be more than one mechanism underlying this association. First. High LAP is usually accompanied by high levels of TG and low levels of HDL cholesterol. Elevated TG leads to supersaturation of cholesterol in the bile, which increases the formation of cholesterol crystals and the occurrence of gallstones. At the same time, lower HDL cholesterol impairs its ability to remove cholesterol from the tissues, allowing more cholesterol to accumulate in the bile [29–31]. Second. Enlarged WC is usually accompanied by visceral fat accumulation, which is closely related to insulin resistance. Insulin resistance leads to elevated levels of insulin, which in turn promotes the synthesis of more cholesterol by the liver, as well as inhibiting the secretion of bile acids, leading to an increase in the concentration of cholesterol in the bile, which promotes the formation of gallstones [30, 32–34]. Third. High LAP is usually associated with chronic inflammation and oxidative stress states. High concentrations of inflammatory mediators, such as interleukin-6 and C-reactive protein, impair the gallbladder's ability to contract normally, leading to incomplete emptying of the gallbladder and thus increasing the risk of gallstone formation [35, 36]. Fourth. Accumulation of visceral fat and insulin resistance also affects the kinetic function of the gallbladder. It has

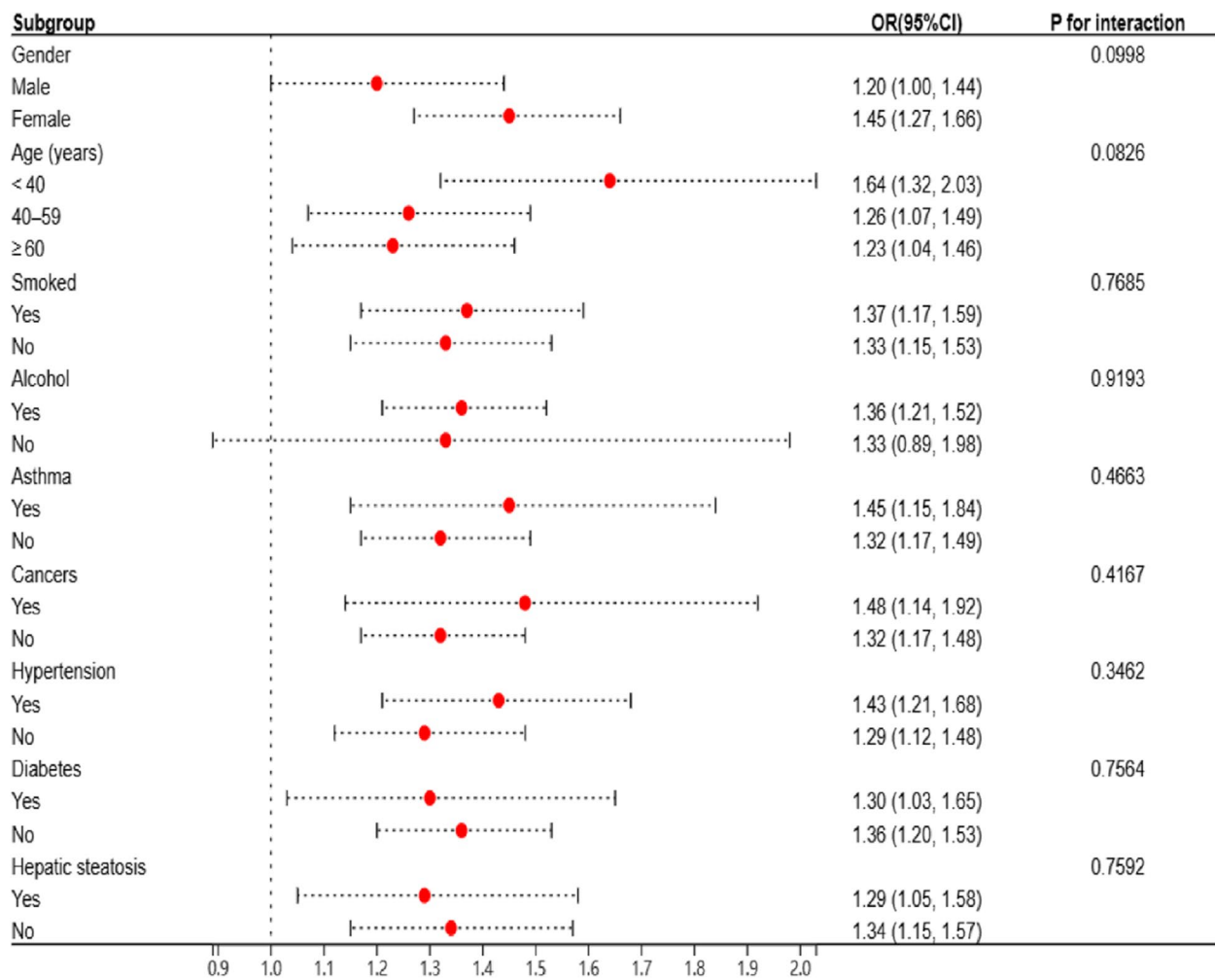


Fig. 3 Subgroup analysis of the association between LAP and gallstones

been found that patients with obesity and metabolic syndrome have significantly reduced gallbladder emptying capacity, leading to cholestasis, which promotes gallstone formation [37]. Furthermore, leptin, a hormone that plays an important role in the development of obesity, has been related to gallstone formation by controlling bile acid metabolism [38, 39].

The results of this study showed consistency across gender and age groups, indicating the broad applicability of LAP as a predictor of gallstone risk. Secondly, the sample of this study was obtained from a representative official database, and it is the first time that this composite index has been utilized to investigate the association between it and gallstones. However, this study has several limitations. First, due to the availability of data on gallstones, this study only included data from 2017 to March 2020, and due to the reason that it was a cross-sectional study lacking time-series data, we were only able to reveal associations without being

able to determine causality. Second, this study used self-reported outcome variables, lacked a more precise imaging diagnosis, and because most gallstones are clinically asymptomatic, the results of the study were influenced by whether participants received regular medical checkups or whether they received appropriate medical care from their family physicians, and there is a possibility that a person could be incorrectly diagnosed with or without gallstones, and thus the report may have potential research bias. In addition, the information on gallstones in this study was based on the question “Have you had gallstones?”, which did not provide any information about the type of gallstones, so we were unable to perform subgroup analyses stratified by gallstone composition. Finally, even though we included many covariates in performing the multivariate regression analyses, there may still be some residual confounding. In view of these limitations, later multicenter investigations as well as observation of the occurrence

of gallstones over time in patients with higher LAP are needed to further evaluate and confirm our findings.

Conclusion

This study demonstrates that excessive LAP levels are linked to a greater risk of gallstones and that active weight management and lifestyle treatments may enhance or minimize the incidence of gallstones.

Abbreviations

BMI	Body mass index
WC	Waist circumference
LAP	Lipid accumulation products
NHANES	National Health and Nutrition Examination Survey
PIR	Poverty-to-income ratio
TG	Triglyceride

Acknowledgements

We would like to thank all participants in this study.

Authors' contributions

HW and QH designed the research. HW, XF, and XZ collected, analyzed the data, and drafted the manuscript. XZ revised the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This work did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Availability of data and materials

The NHANES data that support the findings of this study are openly available at <https://www.cdc.gov/nchs/nhanes/index.htm>.

Data availability

The survey data are publicly available on the internet for data users and researchers throughout the world (www.cdc.gov/nchs/nhanes/).

Declarations

Ethics approval and consent to participate

The NHANES protocol was approved by the NCHS Ethics Review Board, and informed consent was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 18 July 2024 Accepted: 9 September 2024

Published online: 16 September 2024

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