# Dietary patterns associated with magnetic resonance imaging–determined liver fat content in a general population study[1–3]

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**ABSTRACT**

**Background:** The association between diet and fatty liver disease (FLD) has predominantly been analyzed for single nutrients or foods, and findings have been inconsistent.

**Objective:** We aimed to compare associations of hypothesis-driven and exploratory dietary pattern scores with liver fat content.

**Design:** Liver fat was measured by using magnetic resonance imaging as liver signal intensity (LSI) in a population-based, cross-sectional study that included 354 individuals. We applied partial least-squares regression to derive an exploratory dietary pattern score that explained variation in both the intake of 38 food groups, which were assessed by using a food-frequency questionnaire, and LSI. The hypothesis-driven score was calculated on the basis of published studies. Multivariable linear or logistic regression was used to investigate associations between dietary pattern scores and LSI or FLD.

**Results:** A higher percentage of LSI variation was explained by the exploratory (12.6%) compared with the hypothesis-driven (2.2%) dietary pattern. Of the 13 most important food groups of the exploratory dietary pattern, intakes of green and black tea, soups, and beer were also individually associated with LSI values. A 1-unit increase in the exploratory dietary pattern score was positively associated with FLD (OR: 1.56; 95% CI: 1.29, 1.88). Furthermore, a 1-unit increase in the hypothesis-driven dietary pattern score, which consisted of alcohol, soft drinks, meat, coffee, and tea, was positively associated with FLD (OR: 1.25; 95% CI: 1.10, 1.43).

**Conclusion:** We defined a hypothesis-driven dietary pattern and derived an exploratory dietary pattern, both of which included alcohol, meat (poultry), and tea, associated with liver fat content independent from confounders, which should be explored in prospective studies. *Am J Clin Nutr* 2014;99:369–77.

## INTRODUCTION

The excess accumulation of liver fat, which is an entity termed fatty liver disease (FLD)[4], has been shown to be associated with a broad pattern of metabolic alterations related to the metabolic syndrome (1). The metabolic alterations of FLD are closely linked to type 2 diabetes and cardiovascular disease (2), and different genetic variants may play a role in the cause and progression of FLD (3). Although the pathogenesis of FLD is complex and poorly understood, an imbalance between the acquisition and degradation or secretion of triglycerides is the central phenomenon (3). The prevalence of FLD varies in specific populations between 6% and 33%, which is partially because of varying definitions and methods used to define FLD (4).

Considerable research interest has been on the association between dietary habits and FLD (5–7). Evidence mainly from cross-sectional studies has suggested associations of alcohol (8–10), soft drinks (6, 11), meat (5, 6), and coffee and tea (7, 12–14) intakes with FLD or chronic liver diseases. However, overall, the level of evidence relating dietary intake to FLD seems insufficient because no specific nutritional recommendation for the prevention of accumulation of fat in the liver or authoritative clinical nutritional guideline for the therapy of FLD besides weight loss exists (4).

A dietary pattern analysis enables the assessment of adherence to specific dietary habits and has been introduced into nutritional epidemiology to investigate diets as a whole. As opposed to traditional analyses that have focused on single nutrients or foods, this approach takes interactions of nutrients or foods into account (15). Dietary patterns can be derived on the basis of hypotheses (15) (ie, consisting of food groups that have been previously linked to FLD). Although this approach is promising, the selection of food groups is not unambiguous and is limited by the existing scientific evidence (15). Because dietary patterns beyond aspects already known may be of relevance, the identification of dietary patterns by

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[4] Abbreviations used: FLD, fatty liver disease; LSI, liver signal intensity; PLS, partial least squares; VIP, variable importance in the projection.

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means of an exploratory dietary pattern analysis is also of interest (15). Partial least-squares (PLS) regression enables the identification of patterns that captured information on dietary intake useful to model specific health outcomes such as liver fat content (16). To our knowledge, the only previous study to investigate exploratory dietary patterns in relation to FLD was limited to adolescents and showed a higher adherence to a Western dietary pattern to be positively associated with FLD (17).

The assessment of FLD in epidemiologic studies by means of ultrasound (6, 11) has been criticized for a low sensitivity to diagnose mild FLD (18). Studies that assessed the predictive ability of ultrasound to diagnose FLD by using biopsies as the reference method applied higher cutoffs of 10% to define FLD (19) compared with commonly applied cutoffs of 5% (20). A superior approach for the assessment of FLD is to use MRI that enables the assessment of liver fat content on a continuous scale (2). Although FLD is frequently distinguished into nonalcoholic FLD and alcoholic FLD, the joint consideration as a multicausal disorder has been suggested (21) because, among other reasons, pathological findings have been similar, and a single, uniform cutoff to define amounts of harmless alcohol consumption is lacking (21). We aimed to compare associations of hypothesis-driven and exploratory dietary pattern scores with liver fat content determined on a continuous scale by using MRI in a large population-based, cross-sectional study.

## SUBJECTS AND METHODS

### Study design and population

The current cross-sectional analysis was conducted in a subsample of the PopGen control cohort, which is a population-based sample of 747 individuals identified through official population registries in Kiel (Germany) who were initially recruited into the PopGen biobank between June 2005 and February 2006 (22). A first follow-up of this study population was conducted from 2010 to 2012. Study participants were invited by mail to visit the study center for the sampling of blood and a medical examination (22). As part of the phenotypic assessment, MRI was conducted to assess liver fat content and a food-frequency questionnaire was applied. The study was approved by the ethical review board of the Medical Faculty of the Christian-Albrechts University Kiel. Written informed consent was obtained from all study participants.

### Exposure assessment

Dietary intake over the past year was assessed by using a self-administered 112-item food-frequency questionnaire established for German populations (23). All participants were given the option of completing the questionnaire preferably as a web-based version and, optionally, on paper. Macro and micronutrient intakes were obtained by using the German Food Code and Nutrient Database (version II.3) and provided by the Department of Epidemiology of the German Institute of Human Nutrition Potsdam-Rehbrücke (24). To reduce the arbitrariness of food-item grouping for the exploratory dietary pattern analysis (15), food items were classified into 38 food groups according to a slightly modified definition published by Kröger et al (25). Tea was originally proposed as one food group (25); however, in our analysis, we separated green and black tea from fruit and herbal tea. The food groups condiments and yeast and miscellaneous were not considered.

### Assessment of covariates

Information about subject characteristics including sex, age, educational attainment, smoking habit, recreational physical activity, menopause status, and medical history were assessed by using self-administered questionnaires. Participants were asked to report the time spent walking, cycling, engaging in sports and gardening (average of summer and winter seasons), household work, and do-it-yourself activities per week over the past year and the number of flights of stairs climbed per day. The duration of stair climbing per week was calculated with the assumption of 20 steps/flight and that, on average, 72 steps/min were climbed (26). The duration of each physical activity was multiplied by the corresponding metabolic equivalent intensity level and summed for all activities according to Ainsworth et al (27). Women were classified as postmenopausal if they had no regular monthly period for $>1$ y. Type 2 diabetes prevalence was defined by using baseline and follow-up information as either self-reported type 2 diabetes diagnosed by a physician, reference to the respective medication used, glycated hemoglobin $\geq 6.5\%$, or fasting blood glucose concentration $\geq 126$ mg/dL (28). Weight and height were measured with subjects dressed in light clothing without shoes. Two kilograms were subtracted from weight measurements to account for clothing. Waist circumference was measured at the midpoint between the lower ribs and iliac crest on the anterior axillary line in a resting expiratory position. BMI (in $kg/m^2$) was calculated as weight divided by height squared. The waist-to-height ratio was calculated as the waist circumference (in cm) divided by height (in cm).

For the biochemical assessment, EDTA plasma and lithium heparin plasma blood samples were obtained from study participants in a sitting position after an overnight fast. Blood biomarkers were analyzed in fresh blood samples without freeze-thaw cycles. Glycated hemoglobin concentrations were determined by using HPLC and photometric detection (Bio-Rad Laboratories) in EDTA plasma. In lithium heparin plasma, concentrations of alanine aminotransferase and triglycerides were determined by using enzymatic color tests and photometric detection (Roche Diagnostics), and the concentration of glucose was determined by using enzymatic ultraviolet tests (Roche Diagnostics).

### Outcome assessment

Liver fat content was quantified by using liver MRI on the basis of published methods (29, 30). MRI was performed on a 1.5-T whole-body imager (Magnetom Avanto; Siemens Medical Solutions). In-phase and out-of-phase images were acquired during a breath hold by using axial T1-weighted gradient echo MRI with a 10.4-ms repetition time, echo time of 4.76 ms (in-phase) and 7.14 ms (opposed phase), 10° flip angle, $128 \times 80$ matrix, and $275 \times 440$-mm field of view. Signal intensities were obtained by averaging measurements of 3 circular regions of interest (1.03-cm diameter; SD $<10\%$) in the liver parenchyma with the exclusion of vessels or artifact at a similar anatomic placement on paired in-phase and out-of-phase magnetic resonance images with the ImageJ program version 1.45s (31) by a single person in a section basal of the portal vein in the lower right lobe (liver segment 5/6),

in a section of the portal vein in the upper right lobe (liver segment 7/8), and in a section cranial of the portal vein in the left lobe (liver segment 2/4a). Liver fat was quantified as the relative liver signal intensity (LSI) difference of the liver on out-of-phase compared with in-phase images in arbitrary units according to the following formula (32):

$$\text{LSI} = 100 \times [(\text{signal intensity}_{\text{in-phase}} - \text{signal intensity}_{\text{out-of-phase}}) \div \text{signal intensity}_{\text{in-phase}}] \quad (1)$$

In a sample of 40 individuals (55% men; median age: 55.6 y; median BMI: 27.7), liver fat content was additionally measured by T2-corrected $^{1}$H single-voxel proton magnetic resonance spectroscopy on a 1.5-T whole-body imager (Magnetom Avanto; Siemens Medical Solutions) by using a volumetric interpolated sequence package. In the coronal view, a $3 \times 3 \times 3$-cm$^3$ voxel was placed in the dorsal upper right lobe of the liver (segment 7/8), avoiding vessels and bile ducts. After a preacquisition excitation, 5 single average spectra were acquired with progressive echo times of 12, 24, 36, 48, and 72 ms within a single breath hold. T2 correction was performed for water and fat peaks providing the measure of the magnetic resonance spectroscopy fat fraction. Spearman's correlation coefficient between LSI values and the spectroscopic determined liver fat content was $r = 0.609$ ($P < 0.001$).

For selected analyses, the continuous LSI variable was dichotomized in an FLD indicator variable (log LSI $\geq$3.0) according to a cutoff derived by a receiver operating characteristic analysis (AUC: 0.86; 95% CI: 0.74, 0.98) with spectroscopic-determined FLD [liver fat $\geq$5.56% (33)] as the reference method. A log-LSI cutoff $\geq$3.0, for which the maximum Youden index was obtained, corresponded to a specificity of 80.8% and a sensitivity of 78.6% to predict spectroscopic-determined FLD.

### Statistical analysis

The LSI was natural logarithmically transformed before analyses because of its skewed distribution. We calculated a hypothesis-driven dietary pattern score that consisted of food groups that have been associated with FLD or chronic liver disease in $\geq$2 previous studies. Previous studies observed that higher intakes of alcoholic beverages (8–10), soft drinks (6, 11, 34), and meat (5, 6) and lower intakes of coffee and tea (7, 12–14, 35, 36) were associated with FLD or chronic liver disease. In particular, standardized intakes (in g/d) of alcohol from alcoholic beverages, soft drinks, and meat were summed, and the standardized intake of coffee and tea was subtracted to obtain the hypothesis-driven diet score (37).

PLS regression was used to derive an exploratory dietary pattern score associated with liver fat content by using the PLS procedure and applying the nonlinear iterative PLS algorithm in SAS software (version 9.2; SAS Institute Inc) (16). The method (including the SAS code) and its applicability in nutritional epidemiology have already been described in detail by Hoffmann et al (16). In brief, PLS regression derives components, also termed dietary pattern scores in the following, which are predictors of the outcome (here: liver fat content) and also model explanatory variables (here: 38 food groups) (38). All dietary intake variables were adjusted for energy intake by using the residual method (39) before entering into the PLS model to account for possible confounding due to varying total energy intake. Moreover, all variables were then standardized to unit variance and a zero mean.

Because the first extracted dietary pattern explained the maximal variation in LSI, and the subsequent 2 PLS-derived dietary patterns would have explained only 2.6% and 1.8% of the LSI variation, the final PLS model was limited to one extracted pattern. To obtain the dietary pattern score, a characteristic value defined as the weighted sum of intake of single food groups and, thus, indicating compliance with this dietary pattern was assigned to each participant. To assess the importance of an explanatory variable to the PLS model, the variable importance in the projection (VIP) statistic is commonly applied (40). To derive a VIP statistic, a weighted sum of squares of PLS weights is calculated. As proposed, a VIP statistic $>$1.0 was used to identify foods and food groups with high contributions to the final PLS model (40).

For description, the study population was divided into tertiles on the basis of the distribution of LSI values. Trends of continuous variables across tertiles of LSI were assessed for statistical significance by using a $t$ test of the slope in a linear regression model. For this purpose, each participant was assigned the median LSI value for the tertile, and this variable was treated as a continuous variable. Trends of categorical variables across tertiles of LSI were assessed for statistical significance by using the Cochran-Armitage test.

The association between dietary pattern scores and LSI and FLD was analyzed by using multiple linear regression and logistic regression models, respectively. Models were adjusted for sex and age (continuous) as potential confounding factors. A second model was further adjusted for years of education [$\leq$9 y (no level of general education completed or secondary general school–leaving certificate), 10 y (intermediate school–leaving certificate), or $\geq$11 y (university of applied sciences or university entrance qualification)], smoking status [never (smoking period $\leq$3 mo), former (smoking period $>$3 mo), or current], smoking duration (y), physical activity (metabolic equivalent task hours/wk), and total energy intake (kcal/d). All models were additionally stratified by sex (men and women), age ($\leq$67.6 and $>$67.6 y of age), BMI (men: $<$26.7 and $\geq$26.7; women: $<$27.0 and $\geq$27.0), and diabetes status (yes or no). The median age of the study population was 67.6 y, and the median BMI was 26.7 in men and 27.0 in women. We investigated potential effect modifications by sex, age ($\leq$67.6 and $>$67.6 y of age), BMI (men: $<$26.7 and $\geq$26.7; women: $<$27.0 and $\geq$27.0), and diabetes status (yes or no) by inclusion of interaction terms in regression models. Furthermore, models were stratified by alcohol consumption ($\leq$20 and $>$20g/d).

In a secondary analysis, we restricted the study population to individuals without FLD (LSI $<$3.0) to explore associations between dietary pattern scores with lower amounts of liver fat.

All tests were 2-sided, and $P$ values $<$0.05 were considered statistically significant. All statistical analyses were performed with SAS statistical analysis software (version 9.2).

## RESULTS

For the current project, the cross-sectional data of the 569 individuals who agreed to participate in this follow-up examination were analyzed (response proportion: 76%). The exclusion of individuals with a missing MRI assessment ($n$ = 161), images of insufficient quality because of noncompliance to the MRI

breathing protocol ($n$ = 18), missing information on covariates ($n$ = 21), or self-reported liver disease [hepatitis A, B, C, or D virus infection, hemochromatosis, autoimmune liver disease, or liver cirrhosis ($n$ = 15)] resulted in 354 individuals available for this cross-sectional analysis. There was no individual with an implausible energy intake (<800 or >6000 kcal/d) (41).

Characteristics of the study population stratified by tertiles of LSI are displayed in **Table 1**. Participants with a higher LSI had a higher BMI, waist circumference, and waist-to-height ratio. The median BMI for the population was 26.8, the median waist circumference was 97.1 cm, and the median waist-to-height ratio was 0.57. Plasma concentrations of alanine aminotransferase and

**TABLE 1**
Characteristics of the study participants according to tertiles of liver signal intensity ($n$ = 354)

| | Tertile of liver signal intensity | | | |
|---|---|---|---|---|
| Participant characteristics | 1 ($n$ = 118) | 2 ($n$ = 118) | 3 ($n$ = 118) | $P$-trend[1] |
| Liver signal intensity | 2.7 (2.5, 2.8)[2] | 3.0 (2.9, 3.1) | 3.4 (3.3, 3.6) | |
| Fatty liver disease [$n$ (%)][3] | 0 (0.0) | 53 (44.9) | 118 (100.0) | <0.001 |
| Age (y) | 66.1 (60.3, 72.2) | 68.2 (61.3, 72.6) | 68.4 (62.3, 72.4) | 0.445 |
| Participants (M) [$n$ (%)] | 71 (60.2) | 66 (55.9) | 65 (55.1) | 0.430 |
| Education [$n$ (%)] | | | | |
| ≤9 y | 45 (38.1) | 41 (34.8) | 46 (39.0) | 0.893 |
| 10 y | 35 (29.7) | 44 (37.3) | 39 (33.1) | 0.581 |
| ≥11 y | 38 (32.2) | 33 (28.0) | 33 (28.0) | 0.475 |
| Smoking status [$n$ (%)] | | | | |
| Never | 60 (50.9) | 57 (48.3) | 50 (42.4) | 0.192 |
| Former | 51 (43.2) | 49 (41.5) | 60 (50.9) | 0.239 |
| Current | 7 (5.9) | 12 (10.2) | 8 (6.8) | 0.806 |
| Pack-years of smoking | 0.0 (0.0, 15.8) | 1.6 (0.0, 19.0) | 5.5 (0.0, 22.0) | 0.149 |
| Physical activity (metabolic equivalent task hours/wk) | 99.0 (63.3, 143.6) | 94.6 (62.2, 129.0) | 93.5 (67.5, 140.7) | 0.540 |
| BMI (kg/m$^2$) | 25.6 (23.2, 28.1) | 25.9 (24.0, 28.5) | 29.2 (26.9, 31.1) | <0.001 |
| Waist circumference (cm) | 92.5 (84.3, 102.0) | 95.8 (88.5, 102.2) | 102.7 (95.0, 109.1) | <0.001 |
| Waist-to-height ratio | 0.54 (0.50, 0.59) | 0.56 (0.52, 0.59) | 0.61 (0.56, 0.65) | <0.001 |
| Menopause (F only) [$n$ (%)] | 47 (100.0) | 48 (92.3) | 50 (94.3) | 0.193 |
| Alanine aminotransferase (U/L) | 21 (16, 26) | 20 (17, 26) | 29 (21, 37) | <0.001 |
| Triglycerides (mmol/L) | 1.1 (0.8, 1.5) | 1.2 (0.9, 1.5) | 1.4 (1.1, 2.0) | <0.001 |
| Type 2 diabetes [$n$ (%)][4] | 11 (9.3) | 13 (11.0) | 31 (26.3) | <0.001 |
| Food and food group intakes (g · 1000 kcal$^{-1}$ · d$^{-1}$) | | | | |
| Hypothesis-driven dietary pattern | | | | |
| Alcohol | 3.2 (1.2, 7.2) | 4.0 (1.1, 6.8) | 4.0 (1.1, 10.0) | 0.002 |
| Soft drinks | 4.2 (2.9, 8.5) | 4.8 (2.8, 9.6) | 3.8 (2.8, 7.4) | 0.741 |
| Meat | 48.7 (36.9, 68.5) | 48.7 (32.3, 66.9) | 54.1 (41.7, 68.8) | 0.468 |
| Coffee | 165.6 (98.8, 268.4) | 180.4 (135.1, 259.9) | 167.2 (109.7, 243.2) | 0.323 |
| Tea | 107.2 (12.4, 207.4) | 69.3 (11.8, 185.9) | 40.1 (8.0, 123.6) | <0.001 |
| Exploratory dietary pattern[5] | | | | |
| Fruit and herbal tea | 7.8 (1.1, 81.7) | 9.4 (1.0, 97.2) | 4.3 (0.9, 28.5) | 0.061 |
| Green and black tea | 15.3 (3.5, 123.7) | 16.8 (3.4, 113.5) | 10.1 (3.0, 59.8) | 0.001 |
| Sugar and confectionary | 21.8 (14.3, 30.3) | 25.0 (18.8, 32.2) | 20.3 (13.0, 28.7) | 0.261 |
| Other fats | 0.9 (0.7, 1.2) | 0.9 (0.7, 1.0) | 0.9 (0.7, 1.2) | 0.471 |
| Bread | 44.4 (34.6, 60.2) | 39.4 (32.0, 53.4) | 41.9 (32.9, 53.5) | 0.478 |
| Breakfast cereals | 0.9 (0.6, 2.5) | 0.9 (0.6, 2.3) | 0.7 (0.6, 1.5) | 0.333 |
| Cheese | 15.4 (11.6, 21.3) | 16.6 (12.8, 20.6) | 14.2 (11.1, 18.1) | 0.082 |
| Soups | 14.7 (11.7, 21.9) | 15.3 (11.2, 20.3) | 18.4 (12.6, 27.1) | 0.003 |
| Beer | 8.4 (0.0, 32.4) | 5.0 (2.1, 38.3) | 10.8 (2.4, 62.5) | 0.009 |
| Wine | 13.4 (5.7, 43.0) | 19.9 (5.2, 47.4) | 15.8 (4.4, 55.2) | 0.066 |
| Poultry | 6.1 (2.8, 8.6) | 5.1 (2.6, 8.5) | 6.3 (3.8, 9.5) | 0.108 |
| Juices | 26.1 (11.8, 83.8) | 29.7 (11.1, 81.5) | 23.3 (12.3, 76.0) | 0.383 |
| Eggs | 5.7 (3.1, 9.2) | 6.6 (3.2, 9.2) | 7.7 (4.4, 10.3) | 0.375 |
| Hypothesis-driven dietary pattern score | −0.63 (−1.33, 0.82) | −0.32 (−1.21, 0.68) | 0.24 (−0.52, 1.65) | <0.001 |
| Exploratory dietary pattern score | −0.28 (−0.95, 0.19) | −0.20 (−0.91, 0.45) | 0.39 (−0.39, 1.55) | <0.001 |

[1] $P$-trend values across categories of liver signal intensity were based on the Cochran-Armitage test for categorical variables and linear regression analysis for continuous variables with the median liver signal intensity variable within tertiles.

[2] Median; IQR in parentheses (all such values).

[3] Liver signal intensity ≥3.0.

[4] Defined by using baseline and follow-up information as self-reported type 2 diabetes diagnosed by a physician, reference to the respective medication used, glycated hemoglobin ≥6.5%, or a fasting blood glucose concentration ≥126 mg/dL.

[5] Variable importance in the projection statistic (40) was used to assess the importance of a food group to the partial least-squares model. Food groups with variable importance in the projection statistic ≤1.0 in the partial least-squares model were excluded from the table.

**TABLE 2**
Food groups important for the modeling of LSI in the PLS regression analysis ($n$ = 354)[1]

| Food groups | Regression coefficient for standardized food item in the PLS regression model | Variable importance in the projection statistic | Variation in food groups explained by exploratory dietary pattern score |
|---|---|---|---|
| | | | % |
| Inverse association with LSI | | | |
| Fruit and herbal tea | −0.09 | 1.89 | 7.05 |
| Green and black tea | −0.08 | 1.77 | 7.82 |
| Sugar and confectionary | −0.08 | 1.74 | 18.41 |
| Other fats | −0.07 | 1.46 | 1.59 |
| Bread | −0.07 | 1.36 | 10.15 |
| Breakfast cereals | −0.06 | 1.17 | 6.27 |
| Cheese | −0.05 | 1.04 | 9.35 |
| Positive association with LSI | | | |
| Soups | 0.12 | 2.47 | 23.98 |
| Beer | 0.09 | 1.96 | 15.27 |
| Wine | 0.08 | 1.59 | 9.70 |
| Poultry | 0.07 | 1.40 | 8.41 |
| Juices | 0.07 | 1.38 | 3.64 |
| Eggs | 0.06 | 1.34 | 7.97 |

[1] The variable importance in the projection statistic (40) was used to assess the importance of a food group to the PLS model. Food groups with a variable importance in the projection statistic ≤1.0 in the PLS model were excluded from the table. LSI, liver signal intensity; PLS, partial least squares.

triglycerides increased with the increasing LSI tertile. Age, educational attainment, smoking status, pack-years of smoking, physical activity, or menopause status (women only) did not differ across LSI tertiles. Type 2 diabetes was most prevalent in individuals in the highest tertile of LSI.

Of dietary food groups included in the hypothesis-driven dietary pattern score, the intake of alcohol increased with increasing LSI values, whereas the intake of tea decreased (Table 1). Although no trend across LSI tertiles was observed for the remaining food groups (intake of soft drinks, meat, or coffee) the hypothesis-driven dietary pattern score nevertheless increased with increasing LSI values. Similarly the exploratory PLS-derived dietary pattern score increased across LSI tertiles. However, the median intake of single food groups important to the PLS model defined by means of a VIP statistic >1 did not vary significantly across tertiles of LSI in the univariable linear regression analysis except for green and black tea, soups, and beer. Detailed information of food groups important to the PLS model (VIP statistic >1) are summarized in **Table 2** and listed first for food groups inversely related to the LSI and second for food groups positively related to the LSI in the ordering of decreasing VIP values. Fruit and herbal tea, green and black tea, sugar and confectionary, other fats, bread, breakfast cereals, and cheese had negative regression coefficients. Soups, beer, wine, juices, poultry, and eggs had positive regression coefficients. The variation in food groups explained by the exploratory dietary pattern score was highest for soups (23.98%) and sugar and confectionary (18.41%).

In the univariable linear regression analysis, the hypothesis-driven dietary pattern score explained 2.2% of variation in the LSI, and the exploratory dietary pattern score explained 12.6% of LSI variation (data not shown). The LSI was, on average, 0.04 units higher per 1-unit increase in the hypothesis-driven dietary pattern score (95% CI: 0.02, 0.07) (**Table 3**). Per 1-unit increase in the exploratory dietary pattern score, the LSI was, on average, 0.12 units higher (95% CI: 0.09, 0.15). After adjustment for age, sex, educational attainment, smoking status, physical activity, and total energy intake, both scores remained associated with the LSI. The exploratory dietary pattern score was more strongly associated with LSI in older individuals defined as ≥67.6 y of age ($P$-interaction = 0.002), whereas no difference was observed for the hypothesis-driven dietary pattern score ($P$-interaction >0.05). The association between the hypothesis-driven or exploratory dietary pattern score and LSI was not modified by sex, BMI, or diabetes status (all $P$-interaction > 0.05). Although the association between the hypothesis-driven dietary pattern score and LSI was stronger in individuals who consumed >20 g alcohol/d than in individuals who consumed less alcohol per day, no such difference was observed for the exploratory dietary pattern score.

In logistic regression models adjusted for age, sex, educational attainment, smoking status, physical activity, and total energy intake, a 1-unit increase in the hypothesis-driven dietary pattern score was associated with a higher OR for FLD (OR: 1.25; 95% CI: 1.10, 1.43), with the dichotomized outcome that was based on the LSI cutoff (**Table 4**). A 1-unit increase in the exploratory dietary pattern score was positively associated with FLD in multivariable-adjusted logistic regression models (OR: 1.56; 95% CI: 1.29, 1.88). As concerned the association between the hypothesis-driven dietary pattern score or the exploratory dietary pattern score and LSI, subgroup analyses revealed no significant interaction with age, sex, BMI, or type 2 diabetes status (all $P$-interaction > 0.05). In multivariable-adjusted logistic regression models, the hypothesis-driven dietary pattern score was more strongly associated with FLD in individuals who consumed >20 g alcohol/d than in individuals who consumed lower amounts.

When analyses were restricted to individuals with LSI values below the cutoff to define FLD (LSI <3.0) to specifically evaluate low amounts of liver fat, a 1-unit increase in the hypothesis-driven dietary pattern score was not significantly related to LSI values [regression coefficient ($\beta$): 0.01; 95% CI: −0.02, 0.03] in multivariable-adjusted regression models. In contrast, in individuals with LSI values below the cutoff to define FLD, a 1-unit increase in the exploratory dietary pattern score was still, but

**TABLE 3**
Changes in LSI per 1-unit increase in the hypothesis-driven or exploratory dietary pattern score stratified by sex, age, BMI, alcohol consumption, and diabetes status ($n$ = 354)[1]

| | | Hypothesis-driven dietary pattern score[2] | | Exploratory dietary pattern score[2] | |
|---|---|---|---|---|---|
| | Total $n$ | Model 1 | Model 2 | Model 1 | Model 2 |
| Overall | 354 | 0.04 (0.02, 0.07) | 0.05 (0.03, 0.08) | 0.12 (0.09, 0.15) | 0.12 (0.09, 0.15) |
| Age | | | | | |
| ≤67.6 y | 178 | 0.04 (0.01, 0.07) | 0.04 (0.01, 0.08) | 0.07 (0.03, 0.12) | 0.07 (0.02, 0.12) |
| >67.6 y | 176 | 0.05 (0.02, 0.09) | 0.05 (0.01, 0.09) | 0.17 (0.13, 0.22) | 0.17 (0.12, 0.22) |
| *P*-interaction | — | 0.832 | 0.914 | 0.002 | 0.002 |
| Sex | | | | | |
| M | 202 | 0.04 (0.02, 0.07) | 0.06 (0.03, 0.09) | 0.11 (0.06, 0.15) | 0.11 (0.06, 0.15) |
| F | 152 | 0.04 (<–0.01, 0.09) | 0.04 (<–0.01, 0.08) | 0.13 (0.08, 0.18) | 0.13 (0.08, 0.18) |
| *P*-interaction | — | 0.875 | 0.753 | 0.632 | 0.623 |
| BMI | | | | | |
| M: <26.7 kg/m$^2$; F: <27.0 kg/m$^2$ | 177 | 0.03 (<–0.01, 0.06) | 0.04 (0.01, 0.07) | 0.11 (0.07, 0.15) | 0.11 (0.07, 0.15) |
| M: ≥26.7 kg/m$^2$; F: ≥27.0 kg/m$^2$ | 177 | 0.06 (0.02, 0.09) | 0.06 (0.03, 0.10) | 0.10 (0.05, 0.15) | 0.10 (0.04, 0.15) |
| *P*-interaction | — | 0.275 | 0.234 | 0.654 | 0.646 |
| Type 2 diabetes | | | | | |
| No | 299 | 0.04 (0.02, 0.07) | 0.06 (0.03, 0.08) | 0.11 (0.07, 0.15) | 0.11 (0.07, 0.15) |
| Yes | 55 | 0.05 (<0.01, 0.10) | 0.04 (−0.01, 0.10) | 0.12 (0.05, 0.19) | 0.13 (0.05, 0.22) |
| *P*-interaction | — | 0.945 | 0.896 | 0.846 | 0.791 |
| Alcohol consumption[3] | | | | | |
| ≤20 g/d | 286 | 0.02 (−0.01, 0.05) | 0.03 (<–0.01, 0.06) | 0.13 (0.08, 0.17) | 0.12 (0.08, 0.17) |
| >20 g/d | 68 | 0.08 (0.04, 0.12) | 0.09 (0.05, 0.14) | 0.11 (0.05, 0.17) | 0.12 (0.05, 0.19) |

[1] Model 1 was adjusted for age (y) and sex (M or F). Model 2 was adjusted for age (y), sex (M or F) except sex strata, years of education (≤9, 10, or ≥11 y), smoking status (never, former, or current), smoking duration (y), physical activity (metabolic equivalent task hours/wk), and total energy intake (kcal/d). LSI, liver signal intensity.

[2] All values are regression coefficients ($\beta$s); 95% CIs in parentheses.

[3] No *P*-interaction is shown because alcohol consumption was included in dietary pattern scores.

less strongly, positively related to the LSI ($\beta$: 0.06; 95% CI: 0.02, 0.10) in multivariable-adjusted regression models (data not shown).

## DISCUSSION

### Principal findings

In this cross-sectional, population-based study, a higher percentage of LSI variation was explained by the exploratory dietary pattern (12.6%) than hypothesis-driven dietary pattern (2.2%), including alcohol, soft drinks, meat, coffee, and tea. Higher exploratory dietary pattern scores were characterized by lower intakes of fruit and herbal tea, green and black tea, sugar and confectionary, other fats, bread, breakfast cereals, and cheese and higher intakes of soups, beer, wine, juices, poultry, and eggs. The exploratory and hypothesis-driven dietary pattern scores were related to the MRI-measured liver fat content independent from possible confounding factors. Common food groups of both patterns included alcohol, meat (poultry), and tea.

### In the context of current literature

To our knowledge, only one observational study has previously been conducted that investigated a hypothesis-driven dietary pattern in relation to FLD (42). The study revealed no association between adherence to the Mediterranean diet pattern and FLD in multivariable-adjusted regression analysis (42). Hypothesis-driven dietary pattern scores have been shown to be related to health outcomes even when individual items were unrelated to the health outcome (43). With our study, we confirmed such a relation for FLD. Nevertheless, the hypothesis-driven dietary pattern score explained a substantially lower proportion of LSI variation than did the exploratory dietary pattern score. To our knowledge, only one observational study has previously investigated exploratory dietary patterns and FLD, which was limited to adolescents (17). Dietary habits assessed at the age of 14 y were related to FLD status at the age of 17 y as assessed by using an ultrasound (17). With the application of factor analysis, the authors obtained a healthy dietary pattern, which was unrelated to the prevalence of FLD (17) and a Western dietary pattern that was positively associated with FLD and dominated by high intakes of soft drinks, red meat, processed meats, confectionary, takeaway foods, refined grains, chips, sauces, and full-fat dairy products (17). Dietary patterns obtained by either a factor analysis or principal component analysis are based on mathematical algorithms aimed to maximize the covariance or variance in dietary intake variables only and, thus, are not necessarily associated with the disease of interest (16). Because dietary intake variables are commonly highly correlated (ie, multicollinearity in explanatory variables), a standard multivariable regression analysis, might also not be adequate in this context (16). By contrast, PLS regression enables the extraction of dietary pattern scores that are based on a mathematical algorithm aimed to maximize the covariance between explanatory and response variables, thereby virtually ensuring an association with the response. With the use of PLS, we derived an unexpected dietary pattern associated with liver fat content, which consisted of miscellaneous food groups of which the majority were not associated with the LSI in the univariable regression analysis.

**TABLE 4**
ORs (95% CIs) for fatty liver disease per 1-unit increase in the hypothesis-driven or exploratory dietary pattern score stratified by sex, age, BMI, alcohol consumption, and diabetes status ($n$ = 354)[1]

| | | Hypothesis-driven dietary pattern score | | | Exploratory dietary pattern score | |
|---|---|---|---|---|---|---|
| | Total $n$ | Model 1 | Model 2 | No. of cases | Model 1 | Model 2 |
| Overall | 354 | 1.24 (1.10, 1.39) | 1.25 (1.10, 1.43) | 171 | 1.57 (1.31, 1.89) | 1.56 (1.29, 1.88) |
| Age | | | | | | |
| ≤67.6 y | 178 | 1.22 (1.04, 1.43) | 1.24 (1.03, 1.48) | 82 | 1.43 (1.13, 1.82) | 1.46 (1.14, 1.87) |
| >67.6 y | 176 | 1.26 (1.05, 1.51) | 1.25 (1.01, 1.54) | 89 | 1.77 (1.32, 2.38) | 1.74 (1.28, 2.37) |
| *P*-interaction | — | 0.831 | 0.995 | — | 0.258 | 0.282 |
| Sex | | | | | | |
| M | 202 | 1.24 (1.08, 1.43) | 1.35 (1.14, 1.61) | 97 | 1.42 (1.13, 1.79) | 1.47 (1.15, 1.87) |
| F | 152 | 1.24 (0.98, 1.56) | 1.18 (0.93, 1.50) | 74 | 1.82 (1.34, 2.48) | 1.88 (1.36, 2.62) |
| *P*-interaction | — | 0.928 | 0.808 | — | 0.243 | 0.228 |
| BMI | | | | | | |
| M: <26.7 kg/m$^2$; F: <27.0 kg/m$^2$ | 177 | 1.10 (0.94, 1.29) | 1.10 (0.91, 1.32) | 66 | 1.70 (1.26, 2.29) | 1.67 (1.22, 2.29) |
| M: ≥26.7 kg/m$^2$; F: ≥27.0 kg/m$^2$ | 177 | 1.44 (1.18, 1.75) | 1.50 (1.21, 1.87) | 105 | 1.37 (1.07, 1.76) | 1.37 (1.07, 1.77) |
| *P*-interaction | — | 0.105 | 0.082 | — | 0.301 | 0.312 |
| Type 2 diabetes | | | | | | |
| No | 299 | 1.20 (1.05, 1.36) | 1.23 (1.06, 1.43) | 136 | 1.49 (1.22, 1.82) | 1.49 (1.22, 1.82) |
| Yes | 55 | 1.63 (1.14, 2.33) | 1.74 (1.15, 2.64) | 35 | 2.34 (1.17, 4.65) | 3.09 (1.30, 7.33) |
| *P*-interaction | — | 0.258 | 0.280 | — | 0.236 | 0.271 |
| Alcohol consumption[2] | | | | | | |
| ≤20 g/d | 286 | 1.10 (0.96, 1.27) | 1.12 (0.96, 1.31) | 134 | 1.57 (1.24, 1.98) | 1.57 (1.24, 1.99) |
| >20 g/d | 68 | 1.85 (1.29, 2.65) | 2.34 (1.44, 3.80) | 37 | 1.68 (1.16, 2.44) | 1.78 (1.14, 2.79) |

[1] Model 1 was adjusted for age (y) and sex (M or F) except sex strata. Model 2 was adjusted for age (y), sex (M or F) except sex strata, years of education (≤9, 10, or ≥11 y), smoking status (never, former, or current), smoking duration (y), physical activity (metabolic equivalent task hours/wk), and total energy intake (kcal/d).
[2] No *P*-interaction is shown because alcohol consumption was included in dietary pattern scores.

In a comparison of the 2 patterns, common food groups of both patterns were alcohol, meat (poultry), and tea. The intake of alcohol is an established risk factor for FLD (44). The hypothesis-driven dietary pattern score was, to a lesser extent, associated with liver fat content in individuals who consumed ≤20 g alcohol/d than in individuals who consumed higher amounts of alcohol, whereas no such difference was observed for the exploratory dietary pattern score. For meat, which was included in the hypothesis-driven dietary pattern, the intake of poultry was positively associated with liver fat content in the PLS analysis, which might have reflected different regional consumption habits. Tea consumption has been reported to be higher in health-conscious individuals (45) and has been previously shown to be inversely related to FLD (14).

Soft-drink consumption did not appear to be an important factor for the modeling of liver fat content in the exploratory analysis. This outcome might have been a result of the fact that we were not able to distinguish between regular and diet soft drinks. However, juices, which, besides soft drinks, are a major source of fructose, which has drawn increasing attention as a putative risk factor for FLD (11), were identified as important for the modeling of LSI in the PLS analysis. The discrepancy may have been a result of differences in regional consumption habits (46). In addition, coffee was not important to model the fat content in the PLS analysis. Although a higher coffee intake has been shown to be inversely related to FLD (13) or chronic liver disease (7), the caffeine intake did not differ in a cross-sectional study that compared individuals with FLD to individuals without FLD (12). Paradoxically, we noted that liver fat content was inversely associated with the energy-adjusted intake of sugar and confectionary in the PLS model when all other food groups were taken into account. Furthermore, a higher intake of soups, which reflect traditional German eating habits (47), was positively associated with liver fat content in the current study.

We showed some indication that the association between the dietary intake and liver fat content was modified by age. In a different study, stronger associations between fructose consumption and FLD severity were suggested in individuals >48 y of age than in younger individuals (48).

The investigation of the dichotomous FLD-indicator variable enabled the comparison of our results to those of previous studies that mainly relied on a dichotomous FLD outcome (17) and confirmed results of the linear regression analysis. However, liver fat content might represent a continuum of metabolic risk (49), and the investigation of a subtle liver fat accumulation below the threshold for FLD might be of interest in terms of primary prevention (4). The association between the hypothesis-driven dietary pattern score and liver fat content diminished in individuals with a liver fat content below the cutoff to define FLD, whereas the association between the exploratory dietary pattern score and liver fat content remained persistent in this subgroup analysis.

### Potential mechanisms

Approximately 59% of hepatic triglycerides are derived from plasma nonesterified fatty acids, 26% of hepatic triglycerides are derived from de novo synthesis, and 15% of hepatic triglycerides are derived from the diet (3). Dietary carbohydrate intake promotes the release of insulin, which, in interplay with glucose, stimulates de novo synthesis and lipogenesis (3, 50). In addition, adipose tissue lipolysis, which is induced in the fasting state and

has been shown to be less suppressed under insulin resistance, substantially contributes to the plasma nonesterified fatty acid pool (3, 51).

### Strengths and limitations

Because this was a cross-sectional epidemiologic study, no conclusion with regard to causality and temporality could be drawn. We could not rule out that individuals with high liver fat content had already adopted healthier eating patterns before inclusion into the study. However, we included a general population sample who, in the majority, were not expected to receive dietary advice (22). Because we relied on self-reported dietary habits, dietary misreporting might have biased the observed associations. Social desirability might have influenced the reported dietary intake, especially concerning sugar and confectionary intakes. Although our study was based on a random sample drawn from the population registry, generalizability might be questionable because of a possible response bias. Major strengths of our study included the relatively large population-based design, comprehensive assessment of dietary patterns and covariates, determination of liver fat on a continuous scale by using MRI, and validation compared with the use of spectroscopy.

In conclusion, we defined a hypothesis-driven dietary pattern and derived an exploratory dietary pattern, both including alcohol, meat (poultry), and tea, associated with liver fat content independent from several potential confounders. Eating habits beyond aspects already known may be of relevance for liver fat accumulation. Juices may be population-specific more relevant for liver fat content than are soft drinks. A dietary pattern analysis and validation of the investigated patterns in prospective studies are warranted by taking differences in regional consumption habits into account.

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The authors' responsibilities were as follows—MK and UN: designed the study; MK, J Borggrefe, GG, MH, GJ, MJM, AB-W, and UN: collected data; MK: performed the statistical analysis and wrote the manuscript; and all authors: critically reviewed the manuscript and approved the final manuscript. None of the authors had a conflict of interest.

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