Research Article

Intakes of magnesium, calcium and risk of fatty liver and prediabetes: Results from the Third National Health and Nutrition Examination Survey Cohort

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Abstract

Objective: Obesity and insulin resistance play important roles in the pathogenesis of nonalcoholic fatty liver disease (NAFLD). Intake of magnesium is linked to a reduced risk of metabolic syndrome and insulin resistance, people with NAFLD or alcoholic liver disease are at high risk of magnesium deficiency. The purpose of this study was to investigate whether intakes of magnesium and calcium were associated with risk of fatty liver disease and prediabetes by alcohol drinking status.

Design: We analyzed the association between calcium or magnesium intake and fatty liver disease, prediabetes or both prediabetes and fatty liver disease in a cross-sectional analysis.

Setting: The Third National Health and Nutrition Examination Survey (NHANES III) follow-up US adults cohort.

Subjects: A nationally representative sample of US adults in NHANES including 13,489 participants was enrolled in this study.

Results: After adjusting for potential confounders, we found that intake of magnesium was associated with approximately 30% reduced odds of fatty liver disease and prediabetes comparing the highest intake quartile versus the lowest. Magnesium intake may only be related to reduced odds of fatty liver disease and prediabetes in those whose calcium intake was less than 1200 mg per day. Magnesium intake may also only be associated with reduced odds of fatty liver disease among those alcohol drinkers.

Conclusion: This study suggests that high intake of magnesium may be associated with reduced risks of fatty liver disease and prediabetes. Further large studies, particularly prospective cohort studies, are warranted to confirm the findings.

Key Words: magnesium, calcium, fatty liver disease, prediabetes

Introduction

All-cause cirrhosis and cancer of the liver are two of the four top leading causes of death from gastrointestinal and liver diseases in United States[1]. Globally, the mortality rate from cirrhosis and cirrhosis-related diseases has increased over the past 35 years[2]. A large portion of liver cirrhosis and cancer are caused by nonalcoholic fatty liver disease (NAFLD), and alcoholic liver disease[3]. NAFLD is the most common liver disease in the world[4–6], which includes a spectrum of liver injury ranging from steatosis to severe steatohepatitis that can progress to fibrosis, cirrhosis, liver failure, or even liver cancer[7]. Unlike alcoholic liver disease which is caused by chronic heavy alcohol use, the etiology of NAFLD is not clear but may include obesity, type 2 diabetes, use of drugs, and exposure to toxic substances[8–10]. NAFLD is considered a feature of metabolic syndrome[11].

Magnesium may be a factor that is related to the etiology of both alcoholic liver disease and NAFLD. People who chronically drink heavy amounts of alcohol are at high risk of magnesium deficiency[12] and prolonged exposure to alcohol leads to a substantial reduction in magnesium homeostasis in the liver[13]. Furthermore, as many as 50% of type 2 diabetic patients have hypomagnesaemia[14]. As such, one previous study found serum magnesium levels were significantly lower in patients with either alcoholic or non-alcoholic liver steatosis[15]. A meta-analysis of randomized trials indicates magnesium supplementation improves insulin resistance in patients with type 2 diabetes[16]. Magnesium intake has also been linked to a reduced risk of metabolic syndrome[17] and type 2 diabetes[18,19]. Very recently, we reported that high intakes of magnesium may be associated with a reduced risk of mortality due to liver disease particularly among alcohol drinkers and those with hepatic steatosis[20].

In this study, we examined whether the intake of magnesium was associated with the prevalence of fatty liver disease or prediabetes. Although previous studies have examined the association between intake of calcium and type 2 diabetes[21], few studies have examined the role of calcium intake in association with prediabetes[22]. Our recent studies indicate that calcium intake may interact with magnesium intake in relation to diseases of gastrointestinal tract (GI), such as colorectal adenoma[23], adenoma recurrence[24], reflux esophagitis, Barrett's esophagus[25] and other chronic disease[26]. Thus, we hypothesize that intake of calcium may also be related to risk of fatty liver disease and prediabetes.

To test these novel hypotheses and to examine whether these associations differ by alcohol drinking status, we analyzed the data from the Third National Health and Nutrition Examination Survey (NHANE III) follow-up cohort.

METHODS

Study Population

The NHANES III was conducted in the United States from 1988 through 1994 by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC). The investigation was approved by the institutional review board of the CDC, and all participants provided informed consent. It was conducted in two phases, each of which comprised a national probability sample. In total, 39,695 participants were selected from a complex multistage, stratified, clustered probability sample representative of the civilian, noninstitutionalized population. 33,994 (86%) were interviewed in their homes. All interviewed participants were invited to the mobile examination center (MEC) for a medical examination. In our study, we excluded 15,169 participants younger than 20 years old. We also excluded 2,210 participants with (1) a physician's diagnosis of diabetes, (2) glycolated hemoglobin (HbA1c) ≥6.5%, or (3) fasting glucose ≥ 126 mg/dL. 2,178 Participants did not complete dietary or supplemental intakes assessment, 948 participants with no information of fatty liver disease or prediabetes were not included in the study. As a result, 13,489 participants were included in the final analysis.

Classification of key health outcomes

(1) Fatty liver disease: The ultrasound examination was recorded using a Toshiba Sonolayer SSA-90A and Toshiba video recorder among participants aged 20 to 74 years in NHANES III between 1988 and 1994. In 2009-2010, archived gall bladder ultrasound video images were reviewed to assess the presence of fat within the hepatic parenchyma using standard criteria. Followed by the five criteria (liver to kidney contrast; brightness of the liver parenchyma; deep beam attenuation; echogenic walls in the small intrahepatic vessels; the definition of the gallbladder walls), hepatic steatosis (HS) was categorized as normal, mild, moderate, or severe. In order to avoid potential overlap between mild and moderate hepatic steatosis, a categorization of fatty liver disease as "yes" or "no" was generally used. "Yes" indicated moderate or severe hepatic steatosis, while "No" indicated the liver was normal or had mild hepatic steatosis[(27)].

(2) Prediabetes cases: According to American Diabetes Association (ADA), prediabetes meets the following criteria: (i) no diagnosis of diabetes from a doctor, and (ii) fasting plasma glucose level between 100 and 125 mg/dl or HbA1c between 5.7% and 6.4%[(28)].

(3) Both prediabetes and fatty liver disease cases: Have (1) and (2).

(4) Controls: Those who had neither fatty liver disease nor prediabetes were regarded as controls.

Nutrient intake assessments

Detailed dietary and supplemental intakes including magnesium and calcium were derived from a single 24-hour dietary recall and a 30-day supplemental interview which participants completed at the examination center. For this analysis, only dietary recall data which was determined by NHANES to be "reliable (i.e. the individual food files contain records only for participants with complete intake records that were considered to be reliable)" was used. The total intake of these nutrients was calculated by summing up the magnesium and calcium intakes from the dietary and supplemental intakes.

Covariates

We considered a number of factors as potential confounding factors and these include: age (years), sex (men and women); race and ethnicity (non-Hispanic whites, non-Hispanic blacks, and other); educational attainment (lower than high school education, high school diploma, and college graduate or above); ratio of poverty to income (PIR:≤1, 1-3, and > 3); cigarette smoking status (never, former, and current); alcohol drinking status (never alcohol drinker: had less than 12 drinks of any kind of alcoholic beverage in entire life; former alcohol drinker: had more than 12 drinks of any kind of alcoholic beverage in entire life but in the past 12 months had less than 12 drinks of any alcoholic beverage; current alcohol drinker: had more than 12 drinks of any kind of alcoholic beverage in entire life and in the past 12 months had at least 12 drinks alcohol), physical activity status (yes: "have done one or more activities in the past month: jogging/running, swimming, riding a bicycle, aerobics activity, garden/yard work or other activity"; no: "no activity was done in the past month"), body mass index (BMI; kg/m^2), waist to hip ratio, daily intakes of total energy (kcal/day), calcium (mg/day), magnesium (mg/day), use of calcium supplements (yes or no), and use of magnesium supplements (yes or no).

Statistical analysis

All analyses were performed using Survey package in SAS 9.4 software (SAS Institute, Cary, NC, USA) to account for the applicable weighting in the multistage clustered, probability sampling design in the NHANES III cohort. Covariates were compared between cases and controls to evaluate potential confounding factors using Rao-Scott chi-square test for categorical data and Survey regression models for continuous variables. Survey logistic regression models with fatty liver disease or prediabetes or both prediabetes and fatty liver disease as the dependent variable were used to analyze the association between calcium or magnesium intake and fatty liver disease or prediabetes or both prediabetes and fatty liver disease adjusting for potential confounders. Total calcium or magnesium intake was included in the models as categorical variables, using quartiles based on the controls' distribution. To assess the linear trend in the odds of calcium or magnesium quartile, the median value for each quartile was entered into the logistic regression model as an ordinal variable. Stratified analyses by gender (men or women), calcium:magnesium ratio (<2.6, ≥2.6: to be consistent with our previous studies, the cutpoint of 2.6 was used(24)), daily calcium intake (<1200 mg or ≥1200 mg), alcohol drinking status (never, former, or current alcohol drinker) were conducted. All reported P values were two-sided with statistical significance evaluated at 0.05.

Results

We compared demographic characteristics and potential confounding factors of cases with fatty liver disease, cases with prediabetes and cases with both prediabetes and fatty liver disease to normal controls (Table 1). Compared to controls, cases were older and were more likely to be men, former smokers, former alcohol drinkers, non-Hispanic black, and to have lower educational attainment, higher poverty, and higher BMI (body mass index). Cases with prediabetes consumed lower levels of calcium and magnesium compared to controls.

After adjusting for potential confounders, we found that intake of calcium was not related to odds of fatty liver disease, prediabetes and both prediabetes and fatty liver disease. On the other hand, we found that intake of magnesium was associated with approximately 30% reduced odds of fatty liver disease (p for trend, 0.05) and prediabetes (p for trend, 0.02). The association pattern was similar between intake of magnesium and risk of both prediabetes and fatty liver disease although not statistically significant (Table 2).

In stratified analyses, we found that the intake of calcium was marginally associated with increased odds of fatty liver disease among women (Table 3). Also, the intake of calcium may be related to increased odds of prediabetes among those with a calcium:magnesium ratio ≥2.6, and an odds ratio (OR) of 1.98 (95% confidence interval =1.07-3.67) for the highest quartile intake vs. the lowest. In the stratified analysis, no significant association was found by drinking status (p for trend >0.05). None of the interactions were statistically significant.

The inverse association between the intake of magnesium and risk of prediabetes was only significant among those with a calcium:magnesium intake ratio≥2.6 (Table 4). However, the p for interaction were not statistically significant (Table 4). On the other hand, there is a significant interaction between magnesium intake and calcium intake (p for interaction, 0.04) in relation to odds of prediabetes. It appears that the intake of magnesium may only be related to the reduced odds of fatty liver disease (p for trend, 0.04) and prediabetes (p for trend, 0.09) when the intake of calcium < 1200 mg per day. In the stratified analysis according to alcohol drinking status, we found that the intake of magnesium may be associated with reduced odds of fatty liver disease only among former drinkers (p for trend, 0.04) and current drinkers (p for trend, 0.04). However, p for interaction was not statistically significant. We did not find the association between intake of magnesium and risk of fatty liver and prediabetes differed by gender.

Discussion

In this NHANES III cohort, a nationally representative sample of the US general population, we found that the intake of calcium was overall not associated with the odds of fatty liver disease, prediabetes or both. On the other hand, we found that the higher intake of magnesium is significantly associated with lower odds of fatty liver disease and prediabetes. Due to limited sample sizes in stratified analyses, we consider the stratified analyses as exploratory. In the stratified analysis, the only significant interaction was between magnesium intake and calcium intake (p for interaction, 0.04) in relation to odds of prediabetes. None of the other interactions were statistically significant. We found that the inverse association between magnesium intake and prediabetes primarily appeared in those with a calcium intake <1200 mg per day; and in the same subgroup, intake of magnesium was also significantly related to a reduced odds of fatty liver disease. We also found magnesium intake was only related to reduced odds of fatty liver disease among former and current alcohol drinkers.

Our findings of an inverse association between the intake of magnesium and prediabetes is consistent with that of previous studies which have shown that high magnesium intake is associated with a reduced risk of type II diabetes(18,29,30), metabolic syndrome(17,31), insulin resistance(32) and prediabetes(33). Furthermore, we found an inverse association between the intake of magnesium and the risk of fatty liver disease. This finding was not consistent with a null association found in a previous study(34). However, the cross-sectional study conducted in Canadians had a very small sample size, which may have limited the power to detect an association. We also found that the inverse association between the intake of magnesium and fatty liver disease primarily appeared in alcohol drinkers. Although novel, this finding is consistent with the observation that heavy alcohol drinkers are at high risk of magnesium deficiency(12). Future large-scale studies are needed to confirm the findings. This is important because previous studies have found that alcohol caused a substantial reduction in magnesium homeostasis in the liver[13]. It was reported by the National Health and Nutrition Examination Survey (NHANES), 1999–2000, that 79% of US adults do not meet the Recommended Dietary Allowance for magnesium[26]. One study observed that serum concentrations of magnesium were significantly reduced in patients with either alcoholic or non-alcoholic liver steatosis[31].

In a cohort study, the investigators found that intake of magnesium was associated with a reduced risk metabolic syndrome[35]. Magnesium intake was also inversely associated with individual components of metabolic syndrome, particularly fasting glucose level, waist circumference, and high-density lipoprotein cholesterol. Thus, the inverse association between the intake of magnesium and metabolic syndrome is likely mediated through waist circumference or waist to hip ratio. Similarly, in our study, after additionally adjusting for waist to hip ratio, the significant associations disappeared. As such, waist to hip ratio may serve as a pathway to the relationship between magnesium intake and the disease outcomes (i.e. fatty liver disease and/or prediabetes) or it could be an over-adjustment.

In the stratified analyses, we found intake of magnesium may be more significantly related to reduced odds of prediabetes and fatty liver disease when calcium intake was less than 1200 mg per day. This finding suggests that the beneficial effect of magnesium may be suppressed when calcium intake is higher than Dietary Reference Intakes. This finding is consistent with our recent finding indicating that calcium intake may interact with magnesium intake in relation to risks of multiple common diseases[23–26]. Some[36–38], but not all[39], previous human studies indicate that high calcium intake may affect the absorption rate of magnesium. It is known that over 80% of plasma magnesium is ultrafiltrated and reabsorbed in the kidneys. Thus, kidney reabsorption plays a key role in regulating magnesium homeostasis(40). Likewise, 10 g of calcium are filtered daily on average, of which 98% is reabsorbed in the kidneys(41,42). Thus far, clinical trials consistently found that high calcium intake leads to significantly increased excretion of magnesium in the urine(40,43,44). Thus, it is likely that high intake of calcium may lead to relative deficiency of magnesium. We also found magnesium intake may only be associated with reduced odds of fatty liver disease among former and current drinkers. This finding is possible because alcohol drinkers are at high risk of magnesium deficiency(12). However, further large studies studies, particularly longitudinal studies are necessary to replicate the findings.

A strength of our study is that it is based on NHANES, a population-based study with a nationally representative sample. However, although multiple 24-hour dietary recalls are used as a gold standard measure in nutritional epidemiologic studies, a one-time 24-hour dietary recall used in the current study may not have adequately captured long-term dietary intakes of magnesium and calcium. Since inter-day variation in intakes of magnesium and calcium is random, any residual inter-day variation in the current study would lead to non-differential misclassification, which usually biases the result to the null. Thus, the true association between intakes of magnesium and calcium and risk of prediabetes and fatty liver disease may be stronger than what we have observed. We cannot eliminate the possibility that the associations with intakes of magnesium and calcium are due to residual confounding factors or healthy lifestyle in general. However, we have adjusted for physical activity, and BMI as well as total energy intake. Furthermore, in the same analysis, we found the associations of calcium and magnesium are in opposite directions. Thus, it is unlikely our findings are due to confounding by healthy lifestyle in general because those who possess healthy behaviors are likely to use calcium supplements. Finally, like all cross-sectional studies, the temporal sequence for the associations are not clear. However, the inverse association between intake of magnesium and risk of prediabetes is consistent with the associations between magnesium with insulin resistance[16], metabolic syndrome[17,31]and type 2 diabetes[18,19].

In conclusion, our findings suggest that the high intake of magnesium may be associated with lower odds of having fatty liver disease and prediabetes, whereas the high intake of calcium was overall not related to the risk. The associations may primarily appear in those whose calcium intake was less than 1200 mg per day. Further studies, particularly prospective cohort studies, are warranted to confirm or refute the findings.

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Table 1 Baseline demographic and selected risk factors by the status of **disease,** the Third National Health and Nutrition Examination Survey (NHANES III) [a,b]

Characteristics	**Controls (n=6,399)**	**Fatty Liver Disease Cases (n=2,423)**		**Prediabetes Cases (n=5,818)**		**Prediabetes & Fatty Liver Disease Cases (n=1,511)**	
	Value	**Value**	***p*-value[c]**	**Value**	***p*-value[d]**	**Value**	***p*-value[e]**
Age at Screening (years), Mean (SD)	37.8 (0.4)	45.6 (0.5)	<0.0001	51.3 (0.6)	<0.0001	49.3 (0.7)	**<0.0001**
Gender, %			<0.0001		<0.0001		**<0.0001**
Male	2625 (43.3)	1270 (54.7)		3005 (55.4)		646 (59.6)	
Female	3774 (56.7)	1153 (45.3)		2548 (44.6)		505 (40.4)	
Race/Ethnicity, %			0.02		<0.0001		**<0.0001**
Non-Hispanic White	2592 (78.9)	877 (75.7)		2201 (71.9)		363 (69.7)	
Non-Hispanic Black	1737 (9.0)	525 (8.5)		1732 (14.1)		297 (11.5)	

Other	2070 (12.1)	1021 (15.8)		1620 (14.0)		491 (18.8)	
Educational Attainment, %			<0.0001		<0.0001		**<0.0001**
Less Than High School Graduate	1841 (17.7)	1008 (27.3)		2330 (30.3)		524 (33.3)	
High School Graduate	2179 (34.3)	730 (35.6)		1587 (33.9)		327 (34.7)	
Some College or Above	2248 (48.0)	599 (37.1)		1394 (35.8)		245 (32.0)	
Income-to-poverty ratio (PIR) , %			0.04		0.001		**0.02**
≤1	1283 (11.2)	566 (13.9)		1195 (14.0)		279 (15.0)	
1-3	2707 (40.8)	1035 (43.2)		2324 (43.0)		493 (45.1)	
>3	1933 (48.0)	604 (42.9)		1456 (43.0)		267 (39.9)	
Body Mass Index (kg/m^2), Mean (SD)	25.0 (0.1)	29.8 (0.3)	<0.0001	27.5 (0.1)	<0.0001	31.0 (0.3)	**<0.0001**
Smoking status, %			<0.0001		<0.0001		**<0.0001**

No smoker	3373 (48.3)	1127 (42.3)		2543 (41.5)		503 (37.5)	
Former smoker	1171 (21.1)	664 (31.4)		1527 (29.3)		354 (36.8)	
Current Smoker	1855 (30.6)	632 (26.3)		1482 (29.2)		294 (25.6)	
Alcohol drinking status, %			0.001		<0.0001		**0.0009**
No drinker	987 (11.4)	366 (12.4)		954 (13.9)		169 (13.7)	
Former drinker	1973 (27.7)	813 (33.3)		2074 (36.1)		431 (36.0)	
Current drinker	3323 (61.0)	1190 (54.4)		2358 (50.0)		532 (50.4)	
Physical activity last month, yes (%)	5302 (88.4)	1857 (83.9)	<0.0001	4193 (82.4)	<0.0001	866 (81.1)	**0.0002**
Daily nutrients intake, mean (SD)							
Total energy (kcal)	2282.9 (25.4)	2259.5 (36.7)	0.56	2149.3 (26.0)	0.0001	2230.7 (41.6)	0.25
Total calcium (mg)	886.9 (14.3)	882.5 (24.7)	0.84	827.5 (16.0)	0.001	837.1 (29.7)	0.09

Calcium from dietary (mg)	861.9 (14.2)	858.1 (23.6)	0.86	806.4 (15.5)	0.002	817.9 (28.4)	0.12
Calcium from supplement (mg)	175.9 (7.1)	171.0 (17.6)	0.79	172.7 (8.3)	0.76	167.7 (23.0)	0.73
Total magnesium (mg)	325.1 (3.8)	323.7 (6.1)	0.83	314.4 (3.1)	0.01	317.4 (7.5)	0.34
Magnesium from dietary (mg)	309.3 (3.5)	308.5 (5.2)	0.88	300.8 (2.9)	0.04	305.5 (6.7)	0.61
Magnesium from supplement (mg)	101.4 (5.3)	100.5 (8.7)	0.92	99.4 (3.9)	0.74	93.2 (11.2)	0.47
Use of calcium supplements, yes (%)	905 (16.9)	286 (15.5)	0.40	749 (15.4)	0.06	143 (14.3)	0.10
Use of magnesium supplements, yes (%)	925 (17.3)	293 (15.9)	0.39	765 (15.7)	0.04	147 (14.6)	0.10

[a] Value present as unweighted frequency (weighted percentage, %) or weighted mean (SD)

[b] Rao-Scott chi-square test for categorical data, and survey regression model for continuous variables

[c] *P* value for the comparison between fatty liver disease cases and controls

[d] P value for the comparison between prediabetes cases and controls

[e] P value for the comparison between prediabetes & fatty liver disease cases and controls

Table 2 The association between intakes of calcium and magnesium with fatty liver disease, prediabetes, both prediabetes & fatty liver disease in NHANES 1988-1994[a,b]

Daily intake (mg)	Fatty Liver Disease vs Control		Prediabetes vs Control		Prediabetes & Fatty Liver Cases	
	Cases/Controls	OR[a] (95% CI)	Cases/Controls	OR[a] (95% CI)	Cases/Controls	OR[a] (95% CI)
Calcium			All subjects			
≤431	649/1600	1.00	1919/1600	1.00	335/1600	1.00
431-690	621/1604	0.97(0.76-1.24)	1446/1604	0.94(0.74-1.18)	312/1604	0.78(0.55-1.11)
690-1063	616/1596	1.18(0.90-1.54)	1285/1596	1.04(0.82-1.33)	274/1596	0.81(0.64-1.03)
>1063	537/1599	1.19(0.85-1.65)	1168/1599	1.12(0.88-1.44)	230/1599	0.89(0.54-1.47)
***P* for trend**		0.16		0.21		0.76
Magnesium						
≤192	652/1615	1.00	1849/1615	1.00	332/1615	1.00

192-274	572/1600	0.83(0.59-1.18)	1378/1600	0.85(0.65-1.13)	255/1600	0.90(0.60-1.37)
274-383	599/1591	0.79(0.56-1.11)	1329/1591	0.80(0.63-1.02)	302/1591	0.83(0.52-1.32)
>383	600/1593	0.72(0.51-1.02)	1262/1593	0.72(0.53-0.97)	262/1593	0.66(0.35-1.25)
***P* for trend**		**0.05**		**0.02**		0.17

[a] Survey logistic regression models were used after adjusted for age, sex, race, educational attainment, household income, smoking status, alcohol drinking, physical activity, BMI, daily intake of total energy, magnesium or calcium, supplemental calcium intake (yes or no), supplemental magnesium intake (yes or no)

Table 3 The association between intakes of calcium with fatty liver disease, prediabetes, both fatty liver disease & prediabetes stratified by gender, calcium:magnesium ratio and drinking status, NHANES 1988-1994[a,b]

Daily intake (mg)	Fatty Liver Disease vs Control		Prediabetes vs Control		Prediabetes & Fatty Liver Disease vs Controls	
	Cases/Controls	OR[a] (95% CI)	Cases/Controls	OR[a] (95% CI)	Cases/Controls	OR[a] (95% CI)
Calcium			Men			
≤431	284/459	1.00	831/459	1.00	160/459	1.00
431-690	301/599	0.75(0.49-1.15)	741/599	0.82(0.60-1.11)	164/599	0.59(0.35-1.01)
690-1063	337/691	0.97(0.66-1.44)	745/691	1.01(0.72-1.41)	173/691	0.68(0.43-1.08)
>1063	348/876	0.93(0.59-1.48)	792/876	1.12(0.80-1.56)	149/876	0.65(0.31-1.35)
***P* for trend**		0.77		0.19		0.46
Calcium			Women			
≤431	365/1141	1.00	1088/1141	1.00	175/1141	1.00

431-690	320/1005	1.17(0.77-1.78)	705/1005	1.06(0.81-1.39)	148/1005	1.10(0.73-1.65)
690-1063	279/905	1.35(0.87-2.09)	540/905	1.04(0.78-1.40)	101/905	0.99(0.65-1.49)
>1063	189/723	1.45(0.93-2.26)	376/723	1.02(0.76-1.36)	81/723	1.36(0.73-2.56)
***P* for trend**		0.06		0.91		0.48
***P* for interaction**	0.79		0.25		0.52	
Calcium			Ca:Mg ratio <2.6			
≤431	575/1361	1.00	1656/1361	1.00	297/1361	1.00
431-690	392/1036	0.81(0.59-1.09)	912/1036	0.80(0.60-1.06)	203/1036	0.60(0.38-0.94)
690-1063	291/662	1.05(0.74-1.49)	592/662	1.00(0.73-1.38)	144/662	0.65(0.41-1.04)
>1063	98/264	1.59(0.87-2.90)	211/264	1.41(0.82-2.42)	38/264	0.80(0.34-1.83)
***P* for trend**		0.17		0.27		0.27
Calcium			Ca:Mg ratio ≥2.6			

≤431	74/239	1.00	263/239	1.00	38/239	1.00
431-690	229/568	1.88(0.83-4.25)	534/568	1.75(1.08-2.83)	109/568	1.75(0.78-3.94)
690-1063	325/934	1.98(0.73-5.36)	693/934	1.70(0.90-3.22)	130/934	1.78(0.66-4.77)
>1063	439/1335	1.90(0.62-5.76)	957/1335	1.98(1.07-3.67)	192/1335	2.53(0.72-8.97)
***P* for trend**		0.57		0.12		0.22
***P* for interaction**	0.20		0.14		0.89	
			Never alcohol drinkers			
Calcium						
≤431	109/292	1.00	339/292	1.00	64/292	1.00
431-690	98/244	1.32(0.71-2.45)	248/244	0.89(0.57-1.41)	49/244	1.28(0.47-3.49)
690-1063	95/251	1.33(0.57-3.13)	215/251	0.74(0.48-1.14)	30/251	0.77(0.25-2.35)
>1063	64/200	1.14(0.46-2.85)	152/200	0.88(0.49-1.59)	26/200	1.35(0.36-5.14)
***P* for trend**		0.73		0.46		0.94

Calcium			Former alcohol drinkers			
≤431	211/528	1.00	638/528	1.00	118/528	1.00
431-690	232/511	0.94(0.73-1.20)	566/511	0.94(0.73-1.21)	133/511	1.09(0.67-1.77)
690-1063	197/476	1.16(0.89-1.51)	454/476	1.09(0.85-1.40)	98/476	0.94(0.57-1.57)
>1063	173/458	1.18(0.84-1.66)	416/458	1.16(0.90-1.50)	82/458	0.89(0.41-1.93)
***P* for trend**		0.16		0.12		0.64
Calcium			Current alcohol drinkers			
≤431	308/741	1.00	308/741	1.00	147/741	1.00
431-690	283/822	0.82(0.56-1.20)	589/822	0.87(0.64-1.19)	127/822	0.57(0.32-1.00)
690-1063	311/844	1.07(0.77-1.49)	577/844	1.08(0.78-1.49)	140/844	0.78(0.50-1.21)
>1063	288/916	1.13(0.72-1.76)	567/916	1.16(0.84-1.62)	118/916	0.85(0.45-1.59)
***P* for trend**		0.26		0.17		0.93

***P* for interaction**	0.79	0.37	0.24

[a] Survey logistic regression models were used after adjusted for age, sex, race, educational attainment, household income, smoking status, alcohol drinking, physical activity, BMI, daily intake of total energy, magnesium, supplemental calcium intake (yes or no), supplemental magnesium intake (yes or no)

Table 4 The association between intakes of magnesium with fatty liver disease, prediabetes, both fatty liver disease & prediabetes stratified by gender, intake of calcium, calcium:magnesium ratio and drinking status, NHANES 1988-1994[a,b]

Daily intake (mg)	Fatty Liver Disease vs Control		Prediabetes vs Control		Prediabetes & Fatty Liver Disease vs Controls	
	Cases/Controls	OR[a] (95% CI)	Cases/Controls	OR[a] (95% CI)	Cases/Controls	OR[a] (95% CI)
Magnesium			Men			
≤192	234/399	1.00	702/399	1.00	130/399	1.00
192-274	245/488	1.10(0.67-1.81)	697/488	1.04(0.66-1.64)	119/488	0.91(0.49-1.68)
274-383	345/734	0.91(0.54-1.53)	779/734	0.76(0.53-1.10)	193/734	0.82(0.42-1.61)
>383	446/1004	0.79(0.43-1.44)	931/1004	0.76(0.49-1.19)	204/1004	0.60(0.26-1.39)
***P* for trend**		0.19		**0.04**		0.19
Magnesium			Women			
≤192	418/1216	1.00	1147/1216	1.00	202/1216	1.00

192-274	327/1112	0.72(0.48-1.09)	681/1112	0.75(0.56-1.02)	136/1112	0.98(0.58-1.65)
274-383	254/857	0.71(0.45-1.13)	550/857	0.89(0.66-1.20)	109/857	0.81(0.48-1.34)
>383	154/589	0.72(0.42-1.25)	331/589	0.67(0.46-0.98)	58/589	0.67(0.30-1.49)
***P* for trend**		0.20		0.09		0.25
***P* for interaction**	0.88		0.22		0.10	
Magnesium			Calcium: Magnesium <2.6			
≤192	336/771	1.00	1038/771	1.00	178/771	1.00
192-274	306/802	0.77(0.53-1.13)	771/802	0.85(0.61-1.20)	146/802	0.81(0.48-1.37)
274-383	344/831	0.78(0.52-1.18)	768/831	0.81(0.58-1.13)	182/831	0.77(0.42-1.40)
>383	370/919	0.77(0.46-1.29)	794/919	0.79(0.50-1.27)	176/919	0.58(0.27-1.24)
***P* for trend**		0.50		0.34		0.16
Magnesium			Calcium: Magnesium ≥2.6			

≤192	316/844	1.00	811/844	1.00	154/844	1.00
192-274	266/798	0.91(0.56-1.47)	607/798	0.83(0.59-1.19)	109/798	0.99(0.60-1.63)
274-383	255/760	0.81(0.41-1.58)	561/760	0.77(0.51-1.15)	120/760	0.87(0.43-1.78)
>383	230/674	0.69(0.36-1.32)	468/674	0.60(0.38-0.96)	86/674	0.66(0.20-2.20)
***P* for trend**		0.23		**0.04**		0.46
***P* for interaction**	0.25		0.14		0.29	
Magnesium			Calcium intake <1200 mg/d			
≤192	648/1602	1.00	1841/1602	1.00	330/1602	1.00
192-274	543/1498	0.75(0.53-1.08)	1305/1498	0.83(0.63-1.09)	242/1498	0.82(0.53-1.27)
274-383	485/1272	0.70(0.50-0.99)	1091/1272	0.82(0.63-1.07)	245/1272	0.79(0.49-1.28)
>383	341/801	0.66(0.44-0.99)	707/801	0.72(0.49-1.06)	164/801	0.66(0.33-1.30)
***P* for trend**		**0.04**		0.09		0.25

Magnesium			Calcium intake ≥1200 mg/d			
≤192	4/13	1.00	8/13	1.00	2/13	1.00
192-274	29/102	1.13(0.23-5.53)	73/102	2.51(0.28-22.36)	13/102	5.35(0.51-56.12)
274-383	114/319	0.84(0.19-3.72)	238/319	1.63(0.20-13.01)	57/319	2.48(0.24-25.62)
>383	259/792	0.87(0.19-4.07)	555/792	1.58(0.20-12.69)	98/792	2.21(0.20-24.29)
***P* for trend**		0.74		0.40		0.41
***P* for interaction**	0.69		**0.04**		0.34	
Magnesium			Never alcohol drinker			
≤192	135/331	1.00	373/331	1.00	73/331	1.00
192-274	99/288	1.11(0.58-2.14)	253/288	0.87(0.55-1.37)	45/288	1.02(0.37-2.80)
274-383	80/227	0.93(0.46-1.90)	194/227	0.85(0.49-1.46)	34/227	0.86(0.37-1.99)
>383	52/141	1.18(0.57-2.43)	134/141	0.66(0.43-1.03)	17/141	0.64(0.17-2.49)

***P* for trend**		0.85		0.08		0.46
Magnesium			Former alcohol drinkers			
≤192	239/570	1.00	671/570	1.00	141/570	1.00
192-274	190/504	0.78(0.54-1.13)	520/504	0.85(0.63-1.14)	93/504	0.97(0.47-2.02)
274-383	212/457	0.76(0.52-1.11)	480/457	0.79(0.62-1.02)	116/457	1.03(0.55-1.95)
>383	172/442	0.67(0.46-0.98)	403/442	0.72(0.52-1.01)	81/442	0.66(0.25-1.77)
***P* for trend**		**0.04**		**0.03**		0.45
Magnesium			Current alcohol drinkers			
≤192	265/672	1.00	508/672	1.00	115/672	1.00
192-274	267/785	0.66(0.40-1.09)	559/785	0.82(0.53-1.25)	112/785	0.76(0.52-1.11)
274-383	296/885	0.62(0.37-1.05)	615/885	0.72(0.48-1.07)	149/885	0.66(0.38-1.14)
>383	362/981	0.58(0.36-0.94)	676/981	0.70(0.43-1.12)	156/981	0.54(0.29-1.00)

***P* for trend**	**0.04**	0.09	0.13
***P* for interaction**	0.64	0.47	0.33

[a] Survey logistic regression models were used after adjusted for age, sex, race, educational attainment, household income, smoking status, alcohol drinking, physical activity, BMI, daily intake of total energy, calcium, supplemental calcium intake (yes or no), supplemental magnesium intake (yes or no)