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Associations of chronic diarrhoea with non-alcoholic fatty liver disease and obesity-related disorders among US adults

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ABSTRACT

Mechanisms explaining observed associations between diarrhoea and obesity or increased body mass index (BMI) are unclear.

Objective To assess associations of bowel patterns with BMI, metabolic syndrome (MS), non-alcoholic fatty liver disease (NAFLD) and other obesity-related disorders.

Design We performed a cross-sectional analysis of data from adults who completed bowel health questions for the 2005 to 2010 cycles of the National Health and Nutrition Examination Surveys. Relationships were examined using multinomial logistic regression. Confounding effects of demographics, smoking, alcohol and BMI were examined by sequential modelling.

Results Among 13 413 adults, weighted prevalence rates of constipation and diarrhoea were 8.9% and 6.6%, respectively. Mean BMI was associated with bowel patterns ($p<0.001$), and was higher with diarrhoea (30.3 kg/m^2) versus normal bowel patterns (28.6 kg/m^2) and with diarrhoea versus constipation (27.8 kg/m^2). NAFLD was more prevalent (ORs, 95% CI) in diarrhoea versus normal bowel patterns (OR=1.34, 95% CI 1.01 to 1.78) or constipation (OR=1.45, 95% CI 1.03, 2.03) in adjusted analyses. The higher prevalence of MS in diarrhoea versus constipation (OR=1.27, 95% CI 0.97 to 1.67) was not independent of BMI.

Conclusions These findings suggest an association between diarrhoea and NAFLD that is independent of BMI.

Summary box

What is already known about this subject?

- Diarrhoea and accelerated intestinal transit are associated with obesity or increased body mass index (BMI); however, the factors that explain these associations are unclear.
- Despite the well-described association between diarrhoea and obesity, there are limited population-based data that have examined the correlation between bowel habits and specific obesity-related disorders such as metabolic syndrome (MS) and non-alcoholic fatty liver disease (NAFLD).

What are the new findings?

- In this population-based analysis, MS was more common in those with diarrhoea, but this association was not independent of BMI.
- Prevalence of NAFLD was higher in those with diarrhoea than in those with constipation or normal bowel patterns, and this association was independent of BMI.

How might it impact on clinical practice in the foreseeable future?

- A potential independent link between NAFLD and diarrhoea may influence our clinical approach to patients who suffer from these two highly prevalent conditions.
- Further prospective study of potentially shared mechanisms between diarrhoea and NAFLD is warranted.

INTRODUCTION

Functional bowel disorders such as irritable bowel syndrome (IBS) and functional diarrhoea are highly prevalent worldwide.[1] An increased prevalence of diarrhoea has been reported in obese individuals. Multiple studies have linked diarrhoea and accelerated intestinal transit[2] with obesity,[3 4] and high body mass index (BMI).[5 6] Others have reported potential associations between IBS or chronic diarrhoea and obesity-related disorders such as metabolic syndrome (MS) and associated conditions such as non-alcoholic fatty liver disease (NAFLD).[7 8] In a previous cross-sectional study, IBS was associated with higher anthropometric measures, higher transaminase, gamma-glutamyl transferase and lipid levels compared with controls.[7] The mechanisms explaining these associations are yet unclear, although some hypothesise a connexion with eating habits and gastrointestinal (GI) motility.[9] Factors such as altered bile acid homeostasis,[10] the GI microbiome, or increased intestinal permeability[11] may also contribute to associations between lower GI symptoms and obesity.

There are limited population-based data examining associations between bowel habits

and the comorbid conditions associated with overweight or obesity. Understanding the strength of these potential associations could have important implications for clinical management and evaluation of patients with abnormal bowel patterns, and may help generate new hypotheses on the mechanisms that link GI symptoms with BMI or obesity. Thus, the aims of this study were (1) to assess the association between BMI and bowel patterns and (2) to determine if MS or other obesity-related disorders are associated with bowel patterns independent of BMI. Investigating relationships between bowel patterns and MS or other obesity-related disorders may provide further insight into common pathophysiological mechanisms or identify previously unrecognised associations that could impact the future care of patients experiencing these common disturbances in bowel function.

METHODS

Study population

The National Health and Nutrition Examination Surveys (NHANES) is a programme conducted by the National Center for Health Statistics of the Center for Disease Control and Prevention[12] designed to assess health and nutritional status of civilian non-institutionalised persons in the USA through a complex, multistage probability sampling design. Since 1999, it has been a continuous survey programme examining a representative sample of approximately 5000 people per year across the country with over-sampling of specific age and ethnic groups. The protocol for NHANES 2005 through 2010 was approved on 18 March 2005 and annually thereafter by the National Center for Health Statistics research ethics review board in accordance with federal regulations (45 CFR 46.111) and ethical guidelines of the Declaration of Helsinki (adopted in 1964 and subsequently revised many times). Signed consent was obtained from all participants. The analytic sample included participants with available stool type in any of the three NHANES cycles (2005–2006, 2007–2008 and 2009–2010). Combining data across 2-year cycles based on 4 or more years of data will produce estimates of greater precision, and is recommended in the guidelines published by NHANES.[12] Participants with opioid-induced constipation, defined based on previously published reports[13] and those with missing data for relevant variables were excluded.

Bowel health questionnaire

We utilised data from adult participants >20 years old who completed the bowel health questionnaire (BHQ). BHQ questions were completed in a mobile examination centre using a computer assisted personal interviewing system. Stool consistency was assessed using the Bristol Stool Form Scale (BSFS).[14] In all three NHANES cycles, participants were asked to report weekly bowel movement frequency (eg, how many times per week do you usually have a bowel movement) and most common stool type using the BSFS (eg, please look at this card and tell me the number that corresponds to your usual or most common stool type). In NHANES 2009, the BHQ was expanded to assess self-reported constipation and diarrhoea in the last 12 months. (eg, During the past 12 months, how often have you been constipated/have you had diarrhoea?)

Lower GI symptom groups

Based on BHQ responses, participants were classified as having: (1) constipation, (2) diarrhoea and (3) normal bowel patterns. Categories were guided by Rome IV criteria for diarrhoea-predominant and constipation-predominant IBS, functional diarrhoea and functional constipation,[1] although the specific criteria were not applied. Constipation was defined by: (1) most common stool type of 1 or 2 using the BSFS; (2) less than three bowel movements per week; or (3) always/most of the time have been constipated in the last 12 months. Diarrhoea was defined by: (1) most common stool type 6 or 7 using the BSFS or (2) diarrhoea reported as always/most of the time in the past 12 months. Normal bowel patterns were defined by most common stool type 3–5 using the BSFS and bowel movement frequency ≥3 and <21 times per week. Definitions were established based on prior NHANES publications.[4 15 16]

Demographics

Data were collected on demographic and socioeconomic variables: age; gender; race or ethnicity (non-Hispanic White, non-Hispanic Black, Mexican American/other Hispanic, or other); marital status (widowed, separated, divorced or married/cohabiting and never married); education level (less than high school education, high school diploma including general educational development, or education beyond high school).

Anthropometric measures, blood pressure and laboratory values: anthropometric measurements, blood pressure measurements and specimen collections for laboratory analyses were conducted in the mobile examination centre. Data were collected for fasting serum glucose (mg/dL), triglycerides (mg/dL), high-density lipoprotein (HDL) (mg/dL), low-density lipoprotein (LDL) (mg/dL) and total cholesterol (mg/dL).

MS, NAFLD and obesity-related disorders

Participants with any three of the following five factors were considered to have MS as defined by the National Cholesterol Education Program Adult Treatment Panel III[17]: (1) elevated waist circumference (≥102 cm in men and ≥88 cm in women); (2) serum triglycerides >150 mg/dL or drug treatment for elevated triglycerides; (3) serum HDL <40 mg/dL in men or <50 mg/dL in women; (4) blood pressure ≥130/85 mm Hg or drug treatment for elevated blood pressure; (5) elevated fasting glucose ≥100 mg/dL or treatment for elevated blood glucose. Use of medications for blood pressure, cholesterol and blood glucose were ascertained by self-report. Consistent with prior publications,[18] participants with elevated

serum alanine aminotransferase or aspartate aminotransferase levels (males: aspartate aminotransferase >40 or alanine aminotransferase >37; females: aspartate aminotransferase >31 or alanine aminotransferase >31) in the absence of excessive alcohol use or viral hepatitis (defined by a positive test for hepatitis B surface antigen or a positive hepatitis C antibody as in prior publications)[18] were considered to have NAFLD. Additional comorbidities were ascertained by self-report and included: cardiovascular disease (congestive heart failure, coronary heart disease, angina, heart attack, stroke), diabetes, sleep disorders (including sleep apnoea) and cancer. Diabetes was defined as being told of the diagnosis by a doctor/health professional and/or taking insulin or other diabetic medication to lower blood sugar.

Additional covariates

Smoking history (never smoker; past smoker; current smoker) and alcohol consumption (lifetime abstinence; former drinker; moderate current drinker; or excessive drinker) as defined in prior publications[19] were ascertained. Excessive drinking was defined as >14 drinks per week for men, >7 drinks per week for women, or >5 drinks per day in a single day at least once in the past 12 months for either men or women.

Statistical analysis

Data were summarised as means with 95% CIs for continuous variables and proportions with 95% CI for categorical variables. Comparisons between bowel pattern groups were performed using analysis of variance for continuous variables and Rao-Scott χ^2 test for categorical variables. All analyses took into consideration of the complex sampling of NHANES incorporating the sampling weights and sample design.

Relationships between bowel patterns and MS, NAFLD, or other obesity-related disorders including cardiovascular disease, diabetes, sleep disorder and cancer were examined using multinomial logistic regression through sequential modelling with a generalised logit link that controls for the potentially confounding effect of demographics, smoking, alcohol consumption and BMI. In step 1, we fitted separate multinomial logistic regression models to examine associations between each obesity-related disorder and bowel pattern group with adjustment for demographics, smoking and alcohol consumption. In step 2, we added BMI to each model to examine whether each obesity-related disorder was independently associated with bowel pattern after controlling for BMI. In step 3, we included BMI with demographics and all six obesity-related disorders in a single model to examine whether individual obesity-related disorders were independently associated with bowel patterns after adjusting for the other obesity-related disorders. Associations with bowel pattern were evaluated using adjusted ORs and 95% CI, estimated by comparing participants with diarrhoea or normal bowel patterns to those with constipation. All statistical analyses were performed using the SAS software V.9.4. Two-sided p values <0.05 were regarded as significant.

RESULTS

In NHANES 2005–2010, there were 17 132 participants >20 years of age, of whom 16 539 (97%) underwent an interview and medical exam. Among those, 2052 (12.4%) were excluded for missing questionnaire items on stool consistency/frequency, 93 (0.5%) were excluded for opioid-induced constipation, and 981 (5.9%) were excluded for missing information on covariates, leaving a total of 13 413 participants in the analytic sample (figure 1). Excluded subjects were more likely to be non-Hispanic black; to be former or never drinkers; to have cardiovascular disease, NAFLD, or diabetes; and were less likely to be married or living with a partner.

In the analytic sample, mean age was 46.7 (95% CI 46.0 to 47.4) years, 51% were women and 71% were Caucasian. Overall weighted prevalence was 84.5% for normal bowel patterns, 8.9% for constipation and 6.6% for diarrhoea. There were significant differences in age, sex, race/ethnicity, socioeconomic status, smoking status and alcohol consumption across groups (table 1).

As shown in table 1, those with diarrhoea had the highest mean age and were more likely to be Mexican Americans/Hispanics; widowed/divorced/separated; have less than a high school education; past or current smokers; and former drinkers than those with constipation. Those with normal bowel patterns were more likely to be non-Hispanic Whites; men; married/living with a partner; and have more than a high school education than those with diarrhoea or constipation. Those with constipation were more likely to be non-Hispanic blacks; women; never married; have a high school graduate/general educational development or equivalent; have never smoked; or lifetime alcohol abstainers than those with normal bowel patterns or diarrhoea.

BMI and bowel pattern group

Mean BMI for the overall cohort was 28.7 kg/m^2 (95% CI 28.5 to 28.9) and was associated with bowel pattern groups, being highest in those with diarrhoea (30.3 kg/m^2, 95% CI 29.7 to 30.9) and lowest in those with constipation (27.8 kg/m^2, 95% CI 27.3 to 28.3). This association remained significant after adjusting for demographics, smoking status, and alcohol consumption, and other obesity-related disorders (p<0.001). With every five additional point increase in BMI, there was a 17% increase in the estimated odds of having diarrhoea relative to having normal bowel pattern (OR=1.17, 95% CI 1.10 to 1.25) and a 32% increase in the odds of having diarrhoea relative to having constipation (OR=1.32, 95% CI 1.23 to 1.41).

Obesity-related disorders by bowel pattern group

Overall prevalence of MS (table 1) was 30.0% (95% CI 28.6 to 31.4) with a higher prevalence (p<0.001) observed in those with diarrhoea (36.0%, 95% CI 31.5 to 40.6)

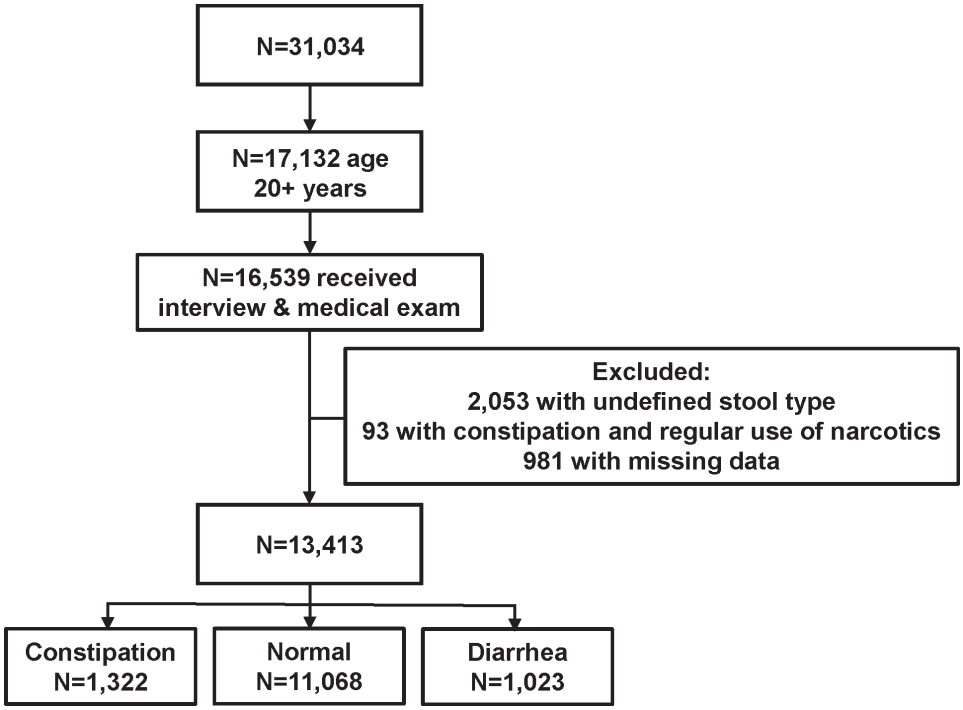

Figure 1 National Health and Nutrition Examination Surveys 2005–2006, 2007–2008 and 2009–2010 patient cohort and analytic sample.

than with constipation (26.1%, 95% CI 22.4 to 29.8) or normal bowel patterns (29.9%, 95% CI 28.7 to 31.2). MS was associated with BMI. Participants with MS had a mean BMI of 32.8 (95% CI 32.5 to 33.1), which was significantly higher than those without MS (mean BMI of 26.9 (95% CI 26.7 to 27.1); p<0.001). The association between MS and bowel pattern group was reduced after adjustment (table 2) for demographic features, smoking and alcohol consumption, mainly because of the confounding effect of age, as older age was associated with both MS and diarrhoea. MS was associated with a statistical trend showing an increase in the odds of diarrhoea versus constipation (OR=1.271, 95% CI 0.970 to 1.666). The inclusion of BMI in the model further reduced the association between MS and bowel symptom group, resulting in a non-significant OR of 0.879 (95% CI 0.673 to 1.149) for having diarrhoea versus constipation.

Overall prevalence of presumed NAFLD (table 1) was higher with diarrhoea (12.9%, 95% CI 9.8 to 15.9) than with constipation (9.0%, 95% CI 7.0 to 11.0) or normal bowel patterns (9.5%, 95% CI 8.7 to 10.4). Participants with NAFLD had a mean BMI of 30.9 (95% CI 30.4 to 31.4), which was higher than those without NAFLD (mean BMI of 28.4 (95% CI 28.2 to 28.6)). After adjusting for demographics, smoking, alcohol consumption, BMI and other obesity-related disorders, this association was still significant, with NAFLD associated with an increased odds of diarrhoea versus normal bowel patterns (OR=1.340, 95% CI 1.007 to 1.784) or constipation (OR=1.445, 95% CI 1.028 to 2.031).

Each of the other four obesity-related disorders was associated with bowel patterns in the unadjusted analysis (p<0.05). Like MS, these associations were weakened or lost (table 2) with the adjustment of demographics, smoking and alcohol consumption. Additional adjustment for BMI further weakened these associations. After adjusting for all covariates (demographics, smoking, alcohol consumption, BMI, other obesity-related disorders), associations of diarrhoea with both diabetes and sleep disorders remained significant. Those with diabetes were more likely to have diarrhoea versus normal bowel patterns (OR=1.260, 95% CI 1.042 to 1.523). Those with a sleep disorder were more likely to have diarrhoea versus normal bowel patterns (OR=1.378, 95% CI 1.025 to 1.853) or constipation (OR=1.459, 95% CI 1.006 to 2.118).

Exploratory analyses after adjustment for anti-diabetic medications

Additional analyses were conducted to evaluate whether bowel pattern group was associated with the use of anti-diabetic medications and how adjusting for anti-diabetic medications affected the study findings. In the analytic sample, 4.5% of participants used anti-diabetic medications including metformin, acarbose and exenatide. Frequencies were 3.3%, 4.3% and 9.0% for those with constipation, normal bowel patterns and diarrhoea, respectively (p<0.001). Relationships between bowel patterns and each obesity-related disorder were examined using multinomial logistic regression through sequential modelling to control for demographics, BMI, other obesity-related disorders and use of anti-diabetic medications. The observed associations of bowel pattern group with BMI (p<0.001) remained significant even

Table 1 Participant demographics and clinical characteristics by bowel pattern group

Data show % and 95% CI (CI) except where specified	Normal (N=11 068)		Constipation (N=1322)		Diarrhoea (N=1023)	
	%	95% CI	%	95% CI	%	95% CI
Age, years (mean)	46.7	45.9 to 47.4	44.4	43.4 to 45.4	50.5	49.2 to 51.9
Women	48.2	47.2 to 49.1	74.6	71.7 to 77.6	56.2	52.3 to 60.1
BMI, kg/m^2 (mean)	28.6	28.4 to 28.9	27.8	27.3 to 28.3	30.3	29.7 to 30.9
BMI class						
Underweight or normal weight	31.2	29.6 to 32.8	38.3	34.6 to 42.1	25.6	21.7 to 29.4
Overweight	34.2	33.0 to 35.5	32.5	29.5 to 35.5	31.1	27.6 to 34.7
Class I obesity	20.2	19.2 to 21.2	15.5	13.3 to 17.7	19.8	16.2 to 23.5
Class II obesity	8.7	7.9 to 9.4	8.3	6.0 to 10.6	13.5	11.0 to 15.9
Class III obesity	5.7	5.2 to 6.3	5.4	4.0 to 6.7	10.0	7.1 to 12.9
Race						
Non-Hispanic White	72.5	69.1 to 75.9	64.4	58.4 to 70.3	67.2	60.8 to 73.6
Non-Hispanic Black	9.7	(8.0 to 11.4)	16.3	12.5 to 20.2	11.7	9.2 to 14.2
Hispanic	12.3	10.0 to 14.7	14.6	11.1 to 18.1	15.6	11.3 to 19.8
Other	5.5	4.6 to 6.3	4.7	2.7 to 6.7	5.5	3.5 to 7.6
Marital status						
Married, living with partner	66.1	64.3 to 67.9	60.3	56.7 to 64.0	65.4	61.7 to 69.1
Widowed/divorced /separated	17.5	16.6 to 18.5	20.7	18.0 to 23.4	22.1	19.3 to 24.9
Never married	16.3	15.0 to 17.7	19.0	16.1 to 21.8	12.5	9.8 to 15.2
Education						
Less than high school	16.9	15.2 to 18.5	23.1	19.8 to 26.4	27.1	23.4 to 30.9
High school or GED	23.5	22.2 to 24.8	28.7	26.0 to 31.4	24.3	20.2 to 28.3
More than high school	59.6	57.3 to 61.9	48.2	44.0 to 52.5	48.6	43.8 to 53.4
Smoking						
Never	52.6	50.8 to 54.4	59.3	55.3 to 63.2	45.7	41.4 to 49.9
Past smoker	25.4	24.1 to 26.8	19.0	16.4 to 21.5	28.0	24.5 to 31.6
Current smoker	22.0	20.6 to 23.4	21.8	18.2 to 25.3	26.3	22.5 to 30.0
Alcohol						
Lifetime abstainer	10.2	9.0 to 11.3	16.1	13.3 to 19.0	12.0	9.5 to 14.5
Former drinker	15.7	14.4 to 17.0	17.7	15.2 to 20.3	21.6	16.8 to 26.5
Moderate	41.8	40.1 to 43.4	43.1	39.9 to 46.4	37.2	33.6 to 40.7
Excessive	32.4	30.7 to 34.0	23.0	20.3 to 25.7	29.2	24.8 to 33.6
Metabolic syndrome	29.9	28.7 to 31.2	26.1	22.4 to 29.8	36.0	31.5 to 40.6
Cardiovascular disease*	7.7	6.9 to 8.4	7.9	6.1 to 9.7	11.5	8.6 to 14.3
Diabetes	9.7	8.9 to 10.5	9.2	7.3 to 11.2	15.7	12.9 to 18.5
NAFLD†	9.5	8.7 to 10.4	9.0	7.0 to 11.0	12.9	9.8 to 15.9
Sleep disorder	7.3	6.7 to 7.9	5.9	4.3 to 7.4	11.4	8.7 to 14.2
Cancer‡	8.7	7.8 to 9.6	9.6	7.5 to 11.7	12.4	9.9 to 15.0

Comparisons performed using analysis of variance for continuous variables and Rao-Scott χ^2 test for categorical variables.
*P value=0.002.
†P value=0.035.
‡P value=0.005; all other p values <0.001.
BMI, body mass index; GED, general educational development; NAFLD, non-alcoholic fatty liver disease.

after adjustment for all covariates and anti-diabetic medications. Associations of bowel pattern groups with sleep disorders and NAFLD remained significant, while the association of bowel pattern group with diabetes was no longer significant. Those with a sleep disorder were more likely to have diarrhoea versus normal bowel patterns

Table 2 Adjusted associations between bowel pattern group and obesity-related disorders

		Step 1 models		Step 2 models		Step 3 models	
		OR	95% CI	OR	95% CI	OR	95% C
Metabolic syndrome	Normal versus Constipation	1.188	0.967 to 1.458	1.019	0.822 to 1.263	1.058	0.838 to 1.33
	Diarrhoea versus Constipation	1.271	0.970 to 1.666	0.879	0.673 to 1.149	0.836	0.635 to 1.102
	Diarrhoea versus Normal	1.070	0.883 to 1.297	0.863	0.689 to 1.082	0.790	0.619 to 1.008
Cardiovascular disease	Normal versus Constipation	0.778	0.584 to 1.038	0.756	0.569 to 1.006	0.767	0.579 to 1.018
	Diarrhoea versus Constipation	0.916	0.620 to 1.355	0.851	0.578 to 1.251	0.826	0.558 to 1.222
	Diarrhoea versus Normal	1.177	0.904 to 1.533	1.125	0.865 to 1.462	1.077	0.823 to 1.408
Diabetes	Normal versus Constipation	1.013	0.788 to 1.302	0.905	0.705 to 1.163	0.918	0.688 to 1.224
	Diarrhoea versus Constipation	1.385	1.036 to 1.852	1.091	0.809 to 1.471	1.156	0.828 to 1.615
	Diarrhoea versus Normal	**1.367**	**1.138 to 1.642**	**1.205**	**1.015 to 1.430**	**1.260**	**1.042 to 1.523**
Non-alcoholic fatty liver disease	Normal versus Constipation	1.136	0.862 to 1.49	1.083	0.825 to 1.42	1.078	0.823 to 1.412
	Diarrhoea versus Constipation	**1.597**	**1.129 to 2.26**	**1.437**	**1.021 to 2.02**	**1.445**	**1.028 to 2.031**
	Diarrhoea versus Normal	**1.406**	**1.053 to 1.878**	1.326	0.994 to 1.769	**1.340**	**1.007 to 1.784**
Sleep disorder	Normal versus Constipation	1.142	0.866 to 1.505	1.034	0.772 to 1.384	1.059	0.787 to 1.424
	Diarrhoea versus Constipation	**1.802**	**1.253 to 2.590**	1.440	0.993 to 2.089	**1.459**	**1.006 to 2.118**
	Diarrhoea versus Normal	**1.578**	**1.168 to 2.131**	**1.393**	**1.032 to 1.880**	**1.378**	**1.025 to 1.853**
Cancer	Normal versus Constipation	**0.768**	**0.593 to 0.996**	**0.770**	**0.594 to 0.996**	0.780	0.604 to 1.008
	Diarrhoea versus Constipation	0.973	0.674 to 1.403	0.980	0.680 to 1.413	0.992	0.690 to 1.426
	Diarrhoea versus Normal	1.266	0.987 to 1.624	1.274	0.994 to 1.633	1.271	0.988 to 1.636

Comparisons based on multinomial logistic regression.

(OR=1.373, 95% CI 1.021 to 1.845) or constipation (OR=1.452, 95% CI 1.000 to 2.110). Those with NAFLD were more likely to have w diarrhoea versus normal bowel patterns (OR=1.344, 95% CI 1.011 to 1.787) or constipation (OR=1.450, 95% CI 1.030 to 2.042).

DISCUSSION

This study is the first to examine the association of bowel patterns with MS and NAFLD among a representative sample of US adults. As associations between obesity and diarrhoea have previously been well described,[4–6 20] it is not surprising that our findings demonstrate an association between BMI and diarrhoea. Possible mechanisms explaining this association include alterations in regional GI transit,[21 22] bile acid malabsorption, increased intestinal permeability, or low-grade inflammation (reviewed in[23]). Changes in the intestinal microbiome have also been associated with functional bowel disorders, obesity and MS[24] and may represent a common pathophysiological exposure. In this cross-sectional study, although MS was more prevalent in individuals reporting diarrhoea, this association was not statistically significant and was weakened after adjusting for BMI, suggesting that MS is not independently

associated with diarrhoea. This is not unexpected given that bowel disorders and MS are both clinically heterogeneous conditions. As BMI is correlated with waist circumference and other components of MS, it is not unexpected that the relationship between MS and bowel patterns is no longer significant after adjusting for BMI. However, this association is still an important one to explore as several studies have demonstrated the concept of 'normal weight obesity' that is associated with MS, insulin resistance, or other obesity-related disorders.[25 26] In contrast, examination of other obesity-related disorders revealed that NAFLD was independently associated with diarrhoea versus normal bowel patterns or constipation even after adjusting for BMI and other obesity-related disorders. Presence of diabetes was also independently associated with diarrhoea versus normal bowel patterns while presence of a sleep disorder was independently associated with diarrhoea versus normal bowel patterns or constipation.

The association between diarrhoea and NAFLD is important to note and may help guide future studies of the mechanisms that link obesity or increased BMI with diarrhoea. For example, bile-acid mediated mechanisms may be of particular interest as the role of bile acids has been implicated in the pathophysiology of both chronic diarrhoea and NAFLD. Clinical studies have identified genetic variations in the bile acid receptor, Takeda G-protein-coupled receptor-5 (TGR5 or GPBAR1) that may contribute to altered transit in lower functional bowel disorders.[27] Activation of TGR5 may also have important effects on glucagon-like peptide-1 associated metabolic regulation[28] relevant to NAFLD. Impaired production of fibroblast growth factor 19 (FGF19), which regulates hepatic synthesis of bile acids, has been proposed as a mechanisms for bile acid diarrhoea[29] and has also been implicated in the pathogenesis of NAFLD.[30] Furthermore, bile acid-activated farnesoid X receptor agonists, such as obeticholic acid, have been studied for the treatment of both bile acid diarrhoea and in NAFLD. Among patients with primary bile acid diarrhoea, obeticholic acid was associated with increased median fasting FGF-19 and improvements in bowel functions.[31] Meanwhile, in a multicentre double-blind randomised controlled trail among patients with non-alcoholic steatohepatitis, obeticholic acid improved biochemical and histological features of NASH compared with placebo.[32]

Important to note is that bile acid diarrhoea may be an aetiology in up to 50% of patients with chronic diarrhoea[33] and has been positively associated with BMI.[2] In a recent retrospective study, Appleby *et al* reported an increased prevalence of fatty liver disease in bile acid diarrhoea,[8] although confounding by BMI could not be excluded. A subsequent prospective study of NAFLD patients found associations between increased hepatic bile acid synthesis with diarrhoea and increased NAFLD fibrosis score[10] as well as a higher than expected incidence of chronic diarrhoea (25%). However, no control group was available for comparison. In our analysis, the association between NAFLD and diarrhoea in a large nationally representative sample of the general US population remained significant even after adjusting for BMI and other obesity-related disorders although the prevalence of bile acid diarrhoea and other mechanisms for bowel dysfunction could not be determined from the cross-sectional NHANES data. Taken together, findings from our study add to the body of evidence suggesting that NAFLD and chronic diarrhoea may be independently linked and that further attention to the gut-liver axis may be required among patients with common bowel disorders such as functional diarrhoea or IBS. These potential relationships, however, are likely complex and bidirectional and may involve additional factors such as the GI microbiome and transit. It should further be noted that the magnitude of the observed associations between NAFLD and bowel patterns in our study were modest, suggesting that multiple factors contribute to the pathogenesis of NAFLD and bowel symptoms. However, the strength of these associations may have been diminished by the broad definitions of diarrhoea and constipation used in this study, which likely contributed to the heterogeneity of the bowel pattern groups. Thus, further prospective investigation of intraluminal bile acids, NAFLD and diarrhoea are warranted to validate these associations. Although it is possible that associations between NAFLD and diarrhoea may have been confounded by residual factors such as medication use (eg, lactulose for hepatic encephalopathy), only 10 individuals in the analytic sample were identified as having NASH cirrhosis. Thus, confounding by factors associated with clinical features of cirrhosis were unlikely to have an important effect.

Associations between diarrhoea and sleep disorders including insomnia, sleep apnoea and restless leg syndrome in this population-based study may support previous hypotheses involving the role of the brain-gut axis in lower functional bowel disorders. Sleep disturbances including abnormal REM sleep,[34] sleep apnoea[35] and sleep impairment[36] have been associated with IBS. Contrary to our findings, in one prior study,[36] sleep impairment was more common in constipation-predominant IBS patients than in diarrhoea-predominant IBS. Observed associations between diarrhoea and diabetes in our study are consistent with a recently published study[37] which reported an increased prevalence of chronic diarrhoea in diabetics compared with non-diabetics using data from the 2009 to 2010 NHANES dataset. It is possible that these associations may reflect the use of anti-diabetic medications such as metformin.[38] To explore this question, we conducted additional analyses to evaluate whether the associations of bowel pattern group with obesity-related disorders were influenced by the use of anti-diabetic medications (eg, metformin, acarbose and exenatide) to demonstrate that although the association of bowel pattern group with diabetes was no longer significant, the associations of bowel pattern group with BMI, sleep disorders and NAFLD remained significant. Other potential mechanisms may include bile

acid malabsorption,[39] bacterial overgrowth,[40] autonomic neuropathy[41] and consumption of artificial sweeteners. As presence of a sleep disorder or diabetes was based on self-report, further studies to confirm these findings and to evaluate the associations of specific types of sleep disorders or diabetes type with bowel patterns will be required.

Our study has several limitations, including the cross-sectional nature of the NHANES data, reliance on self-report data with potential for recall bias, lack of information on presence of celiac disease or inflammatory bowel disease (available only for the 2009–2010 cycle for subjects ages 20–69), and lack of data on symptom duration or other GI conditions such as microscopic colitis. Although definitions for constipation and diarrhoea were based on prior NHANES publications,[4 15 16] these definitions are not universally agreed on. In this study we defined constipation and diarrhoea based on responses to the BHQ. The BHQ is a broad tool assessing only stool consistency and frequency, and it does not assess for other symptoms such as abdominal pain. Therefore, we were unable to apply Rome IV diagnostic criteria. Furthermore, data on whether participants underwent additional diagnostic testing for their bowel symptoms with blood tests, stool tests, colonoscopy or radiographic imaging, or other secondary tests where indicated was not available.[42] Hence, the generalisability of our findings to patients with IBS, functional constipation and functional diarrhoea may be limited. Some patients with NAFLD may have normal liver tests, and abnormal liver test are not required to make a diagnosis of NAFLD. In this cohort, we did not have histological or radiological confirmation of a clinical diagnosis of NAFLD. Together, these factors may have led to underestimation of the prevalence of NAFLD. In addition, analyses were not adjusted for multiple testing and our findings are more suggestive than definitive. However, the results are informative and hypothesis generating as this is the first population-based study to report an association between NAFLD and chronic diarrhoea that is independent of BMI.

In summary, among a representative sample of US adults, results of our population-based cross-sectional analysis support previously reported associations between BMI or obesity and diarrhoea that are not clearly explained by eating behaviours or socioeconomic characteristics in prior studies.[5] Although there does not seem to be a significant association between MS and bowel patterns independent of BMI, the results suggest that diarrhoea may be independently linked to NAFLD, which may warrant further prospective evaluation of shared aetiological mechanisms between these two highly prevalent conditions.

Contributors AS: conceptual development, study design, data interpretation, drafting and review of manuscript. HX: study design, statistical analysis, drafting and review of manuscript. TFI: data interpretation, drafting and review of manuscript.

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