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Association of dietary phytosterols with prevalence of metabolic dysfunction-associated fatty liver disease in adult population of Northeastern China: An internet-based cross-sectional study

Jiayu Zhu[1,2#], Jiaqi Zhang[1,2#], Qi Yu[1,2], Liyan Liu[1,2*], Rennan Feng[1,2*]

Abstract

Objective: The benefits of phytosterols have attracted growing interest, but their association with Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD) has rarely been reported in population-based studies. This research aimed to investigate the correlation between dietary phytosterols and MAFLD. **Methods:** Phytosterols intake was evaluated using an internet-based dietary questionnaire targeted at the Chinese population. Conditional logistic regression models were employed to investigate dose-response relationships between phytosterol intake and MAFLD, as well as the potential preventive role of phytosterols. Restricted Cubic Spline (RCS) analyses were conducted to examine associations between phytosterols intake and MAFLD. Additionally, a quantile-based g-computation (qgcomp) method was applied to explore the combined effect of campesterol, stigmasterol, β-sitostelane, campestane, and β-sitosterol on MAFLD. **Results:** Significant inverse relationships were found between total phytosterols and MAFLD (OR, 0.19; 95% CI, 0.11-0.32; *P* < 0.001), campesterol (OR, 0.22; 95% CI, 0.13-0.37; *P* < 0.001), stigmasterol (OR, 0.17; 95% CI, 0.10-0.30; *P* < 0.001), β-sitostelane (OR, 0.26; 95% CI, 0.16-0.45; *P* < 0.001), campestane (OR,0.23; 95% CI, 0.14-0.39; *P* < 0.001), and β-sitosterol (OR, 0.17; 95% CI, 0.10-0.29; *P* < 0.001). The qgcomp analysis showed a significant negative association between the five phytosterols and MAFLD (OR, 0.58; 95% CI, 0.50-0.67; *P* < 0.001). Additionally, the qgcomp analysis revealed that the combination of these five phytosterols was inversely associated with MAFLD, with stigmasterol contributing the most (weight = 0.70). **Conclusion:** Higher intake of phytosterols was associated with a reduced prevalence of MAFLD, with stigmasterol showing the most significant inverse relationship. Further research is needed to clarify the relationship between phytosterols and MAFLD.

Keywords

phytosterols; metabolic dysfunction-associated fatty liver disease; Northeastern China

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[1]*Department of Nutrition and Food Hygiene, School of Public Health, Harbin Medical University, Harbin 150081, China*
[2]*Key Laboratory of Precision Nutrition and Health of Ministry of Education, School of Public Health, Harbin Medical University, Harbin 150081, China*

**Corresponding authors Rennan Feng, fengrennan@yeah.net; Liyan Liu, E-mail: yanziliu2100@163.com*
[#]*These authors contributed equally to this work.*

1 Introduction

Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD), previously referred to as Non-Alcoholic Fatty Liver Disease (NAFLD), has emerged as the primary cause of chronic liver disease and represents a significant global threat to human health[1]. MAFLD covers a range of liver diseases, from basic fat accumulation to non-alcoholic steatohepatitis, which can progress to cirrhosis and ultimately result in hepatocellular carcinoma[2-4]. The Global Burden of Disease study showed that MAFLD has become the fastest-growing global contributor to the disease burden from complications of chronic liver disease[5-7]. The documented prevalence of MAFLD was 30% in Western nations and ranged from 12% to 24% in Asian nations[8]. Additionally, research has shown an association between cold exposure and a higher prevalence of MAFLD[9].

Phytosterols, considered a fundamental component of plant cell membranes, are commonly present in seeds, nuts, and oils derived from them[10]. Phytosterols and plant stanols are recognized as natural dietary components that effectively disrupted the process of absorbing cholesterol in the intestines[11]. Evidence suggests that the daily use of phytosterols and plant stanols can reduce blood cholesterol levels by approximately 10%[12]. Animal studies have shown that the ingestion of phytosterols effectively reduces hepatic triacylglycerol and total cholesterol levels[13]. Additionally, phytosterols reduce the expression levels of uncoupling protein, transforming growth factor-β, and tumor necrosis factor (TNF)-α, while concurrently elevating the expression of liver X receptor-alpha[14-15]. Since phytosterols are not produced by the human body, their levels in the blood have been utilized to assess the activity of cholesterol transporters in the liver and intestines[16]. Recent research has found that phytosterols can improve metabolic-related liver disorders[17-18].

A longitudinal investigation was undertaken across multiple centers in China to examine the prevalence of MAFLD in different regions. The multivariate regression analysis indicated that the prevalence of MAFLD in Northeastern China was nearly double that found in Southern China[19]. The epidemiological research revealed that the likelihood of developing MAFLD increased during the winter season, regardless of other factors[20]. Compared with the south, the winter in the north lasted longer and the average temperature was lower, which greatly affects the MAFLD prevalence rate among the population in the north[21]. Hence, this study chose to use a sample from the northeast region of China.

Currently, there is a lack of population-based research on dietary phytosterols and MAFLD. Therefore, the goal of this study was to explore the relationship between the intake of phytosterols, including stigmasterol, campesterol, β-sitostanol, campestanol, β-sitosterol, and the risk of MAFLD in Northeastern China.

2 Methods

2.1 Study population

2.1.1 Subjects and exclusion criteria

Data were collected using a validated internet-based dietary questionnaire for the Chinese population (IDQC)(www.yyjy365.org/diet)[22-24]. This study was a cross-sectional study that included a total of 14, 884 individuals. The subjects were recruited from Northeastern China between March 2014 and June 2023. Internet-based nutritional surveys, due to their online nature, proved to be more efficient than traditional methods, resulting in improved data quality, reduced costs, and higher response rates[25]. Online informed consent was obtained from all participants, after which the IDQC collected data on food intake, demographic information, and the prevalence of Chronic Metabolic Diseases (CMDs).

The final sample included 1520 participants (304 cases and 1216 controls) who were subjected to statistical analysis. The exclusion criteria were as follows: (1) participants under 18 years of age, pregnant women, participants with extreme daily energy intake (< 600 kcal/d for all, > 4000 kcal/d for females, and > 4200 kcal/d for males), and participants not residing in Northeastern China; (2) participants for whom it was not possible to determine whether they had MAFLD or whose dietary intake of phytosterols deviated from the mean by more than two standard deviations. Based on age and gender, cases were matched with healthy controls at a 1 ： 4 ratio (Fig. 1).

This research received approval from the Ethics Committee of Harbin Medical University (HMUIRB2019006PRE) and was conducted with the explicit consent of all participants, in full compliance with the ethical standards set forth in the Declaration of Helsinki.

2.1.2 Ascertainment of NAFLD/MAFLD

MAFLD is diagnosed when hepatic steatosis coexists with either type 2 diabetes, overweight/obesity, or at least two metabolic risk factors. These risk factors include abdominal obesity, hypertension, dyslipidemia, prediabetes, insulin resistance (HOMA-IR ≥2.5), or elevated high-sensitivity C-reactive protein (hs-CRP > 2 mg/L)[26].

2.2 Statistical Analysis

The chi-square test was used to evaluate the significance of frequency differences in categorical data, while One-way Analysis of Variance (ANOVA) or Student's *t*-test was employed to compare the mean values of continuous variables.

Odds Ratios (OR) and 95% confidence intervals (95% CI) for the association between dietary phytosterol consumption and MAFLD were derived using a conditional logistic regression model. To assess the potential non-linear relationship between phytosterol consumption and MAFLD, the Restricted Cubic Spline (RCS) model was applied. The quantile g-computation (qgcomp) method was used to evaluate the combined effect of five dietary phytosterols on the likelihood of developing MAFLD[27]. Only dietary phytosterols with an estimated weight exceeding 0.05 were included in the qgcomp score.

The above analyses were performed using R (version 4.4.0). Conditional logistic regression, RCS, and qgcomp models were constructed using the survival, RMS, and qgcomp packages, respectively. All models were adjusted for energy intake, age, gender, BMI, alcohol consumption, smoking, work intensity, education level, and income.

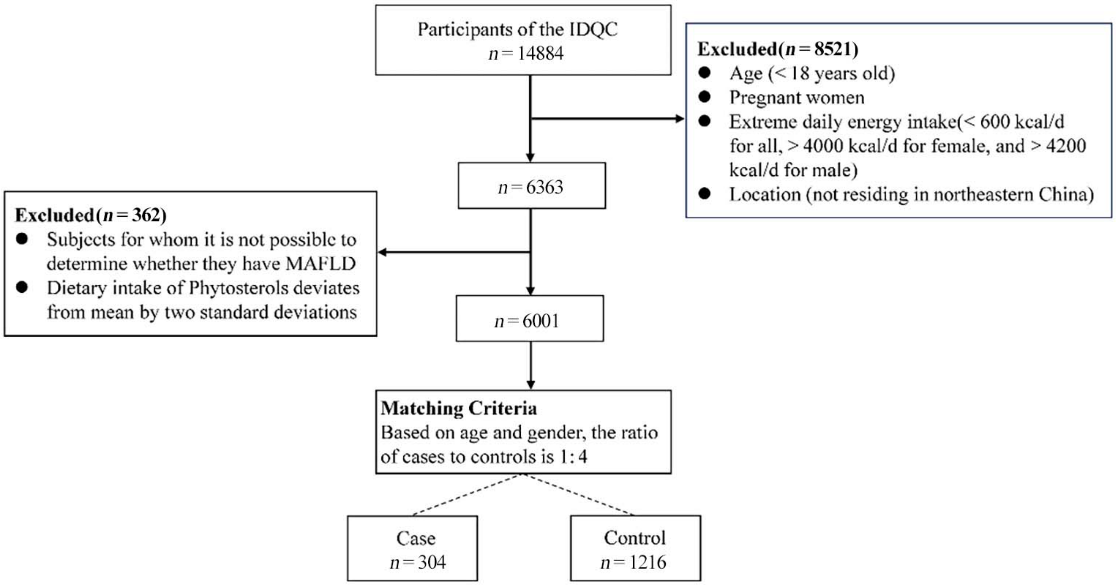

Fig. 1 Screening flowchart of research subjects

3 Results

3.1 Demographic information of participants

This study included 304 MAFLD patients and 1216 healthy controls, totaling 1520 subjects. The demographic characteristics and nutrient intake of the study participants are shown in Table 1. Compared to the healthy control group, the MAFLD group exhibited statistically significant differences in BMI, education level, work intensity, and monthly income (P < 0.05). Statistical analysis revealed no significant differences in the consumption of dietary energy and carbohydrates (P > 0.05); however, significant differences were observed in energy intake (P < 0.05). The MAFLD group consumed significantly less total phytosterols, β-sitosterol, campesterol, stigmasterol, β-sitostelane, and campestane compared to the healthy control group (P < 0.05).

3.2 Relationship between phytosterols and MAFLD

The control group was defined as the lowest consumption quartile (Q1) in Fig. 2. This study showed that higher consumption of phytosterols, including total phytosterols, campesterol, stigmasterol, β-sitostelane, campestane and β-sitosterol, was associated with a reduced incidence of MAFLD. Additionally, a dose-response relationship was observed between MAFLD and campesterol, stigmasterol, and β-sitosterol. The prevalence of MAFLD was lower in the Q4 group [OR (95% CI) 0.22 (0.13-0.37), 0.17 (0.10-0.30), and 0.17 (0.10-0.29), respectively; all P < 0.001]. Compared to Q1, there was no significant association between β-sitostelane and MAFLD in Q2, whereas a significant association was found

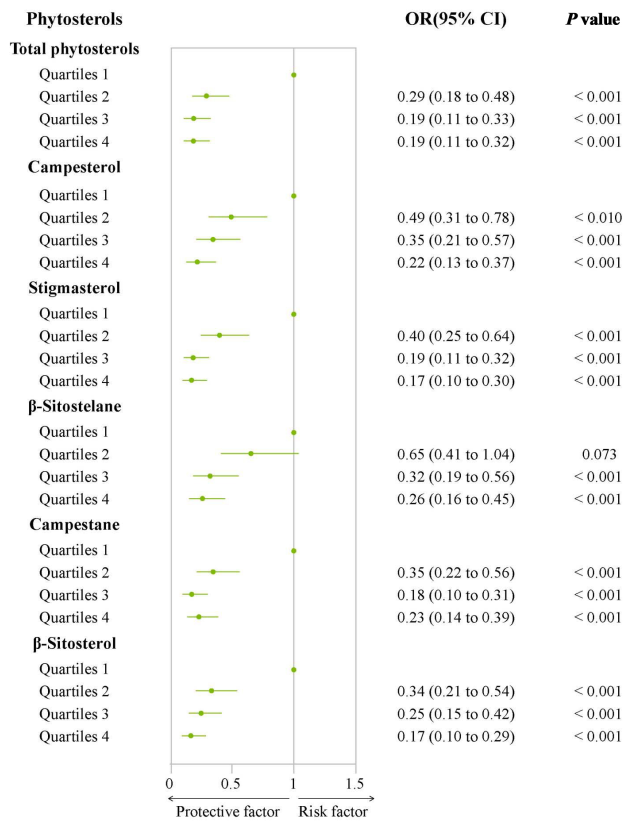

Fig. 2 Multivariable-adjusted odds ratios (OR) and 95% confidence intervals (CI) for MAFLD by quartile of phytosterols dietary intake

All models were adjusted for energy intake, age, gender, BMI, alcohol consumption, smoking, work intensity, education level, and income.

Table 1 Basic demographic information and nutrients intake of the subjects

Variable	Control (*n* = 1216)	MAFLD (*n* = 304)	*P* value
Demographic factors			
Age, year	53.01 ± 12.59	52.98 ± 12.57	0.97
Male, *n* (%)	456 (37.50)	114 (37.50)	
Female, *n* (%)	740 (66.07)	185 (66.07)	
BMI, kg/m^2	24.11 ± 2.96	27.22 ± 3.59	< 0.01
Smoking, (%current)	164 (13.49)	30 (9.87)	0.11
Drinking, (%current)	191 (15.71)	25 (8.22)	< 0.01
Income per month, Yuan, *n* (%)			< 0.01
< 1000	221 (18.17)	52 (17.11)	
1000-2000	296 (24.34)	58 (19.08)	
2000-3000	359 (29.52)	77 (25.33)	
3000-4000	192 (15.79)	42 (13.82)	
4000-5000	88 (7.24)	27 (8.88)	
5000-6000	33 (2.71)	26 (8.55)	
> 6000	27 (2.22)	22 (7.24)	
Education levels, *n* (%)			< 0.01
Junior school and below	533 (43.83)	94 (30.92)	
Senior high school or equivalent	257 (21.13)	78 (25.66)	
College or equivalent	399 (32.81)	117 (38.49)	
Postgraduate or above	27 (2.22)	15 (4.93)	
Work intensity, *n* (%)			
Light	780 (64.14)	249 (81.91)	<0.001
Medium	168 (13.82)	31 (10.20)	
Heavy	268 (22.04)	24 (7.89)	
Dietary factors			
Energy, kcal/day	2150.37 ± 773.51	2072.02 ± 707.80	0.11
Protein, g/day	80.46 ± 14.75	82.75 ± 16.68	< 0.05
Fat, g/day	66.00 ± 20.75	62.38 ± 19.75	< 0.01
Carbohydrates, g/day	311.41 ± 52.13	318.08 ± 46.88	< 0.05
β-Sitosterol, mg/day	629.26 ± 548.63	453.11 ± 553.48	< 0.01
Campesterol, mg/day	63.20 ± 44.14	48.76 ± 43.94	< 0.01
Stigmasterol, mg/day	60.99 ± 37.88	44.61 ± 39.16	< 0.01
β-Sitostelane, mg/day	65.69 ± 75.18	48.66 ± 70.32	< 0.01
Campestane, mg/day	164.43 ± 193.50	120.61 ± 179.37	< 0.01
Total phytosterols, mg/day	1009.44 ± 813.08	725.43 ± 846.66	< 0.01

The *P* values were determined using the Chi-squared test for categorical variables, Student's *t*-test for continuous variables. Data were expressed as mean ± SD, and as frequencies and percentages where appropriate; MAFLD: non-alcoholic fatty liver disease.

in the Q4 group [OR (95% CI) 0.26 (0.16-0.45), $P < 0.001$]. Campestane had the most significant effect in the Q3 group [OR (95% CI) 0.18 (0.10-0.31), $P < 0.001$]. The RCS model analysis showed that the intake levels of total phytosterols, campesterol, stigmasterol, β-sitostelane, campestane, and β-sitosterol were significantly associated with the risk of MAFLD ($P < 0.05$), demonstrating a significant non-linear relationship ($P < 0.05$)(Fig. 3).

Using qgcomp regression analysis to assess the combined association of the five phytosterols with MAFLD (Fig. 4), the mixture of the five phytosterols was significantly negatively associated with MAFLD [OR (95% CI) 0.58 (0.50-0.67), $P < 0.001$]. Qgcomp regression analysis also revealed the weights of each phytosterols in the qgcomp index. In the negative direction, the weights of stigmasterol, β-sitosterol, campesterol, campestane, and β-sitostelane were 0.70, 0.23, 0.04, 0.02, and 0.01, respectively (Fig. 4).

4 Discussion

This study used an online questionnaire to investigate the associations between phytosterol consumption and the occurrence of MAFLD in a northeastern Chinese population. The results showed that the intake of five specific phytosterols was associated with a reduced risk of MAFLD. Notably, the incidence of MAFLD decreased with increasing doses of β-sitosterol, campesterol, and stigmasterol, with stigmasterol showing the most favorable effect.

The findings indicated a significant correlation between phytosterol consumption and a reduced prevalence of MAFLD. The

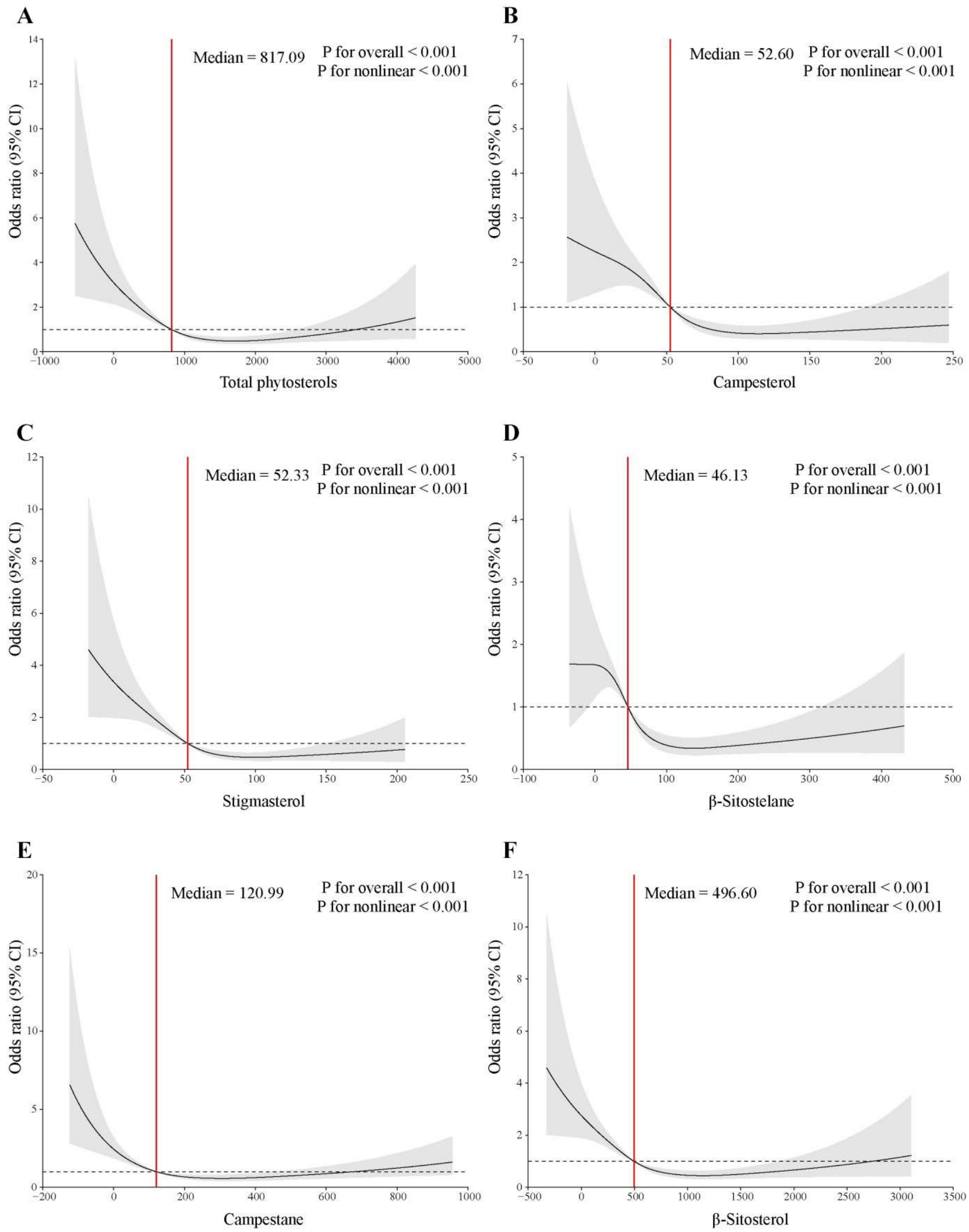

Fig. 3 Restricted multivariable cubic spline plots illustrating the association between phytosterols intake and the risk of MAFLD

(A) Total phytosterols; (B) Campesterol; (C) Sigmasterol; (D) β-Sitostelane; (E) Campestane; (F) β-Sitosterol. All models were adjusted for energy intake, age, gender, BMI, alcohol consumption, smoking, work intensity, education level, and income.

development of MAFLD is primarily driven by lipid-induced inflammation. Phytosterols may reduce lipid molecules, thereby inhibiting the progression of MAFLD[28]. A cross-sectional study demonstrated that increased phytosterol intake was associated with a lower body mass index, reduced serum cholesterol, and a decreased prevalence of overweight/obesity and abdominal obesity among Chinese individuals[29]. Additionally, a randomized controlled trial confirmed that phytosterol-enriched rapeseed oil supplements significantly alleviated hepatic steatosis in obese patients[30]. A study investigating lipid reduction found that participants with higher campesterol levels had a lower incidence of cardiovascular disease in the absence of lipid-lowering medica-

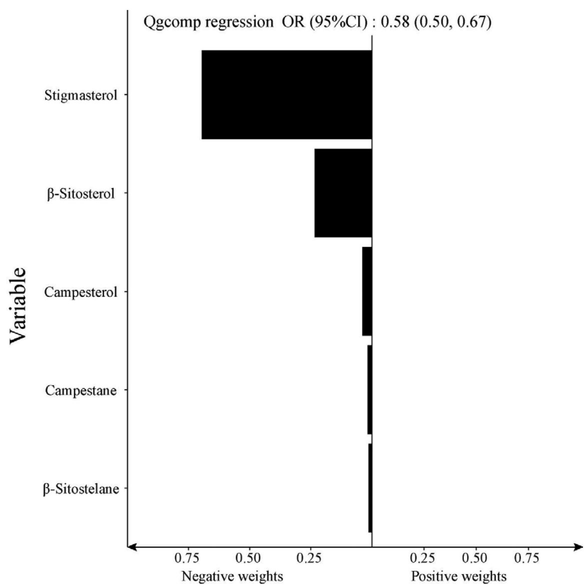

Fig. 4 Qgcomp model regression index weights for each phytosterol in relation to MAFLD

The model was adjusted by energy intake, age, gender, BMI, alcohol consumption, smoking, work intensity, education levels, and income.

tions[31]. Previous animal studies have confirmed the role of phytosterols in lowering blood cholesterol levels, modifying fat processing, and reducing the severity of NAFLD/MAFLD in mice fed a high-fat diet[32]. An experiment conducted on Wistar rats demonstrated the preventive effect of phytosterols on non-alcoholic liver steatosis. Furthermore, two clinical trials employing a double-blind, placebo-controlled design supported the adjuvant role of phytosterols in managing MAFLD[33-34].

The findings indicated that stigmasterol and β-sitosterol had a notable influence on MAFLD, as evidenced by their respective negative weights of 0.70 and 0.23 in the qgcomp regression analysis. The primary impact of stigmasterol on MAFLD can be explained by the following mechanisms. Stigmasterol, a type of phytosterol, exhibited antioxidant, anti-inflammatory, and anti-hyperlipidemic effects[35]. Both animal and clinical studies have confirmed that stigmasterol can lower cholesterol levels and reduce several inflammatory markers[36]. Additionally, stigmasterol can alleviate steatohepatitis by enhancing alternative pathways of bile acid production[37]. Furthermore, extensive research has suggested that β-sitosterol can effectively prevent hepatic steatosis by inhibiting c-Jun N-terminal kinases and the IKKβ/NF-κB signaling pathway[38-39], which reduces the quality of fatty tissue and limits the formation of precursor fat cells. Moreover, β-sitosterol competes with cholesterol at the cholesterol receptor binding site, inducing beneficial conformational changes[40]. In conclusion, both stigmasterol and β-sitosterol may exert a positive effect on MAFLD by regulating cholesterol production, breakdown, and elimination.

Due to the influence of agricultural traditions, climate, dietary culture, and the market economy, the population in Northeastern China may have a higher intake of soybeans and nuts compared to the southern region[41-42]. As a result, the northeastern population might consume more phytosterols than their southern counterparts. This study suggests that dietary phytosterols may have the potential to reduce the prevalence of MAFLD. Therefore, promoting higher phytosterol intake could be beneficial to health. While dietary phytosterols were associated with a lower risk of MAFLD, further studies are needed to confirm the practical benefits and feasibility of incorporating phytosterols into regular diets[33,43]. Additionally, more research is required to explore how dietary phytosterols impact the progression of MAFLD and their interactions with other nutritional and lifestyle factors.

This is the first study to show that higher phytosterol intake is associated with a lower incidence of MAFLD in the Chinese population. Furthermore, these findings are consistent with previous research highlighting the protective effects of dietary phytosterol on metabolic liver disease. However, this study has several limitations. First, the cross-sectional and retrospective method limits the ability to demonstrate a causal relationship between dietary phytosterol and the risk of MAFLD, highlighting the need for further studies. Second, the prevalence of MAFLD may have been understated due to the reliance on self-reported data.

5 Conclusion

A significant inverse relationship was found between phytosterol consumption and the incidence of MAFLD in northeast China, with stigmasterol showing the most pronounced protective effect. Identifying these associations can inform targeted public health strategies to potentially reduce the risk of MAFLD and promote healthier dietary habits in the population of this region.

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Research ethics

This study was approved by the Ethics Committee of Harbin Medical University (HMUIRB2019006PRE).

Informed consent

Informed consent was obtained from all individuals included in this study, or their legal guardians or wards.

Author contributions

Feng R N and Liu L Y conceived the study design. Zhu J Y wrote the manuscript. Zhang J Q did the statistical analysis. Yu Q handled the data acquisition. All authors approved the final version of the manuscript.

Use of Large Language Models, AI and Machine Learning Tools

None declared.

Conflict of interest

The authors declare that they have no competing interests.

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Data availability

The data are available from the corresponding author upon reasonable request.

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