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Intakes of magnesium, calcium and risk of fatty liver disease and prediabetes

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Abstract

Objective: Obesity and insulin resistance play important roles in the pathogenesis of non-alcoholic fatty liver disease (NAFLD). Mg intake is linked to a reduced risk of metabolic syndrome and insulin resistance; people with NAFLD or alcoholic liver disease are at high risk of Mg deficiency. The present study aimed to investigate whether Mg and Ca intakes were associated with risk of fatty liver disease and prediabetes by alcohol drinking status.

Design: We analysed the association between Ca or Mg intake and fatty liver disease, prediabetes or both prediabetes and fatty liver disease in cross-sectional analyses.

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

Subjects: Nationally representative sample of US adults in NHANES (n 13 489).

Results: After adjusting for potential confounders, Mg intake was associated with approximately 30 % reduced odds of fatty liver disease and prediabetes, comparing the highest intake quartile *v.* the lowest. Mg intake may only be related to reduced odds of fatty liver disease and prediabetes in those whose Ca intake is less than 1200 mg/d. Mg intake may also only be associated with reduced odds of fatty liver disease among alcohol drinkers.

Conclusions: The study suggests that high intake of Mg 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.

Keywords
Magnesium
Calcium
Fatty liver disease
Prediabetes

All-cause cirrhosis and cancer of the liver are two of the four top leading causes of death from gastrointestinal and liver diseases in the USA[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 is caused by non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease[3]. NAFLD is the most common liver disease in the world[4–6] and 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 aetiology 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].

Mg may be a factor that is related to the aetiology of both alcoholic liver disease and NAFLD. People who chronically drink heavy amounts of alcohol are at high risk of Mg deficiency[12] and prolonged exposure to alcohol leads to a substantial reduction in Mg homeostasis in the liver[13]. Furthermore, as many as 50 % of type 2 diabetic patients have hypomagnesaemia[14]. As such, one previous study found that serum Mg levels were significantly lower in patients with either alcoholic or non-alcoholic liver steatosis[15]. A meta-analysis of randomized trials indicated that Mg supplementation improves insulin resistance in patients with type 2 diabetes[16]. Mg 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 intake of Mg may be associated with a

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reduced risk of mortality due to liver disease, particularly among alcohol drinkers and those with hepatic steatosis[20].

In the present study, we examined whether the intake of Mg was associated with the prevalence of fatty liver disease or prediabetes. Although previous studies have examined the association between intake of Ca and type 2 diabetes[21], few studies have examined the role of Ca intake in association with prediabetes[22]. Our recent studies indicated that Ca intake may interact with Mg intake in relation to diseases of the gastrointestinal tract, such as colorectal adenoma[23], adenoma recurrence[24], reflux oesophagitis, Barrett's oesophagus[25] and other chronic disease[26]. Thus, we hypothesized that intake of Ca 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 analysed data from the Third National Health and Nutrition Examination Survey (NHANES III) follow-up cohort.

Methods

Study population

NHANES III was conducted in the USA from 1988 through 1994 by the National Center for Health Statistics of the Centers for Disease Control and Prevention. The institutional review board of the Centers for Disease Control and Prevention approved the investigation, 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, non-institutionalized population. Of these participants, 33 994 (86 %) were interviewed in their homes. All interviewed participants were invited to the mobile examination centre for a medical examination. In our study, we excluded 15 169 participants younger than 20 years old. We also excluded 2210 participants with (i) a physician's diagnosis of diabetes, (ii) glycolated Hb (HbA1c) ≥6·5 % or (iii) fasting glucose ≥126 mg/dl. Furthermore, 2178 participants did not complete dietary or supplemental intake assessment and 948 participants had no information on fatty liver disease or prediabetes, thus they were not included in the study. As a result, 13 489 participants were included in the final analyses.

Classification of key health outcomes

1. Fatty liver disease cases: An ultrasound examination was performed using a Toshiba Sonolayer SSA-90A and Toshiba video recorder among participants aged 20–74 years in NHANES III between 1988 and 1994. In 2009–2010, archived gallbladder ultrasound video images were reviewed to assess the presence of fat within the hepatic parenchyma using standard criteria. Followed by five criteria (liver to kidney contrast; brightness of the liver parenchyma; deep beam attenuation; echogenic walls in the small intrahepatic vessels; definition of the gallbladder walls), hepatic steatosis was categorized as normal, mild, moderate or severe. 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 the American Diabetes Association, 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: Those who had both conditions defined above.
4. Controls: Those who had neither fatty liver disease nor prediabetes were regarded as controls.

Nutrient intake assessments

Detailed dietary and supplemental intakes including Mg and Ca were derived from a single 24 h dietary recall and a 30 d supplemental interview which participants completed at the mobile examination centre. For the current analyses, only dietary recall data 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)' were used. The total intake of these nutrients was calculated by summing up the Mg and Ca intakes from the dietary and supplemental intakes.

Covariates

We considered a number of factors as potential confounding factors, including: age (years), sex (men and women), race and ethnicity (non-Hispanic Whites; non-Hispanic Blacks; Other), educational attainment (lower than high-school education; high-school diploma; college graduate or above), ratio of poverty to income (≤1; 1–3; >3), cigarette smoking status (never; former; current), alcohol drinking status (never alcohol drinker: had less than twelve drinks of any kind of alcoholic beverage in entire life; former alcohol drinker: had more than twelve drinks of any kind of alcoholic beverage in entire life but in the past 12 months had less than twelve drinks of any alcoholic beverage; current alcohol drinker: had more than twelve drinks of any kind of alcoholic beverage in entire life and in the past 12 months had at least twelve 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'), BMI (kg/m^2), waist-to-hip ratio, daily intakes of total energy (kcal/d), Ca (mg/d) and Mg (mg/d), use of Ca supplements (yes; no) and use of Mg supplements (yes; no).

Statistical analysis

All analyses were performed using the Survey package in the SAS statistical software package version 9.4 to account for the applicable weighting in the multistage clustered, probability

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sampling design in the NHANES III cohort. Covariates were compared between cases and controls to evaluate potential confounding factors using the Rao–Scott χ^2 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 analyse the association of Ca or Mg intake with fatty liver disease or prediabetes or both prediabetes and fatty liver disease adjusting for potential confounders. Total Ca or Mg intake was included in the models as a categorical variable, using quartiles based on the controls' distribution. To assess the linear trend in the odds of Ca or Mg quartile, the median value for each quartile was entered in the logistic regression model as an ordinal variable. Stratified analyses by sex (men or women), ratio of Ca intake to Mg intake (Ca:Mg <2·6 or ≥2·6; to be consistent with our previous studies, the cut-off point of 2·6 was used[24]), daily Ca intake (<1200 mg or ≥1200 mg) and 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 with

Table 1 Baseline demographic characteristics and selected risk factors by disease status: US adults aged ≥20 years (*n* 13 489), Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994*,†

	Controls (*n* 6399)		Fatty liver disease cases (*n* 2423)			Prediabetes cases (*n* 5818)			Prediabetes & fatty liver disease cases (*n* 1511)		
Characteristic	Mean or *n*	SD or %	Mean or *n*	SD or %	*P* value‡	Mean or *n*	SD or %	*P* value§	Mean or *n*	SD or %	*P* value‖
Age at screening (years)	37·8	0·4	45·6	0·5	**<0·0001**	51·3	0·6	**<0·0001**	49·3	0·7	**<0·0001**
Sex (%)					**<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	
Ratio of poverty to income (%)					**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	
BMI (kg/m^2)	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**
Never 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**
Never 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 nutrient intakes											
Total energy (kJ)	9551	106	9454	154	0·56	8993	109	**0·0001**	9333	174	0·25
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 Ca (mg)	886·9	14·3	882·5	24·7	0·84	827·5	16·0	**0·001**	837·1	29·7	0·09
Ca from diet (mg)	861·9	14·2	858·1	23·6	0·86	806·4	15·5	**0·002**	817·9	28·4	0·12
Ca from supplements (mg)	175·9	7·1	171·0	17·6	0·79	172·7	8·3	0·76	167·7	23·0	0·73
Total Mg (mg)	325·1	3·8	323·7	6·1	0·83	314·4	3·1	**0·01**	317·4	7·5	0·34
Mg from diet (mg)	309·3	3·5	308·5	5·2	0·88	300·8	2·9	**0·04**	305·5	6·7	0·61
Mg from supplements (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 Ca supplements (% yes)	905	16·9	286	15·5	0·40	749	15·4	0·06	143	14·3	0·10
Use of Mg supplements (% yes)	925	17·3	293	15·9	0·39	765	15·7	**0·04**	147	14·6	0·10

*Values are presented as weighted mean and standard deviation for continuous variables; or as unweighted frequency and weighted percentage for categorical variables.
†*P* values calculated using survey regression model for continuous variables or the Rao–Scott χ^2 test for categorical variables; significant *P* values are indicated in bold font.
‡*P* value for the comparison between fatty liver disease cases and controls.
§*P* value for the comparison between prediabetes cases and controls.
‖*P* value for the comparison between prediabetes & fatty liver disease cases and controls.

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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. Cases with prediabetes consumed lower amounts of Ca and Mg compared with controls.

After adjusting for potential confounders, we found that intake of Ca was not related to the odds of fatty liver disease, prediabetes or both prediabetes and fatty liver disease. On the other hand, we found that intake of Mg 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 Mg and risk of both prediabetes and fatty liver disease although not statistically significant (Table 2).

In stratified analyses, we found that the intake of Ca was marginally associated with increased odds of fatty liver disease among women (Table 3). Also, the intake of Ca may be related to increased odds of prediabetes among those with Ca:Mg ≥2·6, with an OR of 1·98 (95 % CI 1·07, 3·67) for the highest quartile intake *v.* 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 Mg and risk of prediabetes was significant only among those with Ca:Mg ≥2·6 (Table 4). However, the P for interaction were not statistically significant (Table 4). On the other hand, there was a significant interaction between Mg intake and Ca intake (P for interaction = 0·04) in relation to odds of prediabetes. It appears that the intake of Mg may be related to the reduced odds of fatty liver disease (P for trend = 0·04) and prediabetes (P for trend = 0·09) only when the intake of Ca is <1200 mg/d. In the stratified analysis according to alcohol drinking status, we found that the intake of Mg 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 that the association between intake of Mg and risk of fatty liver and prediabetes differed by sex.

Discussion

In the NHANES III cohort, a nationally representative sample of the US general population, we found that the intake of Ca was overall not associated with the odds of fatty liver disease, prediabetes or both. On the other hand, we found that higher intake of Mg was 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 Mg intake and Ca 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 Mg intake and prediabetes appeared primarily in those with a Ca intake <1200 mg/d; and in the same subgroup, intake of Mg was also significantly related to a reduced odds of fatty liver disease. We also found Mg intake was related to reduced odds of fatty liver disease only among former and current alcohol drinkers.

Our finding of an inverse association between the intake of Mg and prediabetes is consistent with that of previous studies which have shown that high Mg intake is associated with a reduced risk of type 2 diabetes[18,29,30], metabolic syndrome[17,31], insulin resistance[32] and prediabetes[33]. Furthermore, we found an inverse association between the intake of Mg and the risk of fatty liver disease. This finding was not consistent with a null association found in a

Table 2 The association of intakes of calcium and magnesium with fatty liver disease, prediabetes and both prediabetes and fatty liver disease, among all subjects: US adults aged ≥20 years (n 13 489), Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994*

	Fatty liver disease *v.* Controls			Prediabetes *v.* Controls			Prediabetes & fatty liver *v.* Controls		
Daily intake (mg)	Cases/controls	OR	95 % CI	Cases/controls	OR	95 % CI	Cases/controls	OR	95 % CI
Ca									
≤431	649/1600	1·00	Ref.	1919/1600	1·00	Ref.	335/1600	1·00	Ref.
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	
Mg									
≤192	652/1615	1·00	Ref.	1849/1615	1·00	Ref.	332/1615	1·00	Ref.
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	

Ref., reference category.
Significant P values are indicated in bold font.
*Survey logistic regression models were used after adjustment for age, sex, race, educational attainment, household income, smoking status, alcohol drinking, physical activity, BMI, daily intakes of total energy, Mg or Ca, supplemental Ca intake (yes or no) and supplemental Mg intake (yes or no).

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Table 3 The association of intake of calcium with fatty liver disease, prediabetes and both fatty liver disease and prediabetes, stratified by sex, ratio of calcium intake to magnesium intake and drinking status: US adults aged ≥20 years (*n* 13 489), Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994*

	Fatty liver disease *v.* Controls			Prediabetes *v.* Controls			Prediabetes & fatty liver disease *v.* Controls		
Daily intake (mg)	Cases/controls	OR	95 % CI	Cases/controls	OR	95 % CI	Cases/controls	OR	95 % CI
Ca					Men				
≤431	284/459	1·00	Ref.	831/459	1·00	Ref.	160/459	1·00	Ref.
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	
Ca					Women				
≤431	365/1141	1·00	Ref.	1088/1141	1·00	Ref.	175/1141	1·00	Ref.
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	
Ca					Ca:Mg <2·6				
≤431	575/1361	1·00	Ref.	1656/1361	1·00	Ref.	297/1361	1·00	Ref.
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	
Ca					Ca:Mg ≥2·6				
≤431	74/239	1·00	Ref.	263/239	1·00	Ref.	38/239	1·00	Ref.
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	
Ca					Never alcohol drinkers				
≤431	109/292	1·00	Ref.	339/292	1·00	Ref.	64/292	1·00	Ref.
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	
Ca					Former alcohol drinkers				
≤431	211/528	1·00	Ref.	638/528	1·00	Ref.	118/528	1·00	Ref.
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	
Ca					Current alcohol drinkers				
≤431	308/741	1·00	Ref.	308/741	1·00	Ref.	147/741	1·00	Ref.
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	

Ref., reference category.
*Survey logistic regression models were used after adjustment for age, sex, race, educational attainment, household income, smoking status, alcohol drinking, physical activity, BMI, daily intakes of total energy and Mg, supplemental Ca intake (yes or no) and supplemental Mg intake (yes or no).

previous study[34]. However, that 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 Mg and fatty liver disease appeared primarily in alcohol drinkers. Although novel, this finding is consistent with the observation that heavy alcohol drinkers are at high risk of Mg deficiency[12]. Future large-scale studies are needed to confirm the findings. This is important because previous studies have found that alcohol causes a substantial reduction in Mg homeostasis in the liver[13]. It was reported by NHANES 1999–2000 that 79 % of US adults do not meet the RDA for Mg[26]. One study observed that serum concentrations of Mg were significantly reduced in patients with either alcoholic or non-alcoholic liver steatosis[31].

In a cohort study, the investigators found that intake of Mg was associated with a reduced risk metabolic syndrome[35]. Mg intake was also inversely associated with individual components of metabolic syndrome, particularly fasting glucose level, waist circumference and HDL cholesterol. Thus, the inverse association between the intake of Mg and metabolic syndrome is likely mediated through waist circumference or waist-to-hip ratio. Similarly, in our study, after additionally adjusting for

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Table 4 The association of intake of magnesium with fatty liver disease, prediabetes and both fatty liver disease and prediabetes, stratified by gender, ratio of calcium intake to magnesium intake, intake of calcium and drinking status: US adults aged ≥20 years (*n* 13 489), Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994*

	Fatty liver disease *v.* Controls			Prediabetes *v.* Controls			Prediabetes & fatty liver disease *v.* Controls		
Daily intake (mg)	Cases/controls	OR	95 % CI	Cases/controls	OR	95 % CI	Cases/controls	OR	95 % CI
Mg					Men				
≤192	234/399	1·00	Ref.	702/399	1·00	Ref.	130/399	1·00	Ref.
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	
Mg					Women				
≤192	418/1216	1·00	Ref.	1147/1216	1·00	Ref.	202/1216	1·00	Ref.
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	
Mg					Ca:Mg < 2·6				
≤192	336/771	1·00	Ref.	1038/771	1·00	Ref.	178/771	1·00	Ref.
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	
Mg					Ca:Mg ≥ 2·6				
≤192	316/844	1·00	Ref.	811/844	1·00	Ref.	154/844	1·00	Ref.
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	
Mg					Ca intake < 1200 mg/d				
≤192	648/1602	1·00	Ref.	1841/1602	1·00	Ref.	330/1602	1·00	Ref.
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	
Mg					Ca intake ≥ 1200 mg/d				
≤192	4/13	1·00	Ref.	8/13	1·00	Ref.	2/13	1·00	Ref.
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	
Mg					Never alcohol drinkers				
≤192	135/331	1·00	Ref.	373/331	1·00	Ref.	73/331	1·00	Ref.
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	
Mg					Former alcohol drinkers				
≤192	239/570	1·00	Ref.	671/570	1·00	Ref.	141/570	1·00	Ref.
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	
Mg					Current alcohol drinkers				
≤192	265/672	1·00	Ref.	508/672	1·00	Ref.	115/672	1·00	Ref.
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	

Ref., reference category.
Significant *P* values are indicated in bold font.
*Survey logistic regression models were used after adjustment for age, sex, race, educational attainment, household income, smoking status, alcohol drinking, physical activity, BMI, daily intakes of total energy and Ca, supplemental Ca intake (yes or no) and supplemental Mg intake (yes or no).

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waist-to-hip ratio, the significant associations disappeared. As such, waist-to-hip ratio may serve as a pathway to the relationship between Mg 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 Mg may be more significantly related to reduced odds of prediabetes and fatty liver disease when Ca intake was <1200 mg/d. This finding suggests that the beneficial effect of Mg may be suppressed when Ca intake is higher than the Dietary Reference Intake. This finding is consistent with our recent finding indicating that Ca intake may interact with Mg intake in relation to risks of multiple common diseases[23–26]. Some[36–38], but not all[39], previous human studies indicate that high Ca intake may affect the absorption rate of Mg. It is known that over 80 % of plasma Mg is ultrafiltrated and reabsorbed in the kidneys. Thus, kidney reabsorption plays a key role in regulating Mg homeostasis[40]. Likewise, 10 g of Ca is filtered daily on average, of which 98 % is reabsorbed in the kidneys[41,42]. Thus far, clinical trials have consistently found that high Ca intake leads to significantly increased excretion of Mg in the urine[40,43,44]. Thus, it is likely that high intake of Ca may lead to relative deficiency of Mg. We also found Mg 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 Mg deficiency[12]. However, further large studies, particularly longitudinal studies, are necessary to replicate the findings.

A strength of our study is that it is used data from NHANES, a population-based study with a nationally representative sample. However, although multiple 24 h dietary recalls are used as a gold standard measure in nutritional epidemiological studies, a one-time 24 h dietary recall as used in the current study may not have adequately captured long-term dietary intakes of Mg and Ca. Since inter-day variation in intakes of Mg and Ca 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 Mg and Ca 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 Mg and Ca 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 Ca and Mg are in opposite directions. Thus, it is unlikely our findings are due to confounding by healthy lifestyle in general because those who possess healthy behaviours are likely to use Ca supplements. Finally, like all cross-sectional studies, the temporal sequence for the associations is not clear. However, the inverse association between intake of Mg and risk of prediabetes is consistent with the associations of Mg with insulin resistance[16], metabolic syndrome[17,31] and type 2 diabetes[18,19].

Conclusion

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

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