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VISUAL ABSTRACT

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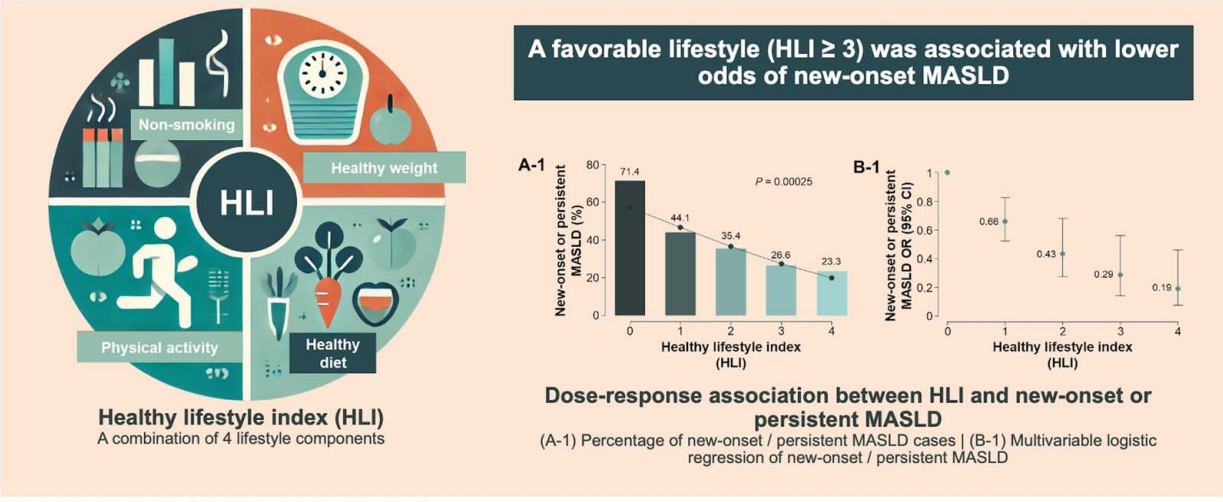

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ORIGINAL ARTICLE

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A healthy lifestyle is prospectively associated with lower onset of metabolic dysfunction–associated steatotic liver disease

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Abstract

Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) is associated with an unhealthy lifestyle. However, there is limited prospective evidence regarding the association between combined lifestyle factors and MASLD. This study aims to test the association of a combination of lifestyle components, expressed as a healthy lifestyle index (HLI), and unhealthful eating behavior habits with MASLD, insulin resistance (IR), liver fibrosis, and metabolic dysfunction–associated steatohepatitis.

Methods: A prospective cohort study was conducted among participants of metabolic and hepatic screening surveys. MASLD was evaluated by ultrasonography or controlled attenuation parameter at 2 time points to assess new-onset, persistence, or remission, and IR was estimated by homeostasis model assessment. Presumed liver fibrosis and metabolic dysfunction–associated steatohepatitis were evaluated using FibroMax biomarkers. The HLI was calculated as the sum of 4 lifestyle components: nonsmoking, healthy weight, healthy diet, and physical activity.

Results: The final cohort included 315 subjects with 6.7 years of follow-up, 40–70 years old. In multivariable analyses, a favorable lifestyle ($\geq$3 components) was independently associated with lower odds of new-onset MASLD (OR = 0.42; 95% CI: 0.19–0.90). Similarly, a favorable lifestyle was associated with lower odds of new-onset/persistent (vs. never/remission) MASLD and IR, respectively (OR = 0.49; 95% CI: 0.30–0.80; OR = 0.40;

Abbreviations: AHA, American Heart Association; AUS, abdominal ultrasound; FEAHQ, family eating and activity habits questionnaire; FLI, fatty liver index; HbA1C, glycated hemoglobin; HLI, healthy lifestyle index; I-MEDAS, Israeli Mediterranean diet adherence screener; IR, insulin resistance; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; MED, Mediterranean diet; MEDAS, Mediterranean diet adherence screener; TLVMC, Tel-Aviv Medical Center.

Preliminary data were presented as an oral presentation in the United European Gastroenterology Week-UEG Week 2023, at Copenhagen.

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95% CI: 0.24–0.66). There was a dose-response association between HLI and new-onset/persistent MASLD and IR. A favorable lifestyle was associated with lower odds of new-onset metabolic dysfunction–associated steatohepatitis (OR = 0.50; 95% CI: 0.27–0.95). Adjusting for HLI, unhealthful eating behavior habits were associated with higher odds of MASLD prevalence (OR = 1.81; 95% CI: 1.07–3.06).

Conclusions: Adherence to a healthy lifestyle is prospectively associated with lower odds of MASLD, markers of liver damage, and IR. A holistic approach that considers overall lifestyle and eating behavior may be useful for preventing MASLD.

Keywords: fatty liver, healthy lifestyle index, insulin resistance, MASLD, steatohepatitis

INTRODUCTION

NAFLD, recently renamed metabolic dysfunction–associated steatotic liver disease (MASLD),[1] is a major public health problem, with an increasing worldwide prevalence, rising from 25.3% in 1990–2006 to 38.0% in 2016–2019, making it a primary cause of chronic liver disease.[2] MASLD histological spectrum encompasses hepatic steatosis and progression to metabolic dysfunction–associated steatohepatitis (MASH) and liver fibrosis, with insulin resistance (IR) as one of the main factors involved in its progression.[3] Many studies have tested the role of different lifestyle factors in the prevention and treatment of MASLD, suggesting moderate physical activity,[4] nonsmoking,[5] maintenance of normal body weight, and adherence to a healthy diet[6,7] as key protective factors. While individual lifestyle factors have been widely assessed in isolation, several lifestyle factors often coexist in the same individual, necessitating research on the joint association between these factors and MASLD.

Indeed, a few cross-sectional studies[8–11] and 1 case-control study[12] showed inverse associations between MASLD and the healthy lifestyle index (HLI), which is the sum of several lifestyle components in 1 variable. Furthermore, in 1 study among US adults,[11] higher adherence to HLI was associated with lower odds of significant liver fibrosis, as evaluated by transient elastography. Six additional prospective cohort studies have focused on the development and progression of MASLD and mortality. A higher lifestyle index during adolescence was significantly associated with a decreased risk of MASLD in adulthood, as evaluated by the hepatic steatosis index and fatty liver index (FLI).[13] Supporting results were found in 3 cohort studies among the Chinese population with fatty liver evaluated using abdominal ultrasound (AUS). In those studies,[14–16] the risk of MASLD decreased among those with higher adherence to a healthy lifestyle. Lastly, 2 prospective cohort studies among patients with MASLD found that adherence to a favorable lifestyle (3–4 healthy lifestyle factors) reduced all-cause mortality by 36% compared to those with unfavorable lifestyle (0–1 healthy lifestyle factors),[17] whereas a higher lifestyle risk index was related to the progression to HCC, cirrhosis, and the development of comorbidities such as cardiovascular disease and cancer.[18] However, there is still a scarcity of prospective studies assessing MASLD by imaging rather than markers, measuring the association with IR as a main factor involved in MASLD pathogenesis, and assessing outcomes of liver fibrosis and MASH. Further studies with diverse populations are required to ensure generalizability; Supplemental Material, http://links.lww.com/HC9/B83.

In addition to the well-studied association of MASLD with lifestyle parameters and nutrient intake,[19] there may also be a clinical significance in eating behavior habits that focus on the behavioral aspects of eating rather than on food and nutrient intake. The substantial changes in household structures, food systems, exposure to an obesogenic environment, and lifestyles in general that have occurred in recent decades have led to new meal patterns and practices, increasing unhealthful eating behavior habits.[20] Few studies have evaluated the association with eating behavior habits.[21–25] Moreover, the existing studies are limited to specific dietary habits (ie, fast eating, eating before bedtime, and frequency of meals) and do not consider the overall eating behavior habit score.

Therefore, the present study aimed to first test the association between HLI and the new-onset or persistence of MASLD, IR, markers of significant liver fibrosis, and MASH, and second, to further test the association between unhealthful eating behavior habits and these outcomes, independent of HLI. We hypothesized that

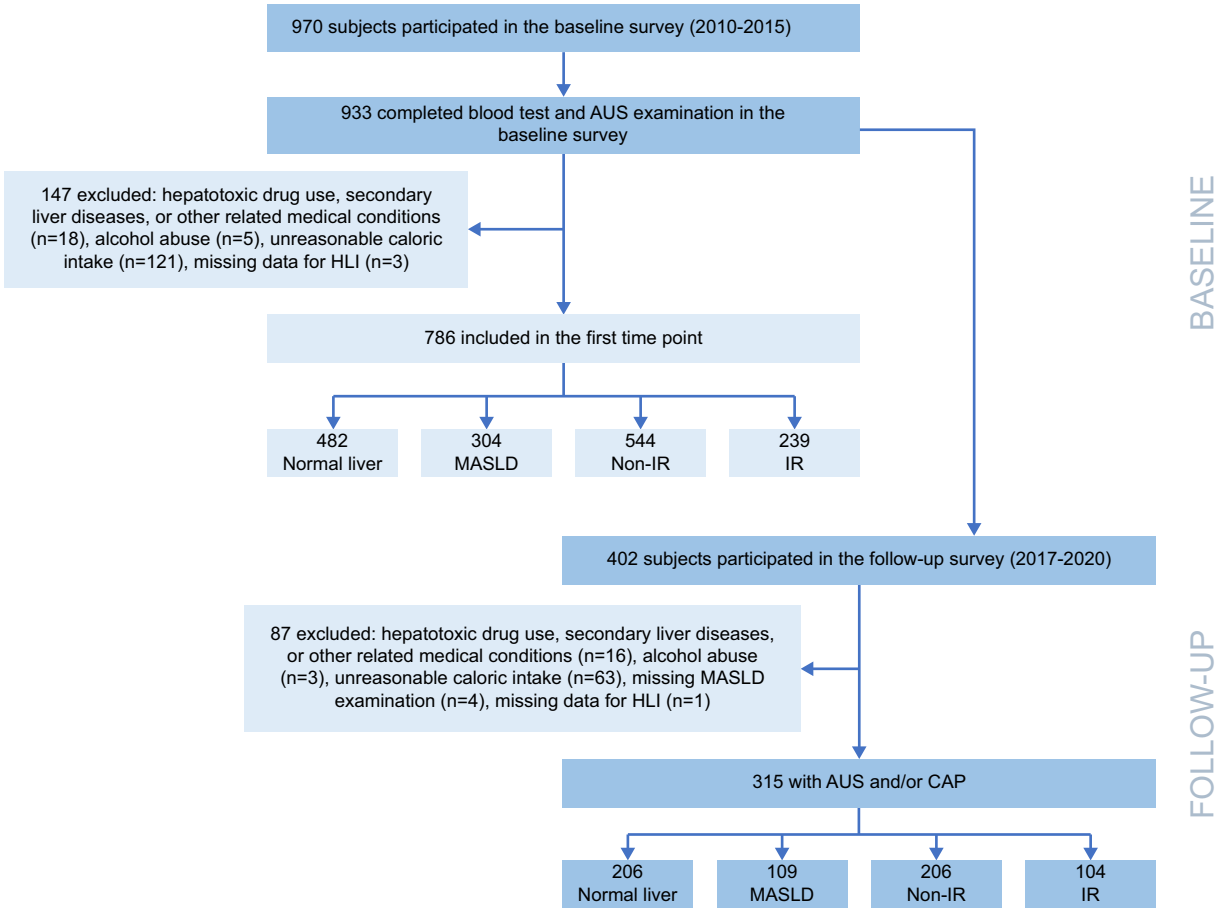

FIGURE 1 Flowchart of the study population. Three subjects in the first time point and 5 in the final prospective analysis did not have an insulin test. Abbreviations: AUS, abdominal ultrasound; CAP, controlled attenuation parameter; HLI, healthy lifestyle index; IR, insulin resistance; MASLD, metabolic dysfunction–associated steatotic liver disease.

low HLI and unhealthful eating behavior habits would be associated with increased odds of MASLD, IR, and markers of liver damage.

METHODS

Study design and population

A prospective cohort study with 2 repeated measurements was conducted among men and women 40–70 years old who participated in a metabolic and hepatic screening survey at Tel-Aviv Medical Center (TLVMC) between 2010 and 2015 and again at the follow-up survey at least 5 years later. Exclusion criteria at both time points included the presence of HBsAg or HCV antibodies, fatty liver suspected to be secondary to hepatotoxic drugs, inflammatory bowel disease, and celiac disease. In addition, participants who reported excessive alcohol consumption ($\geq$30 g/d in men or $\geq$20 g/d in women)[26] or an unreasonable caloric intake below or above the accepted range (800–4000 Kcal/d for men and 500–3500 Kcal/d for women) were excluded (Figure 1). The TLVMC Institutional Review Board approved the study protocol and all participants signed informed consent forms.

Data collection

In both baseline and follow-up screening surveys, participants underwent fasting blood tests, anthropometric measurements, AUS and/or FibroScan, and a face-to-face interview using a structured questionnaire assembled by the Israeli Ministry of Health and used in national surveys, including smoking, physical activity habits, and detailed dietary intake. In addition, we included questions regarding demographic characteristics, medical history, and alcohol and coffee consumption, which may be potential confounders. Moreover, a validated eating behavior habits questionnaire was added to the follow-up survey to elaborate on the associations. To avoid reporting bias, the participants and the research team were informed of the AUS or FibroScan and blood test results only after completing the questionnaires.

Liver-related outcomes evaluation and definition of variables

MASLD, the primary outcome, was evaluated at baseline using AUS in all the subjects. In the follow-up survey, MASLD was diagnosed using one of the following methods: (1) controlled attenuation parameter in the majority of subjects (n = 235, after exclusion criteria) performed by the same operator and the same equipment (FibroScan 502 Touch; Echosens) with a cutoff of ≥294 dB/m indicating fatty liver[27]; or (2) AUS among a subsample (n = 101, of which 21 subjects underwent both) using standardized criteria, performed by the same operator and the same equipment as in the baseline survey (EUB-8500 scanner Hitachi Medical Corporation) to avoid measurement bias. Our study was designed and executed before the updated nomenclature and diagnosis criteria for MASLD. Recent findings indicate that the population diagnosed with NAFLD almost entirely overlaps with that diagnosed with MASLD,[28,29] with at least 98.4% of patients with NAFLD meeting the criteria for MASLD according to the new nomenclature (ie, defined by the presence of NAFLD identified by imaging or biopsy and at least 1 metabolic risk factor).[28] A similar analysis in our study indicated a 99.1% agreement in diagnosis with MASLD (n = 108) out of those diagnosed with NAFLD (n = 109; Supplemental Table S1, http://links.lww.com/HC9/B82).

Secondary outcomes were also evaluated. IR was evaluated using the homeostasis model assessment score and defined as the upper quartile (≥Q4) of the study population's homeostasis model assessment levels[30] (corresponding to a value ≥3.13 at baseline and ≥3.46 at follow-up). All type 2 diabetes subjects were considered to have IR regardless of homeostasis model assessment levels. Type 2 diabetes was defined as fasting glucose ≥126 mg/dL and/or glycated hemoglobin (HbA1C) ≥6.5% and/or the use of antidiabetic medications.[31]

Presumed liver fibrosis and MASH were evaluated noninvasively by FibroMax (BioPredictive), a validated diagnostic tool composed of 3 main serum biomarker panels for the diagnosis of steatosis (SteatoTest), inflammation (NashTest-2), and liver fibrosis (FibroTest).[32,33] FibroTest consists of serum α2-macroglobulin, apolipoprotein-A1, haptoglobin, total bilirubin, and γ-glutamyl transpeptidase, adjusted for age and sex. NashTest-2 contains the same components plus alanine aminotransferase, serum cholesterol, and triglycerides. The procedures used were those recommended by BioPredictive, including the exclusion of unreliable results. The presence of moderate-severe MASH was defined as a value of ≥0.50, and the presence of significant liver fibrosis was defined as a value of ≥0.49.[32,33] Probable MASLD was also evaluated by FLI and used for sensitivity analysis (calculated by an algorithm including body mass index, waist circumference, serum GGT, and triglycerides), with a cutoff of FLI ≥60 indicating MASLD.[34]

Evaluation and definition of the HLI

Four healthy lifestyle components from the strategic goals of the AHA[35,36] guidelines were adapted and defined as follows: (1) lifetime abstinence from smoking; (2) no current obesity (body mass index <30 kg/m^2); (3) physical activity at goal levels (engaging in physical activity for ≥150 min/wk); and (4) healthy dietary pattern, based on adherence to the Mediterranean diet (MED) and in accordance with current recommendations for the prevention and treatment of MASLD.[19,26] Dietary intake was first evaluated using a structured semi-quantitative food frequency questionnaire composed of 117/183 items (for baseline and follow-up surveys, respectively, the difference in the number of items stemming mostly from detailed meat preparation methods in the follow-up survey), assembled by the Food and Nutrition Department Israeli Ministry of Health and designed to include local food items consumed over the past year.[37] Adherence to MED was evaluated for each participant at the 2 time points based on the validated Mediterranean diet adherence screener (MEDAS),[38] previously adapted to the Israeli population, to create a 17-item Israeli Mediterranean diet adherence screener (I-MEDAS).[39] The alcohol item was excluded from the analysis because of conflict with the MASLD guidelines to minimize or avoid alcohol consumption.[26] Detailed information on the criteria for this score and foods included in each I-MEDAS item are presented in Supplemental Table S2, http://links.lww.com/HC9/B82. Adherence to MED was calculated as the sum of all components to which the participants adhered, ranging from 0 to 16, and a value of ≥8/9 (sample median for the baseline and prospective samples, respectively) was defined as a healthy dietary pattern. Finally, HLI was calculated for each subject at the 2 time points as the sum of all 4 lifestyle components to which participants adhered, and ranged from 0 to 4 points. HLI categories were defined as unfavorable or favorable, with adherence to 0–2 or 3–4 healthy lifestyle components, respectively.

Evaluation and definition of eating behavior habits

Eating behavior habits were assessed only in the follow-up survey by the Family Eating and Activity Habits Questionnaire (FEAHQ), a validated questionnaire initially developed and validated in Israel and designed for family-based weight management interventions.[40] The adapted FEAHQ was composed of a 13-item questionnaire given on a 5-point Likert scale (ranging from 0, never to 4, always) examining the frequency of eating behavior habits. The main focus of these

questions was a distracted eating environment, eating following stress, and untidy eating (eg, eating between meals or at night). Detailed information on the adapted FEAHQ is presented in Supplemental Table S3, http://links.lww.com/HC9/B82. Eating behavior habits were calculated as the sum of all 13 items (ranging from 0 to 52; a higher score reflects less appropriate eating behavior habits), and a value of ≥ 14 (sample median at follow-up) was defined as unhealthful eating behavior habits. In addition, the FEAHQ included questions that were analyzed separately, examining reasons for eating and eating patterns, including responses to hunger and satiety cues and eating pace.

Statistical analysis

Statistical analyses were performed using SPSS version 27.0 for Windows (IBM-SPSS) and R programming language (https://www.R-project.org). Continuous variables are presented as mean ± SD. The independent samples *t* test was performed to test the differences in continuous variables between the 2 groups. Pearson chi-square test was performed to test the associations between nominal variables, and *p* for trend was calculated when appropriate. Due to the nature of the study as a prospective cohort with 2 repeated measurements and binary outcomes, we were able to test various changes occurring over time. The entire sample was analyzed for the combined outcome of either new-onset or persistent liver-related outcomes (including new cases at the follow-up survey or the presence of outcomes at both time points). In this analysis, the comparison was made to subjects who never had the outcomes or had remission of the outcome at the follow-up survey. In addition, only subjects without liver-related outcomes at the baseline survey were included in the analysis focusing exclusively on the new-onset of liver-related outcomes. Given our primary interest was the changes in MASLD presence over time and not time-to-event, and since the time range represents the interval between the 2 arrivals to the study rather than the exact time-to-event (due to the unavailability of the exact event dates), we conducted a multivariable logistic regression analysis. This analysis tested the adjusted association between HLI and liver-related outcomes, adjusting for variables that differed between HLI levels (Table 1): sex, age, and energy intake as potential confounding factors. Further adjustments were made for cholesterol intake, fiber intake, and sugared beverages as potential dietary confounders. The required sample size was calculated as 278 people with a significance level of 5% and a power of 80% for the expected results of 5% MASLD new-onset among participants with high HLI versus 16% among those with low HLI, according to a previous study.[14] A sensitivity analysis was conducted in a subsample of subjects undergoing AUS at both time points. This analysis was performed only for the combined outcome of either new-onset or persistent MASLD rather than solely for the incidence of MASLD due to the small sample size. In the HLI dose-response univariable logistic regression analysis, the binary response variable (either new-onset or persistent MASLD, or new-onset or persistent IR) was regressed against the single explanatory variable HLI, with the latter having values in the range of 0–4. In the multivariable logistic regression analysis (with the additional covariates age, sex, and energy intake), ORs were calculated with respect to HLI = 0 and were thus determined by $\mathrm{OR} = \mathrm{e}^{h \cdot \hat{\beta}_{\mathrm{HLI}}}$, where $h = 0, 1, 2, 3, 4$ is the HLI level, and $\hat{\beta}_{\mathrm{HLI}}$ is the estimated coefficient of the HLI variable in the regression. The corresponding 95% CIs were computed using R's confint function, accounting for the value of *h*. A *p* value of ≤ 0.05 was considered statistically significant for all analyses.

RESULTS

Description of the study population and comparison between subjects with high and low HLI

Of the 970 participants who participated in the baseline survey, 786 were included with complete data and after exclusion criteria at the first time point. A total of 402 participants attended the follow-up survey, and 315 were included in the primary prospective analysis after applying the exclusion criteria at both time points (Figure 1). A single participant did not complete the FEAHQ.

In the final sample (n = 315), the mean (SD) follow-up time was 6.66 (0.73) years, 56.8% were men, the mean (SD) baseline age was 58.65 (6.45) years, and the mean (SD) baseline body mass index was 28.12 (5.48) kg/m^2.

Among all subjects at baseline, the mean (SD) baseline HLI was 2.3 (1.08), and 43.5% (n = 137/315) were categorized as having a favorable lifestyle (high HLI; 3–4 healthy lifestyle components). Subjects with a favorable lifestyle had a lower prevalence of MASLD, IR, and type 2 diabetes and a better metabolic profile, including lower serum ferritin and uric acid levels. Furthermore, participants with a favorable lifestyle consumed less cholesterol, fewer sugared beverages, and more fiber (Table 1).

With regard to primary outcomes, new-onset or persistent MASLD was diagnosed in 34.6% (n = 109/315) of the subjects, with 25.5% (n = 35/137) among those with high HLI versus 41.6% (n = 74/178) among those with low HLI ($p = 0.003$). The new-onset MASLD (ie, among those without the outcome at baseline) was 18.3% (n = 36/197), with 12.1% (n = 12/99) among those with high HLI versus 24.5% (n = 24/98) among those with low HLI ($p = 0.025$). With regard to secondary outcomes, new-onset or persistent IR was diagnosed in 33.5% (n = 104/310) of the subjects, with

TABLE 1 Baseline characteristics of the study population and comparison between high and low healthy lifestyle index (mean [SD], unless stated otherwise)

Parameter (units, normal range)	Total (n = 315)	Low HLI[a] (n = 178)	High HLI[a] (n = 137)	*p*
Age (y)	58.65 (6.45)	58.54 (6.65)	58.80 (6.19)	0.733
Sex (male), %	56.80	58.40	54.70	0.513
Time of follow-up (y)	6.66 (0.73)	6.65 (0.68)	6.67 (0.79)	0.772
BMI (kg/m^2)	28.12 (5.48)	29.88 (6.29)	25.83 (2.94)	**< 0.001**
Weight change,[b] %	−0.70 (9.96)	−0.98 (12.44)	−0.32 (5.23)	0.522
MASLD prevalence,[c] %	37.50	44.90	27.70	**0.002**
HOMA-IR (score) (n = 314)	2.75 (1.97)	3.15 (2.27)	2.23 (1.34)	**< 0.001**
Insulin resistance,[d] % (n = 314)	28.70	37.60	16.90	**< 0.001**
Glucose (mg/dL) (n = 314)	89.75 (19.49)	91.79 (22.35)	87.10 (14.59)	**0.026**
Type 2 diabetes,[e] %	13.30	17.40	8.00	**0.015**
Triglycerides (mg/dL) (n = 314)	112.55 (61.13	118.60 (64.24)	104.63 (56.07)	**0.045**
Total cholesterol (mg/dL) (n = 314)	181.34 (34.82)	179.42 (36.07)	183.87 (33.07)	0.262
HDL-C (mg/dL) (n = 312)	54.37 (16.32)	51.94 (15.63)	57.49 (16.70)	**0.003**
ALT (U/L) (n = 314)	27.04 (16.21)	27.82 (15.23)	26.01 (17.42)	0.327
AST (U/L) (n = 310)	25.49 (8.62)	25.63 (9.61)	25.31 (7.17)	0.739
Ferritin (ng/mL) (n = 292)	89.84 (79.37)	98.54 (93.42)	78.05 (53.00)	**0.018**
Uric acid (mg/dL) (n = 314)	5.49 (1.38)	5.70 (1.38)	5.21 (1.34)	**0.002**
Lifestyle habits and dietary intake				
Lifetime nonsmoking, %	50.20	32.60	73.00	**< 0.001**
Nonobese (BMI < 30 kg/m^2), %	71.10	53.90	93.40	**< 0.001**
Physical activity at goal levels (≥ 150 min/wk), %	40.60	14.60	74.50	**< 0.001**
Healthy dietary pattern,[f] %	64.80	44.90	90.50	**< 0.001**
Alcohol (portions/wk)	1.83 (2.79)	1.89 (3.07)	1.74 (2.39)	0.632
Energy intake (kcal/d)	2000.05 (670.29)	2051.84 (691.86)	1932.76 (637.41)	0.118
Protein intake (% of total kcal/d)	18.97 (4.77)	18.87 (4.83)	19.11 (4.71)	0.671
Carbohydrates intake (% of total kcal/d)	41.06 (8.71)	40.99 (8.99)	41.15 (8.35)	0.873
Total fat intake (% of total kcal/d)	36.43 (6.21)	36.83 (6.21)	35.91 (6.19)	0.193
Saturated fat intake (% of total kcal/d)	12.54 (3.52)	12.67 (3.34)	12.38 (3.76)	0.475
Cholesterol intake (mg/d)	338.10 (190.51)	363.80 (219.24)	304.71 (138.75)	**0.004**
Fiber intake (g/d)	23.29 (11.38)	21.73 (10.10)	25.31 (12.61)	**0.006**
Sugared beverages (portions/d)	1.84 (3.28)	2.26 (3.63)	1.29 (2.67)	**0.007**

Note: *p* values < 0.05 are in boldface.

[a]HLI (evaluated at baseline) category definition: low HLI (unfavorable lifestyle) versus high HLI (favorable lifestyle); adherence to 0–2 versus 3–4 healthy lifestyle components, respectively.

[b]Weight change calculated as the percentage change (in kg) from baseline.

[c]MASLD was diagnosed using AUS using standardized criteria.

[d]Insulin resistance was defined as the upper quartile (≥ Q4) of the study population's HOMA levels (corresponding to a value ≥ 3.13 at baseline) or diabetes with no insulin resistance according to the upper quartile of HOMA levels.

[e]Type 2 diabetes was defined as fasting glucose ≥ 126 mg/dL and/or HbA1C ≥ 6.5%, and/or treatment with antidiabetic medications.

[f]A healthy dietary pattern based on adherence to MED (as evaluated by I-MEDAS, 0–16 point score) was defined as a value above the sample median; ≥ 8-point score.

Abbreviations: AUS, abdominal ultrasound; BMI, body mass index; HbA1C, glycated hemoglobin; HLI, healthy lifestyle index; HOMA-IR, homeostasis model assessment of insulin resistance; I-MEDAS, Israeli Mediterranean diet adherence screener; MASLD, metabolic dysfunction–associated steatotic liver disease; MED, Mediterranean diet.

22.4% (n = 30/134) among those with high HLI versus 42.0% (n = 74/176) among those with low HLI ($p < 0.001$). New-onset IR was found in 17.6% (n = 39/222) of the subjects, with 12.4% (n = 14/113) among high HLI versus 22.9% (n = 25/109) among low HLI ($p = 0.039$). New-onset or persistent significant liver fibrosis was diagnosed in 15.6% (n = 43/275) of the subjects, with 10.7% (n = 13/121) among the high HLI group versus 19.5% (n = 30/154) among the low HLI group ($p = 0.048$). New-onset significant liver fibrosis was found in 11.2% (n = 29/260) of the subjects, with 8.5% (n = 10/117) among the high HLI group versus 13.3% (n = 19/143) among those with low HLI ($p = 0.227$). New-onset or persistent MASH was diagnosed in 38.9% (n = 107/275) of the subjects, with 33.9% (n = 41/121) among the high HLI group versus 42.9%

TABLE 2 Multivariable analysis for the prospective associations between high healthy lifestyle index at baseline and liver-related outcomes at follow-up

	New-onset or persistence (vs. never or remission)	New-onset (exclusively among those without the outcome at baseline)
Liver-related outcomes	**OR (95% CI), *p***	
MASLD	109/315 (n cases/n total)	36/197 (n cases/n total)
High HLI[b]		
Model A[a]	0.49 (0.30–0.80), **0.004**	0.42 (0.19–0.90), **0.026**
Model B[c]	0.50 (0.30–0.83), **0.008**	0.42 (0.19–0.94), **0.035**
Insulin resistance[d]	104/310 (n cases/n total)	39/222 (n cases/n total)
High HLI[b]		
Model A[a]	0.40 (0.24–0.66), **<0.001**	0.49 (0.24–1.02), 0.056
Model B[c]	0.41 (0.24–0.70), **0.001**	0.52 (0.24–1.11), 0.092
Significant liver fibrosis (≥0.49)[e]	43/275 (n cases/n total)	29/260 (n cases/n total)
High HLI[b]		
Model A[a]	0.53 (0.26–1.11), 0.094	0.66 (0.29–1.54), 0.338
Model B[c]	0.58 (0.27–1.25), 0.162	0.65 (0.27–1.57), 0.341
MASH (≥0.50)[e]	107/275 (n cases/n total)	68/182 (n cases/n total)
High HLI[b]		
Model A[a]	0.69 (0.41–1.14), 0.143	0.50 (0.27–0.95), **0.035**
Model B[c]	0.69 (0.41–1.17), 0.162	0.49 (0.25–0.96), **0.036**

Note: *p* values <0.05 are in boldface.
[a]Model A: adjusted for potential confounders: baseline age (y), sex, and energy intake (kcal/d).
[b]HLI category definition: low HLI (unfavorable lifestyle) versus high HLI (favorable lifestyle); adherence to 0–2 versus 3–4 healthy lifestyle components, respectively.
[c]Model B: adjusted for model A plus potential dietary confounders: cholesterol intake (mg/d), fiber intake (g/d), and sugared beverages (portions/d).
[d]Insulin resistance was defined as the upper quartile (≥Q4) of the study population's HOMA levels (corresponding to a value ≥3.13 at baseline and ≥3.46 at follow-up) or diabetes with no insulin resistance, according to the upper quartile of HOMA levels at baseline/follow-up.
[e]Significant liver fibrosis and MASH were evaluated noninvasively using Fibromax.
Abbreviations: HLI, healthy lifestyle index; HOMA-IR, homeostasis model assessment of insulin resistance; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease.

(n = 66/154) among the low HLI group ($p = 0.130$). The new-onset MASH was 37.4% (n = 68/182), with 28.2% (n = 22/78) among those with high HLI versus 44.2% (n = 46/104) among those with low HLI ($p = 0.027$).

Multivariable analysis of the prospective association between HLI at baseline and liver-related outcomes

A favorable lifestyle was independently associated with lower odds for both new-onset or persistent MASLD (OR = 0.49; 95% CI: 0.30–0.80; $p = 0.004$) and new-onset MASLD exclusively (OR = 0.42; 95% CI: 0.19–0.90; $p = 0.026$) after adjusting for potential confounders (Table 2). Similarly, a favorable lifestyle was independently associated with lower odds of new-onset or persistent IR (OR = 0.40; 95% CI: 0.24–0.66; $p < 0.001$) and new-onset MASH (OR = 0.50; 95% CI: 0.27–0.95; $p = 0.035$). These associations persisted even after further adjustment for potential dietary confounders (Table 2). Last, a sensitivity analysis that was conducted also revealed an association between a favorable lifestyle and lower odds of new-onset or persistent probable MASLD by FLI ≥60 (OR = 0.30, 95% CI: 0.17–0.51; $p < 0.001$) (Supplemental Table S4, http://links.lww.com/HC9/B82).

Dose-response association between HLI at baseline and new-onset or persistent MASLD or IR

A dose-response association was demonstrated across the 4 HLI score categories with new-onset or persistent MASLD and IR in both univariable (p for trend <0.001) (Figures 2A, B) and multivariable logistic regression analysis (adjusted for age, sex, and energy intake) (Figures 2C, D).

Sensitivity analysis for the association between HLI at baseline and MASLD evaluated only by AUS

A sensitivity analysis was conducted in a subsample of 101 subjects who underwent AUS at both time points.

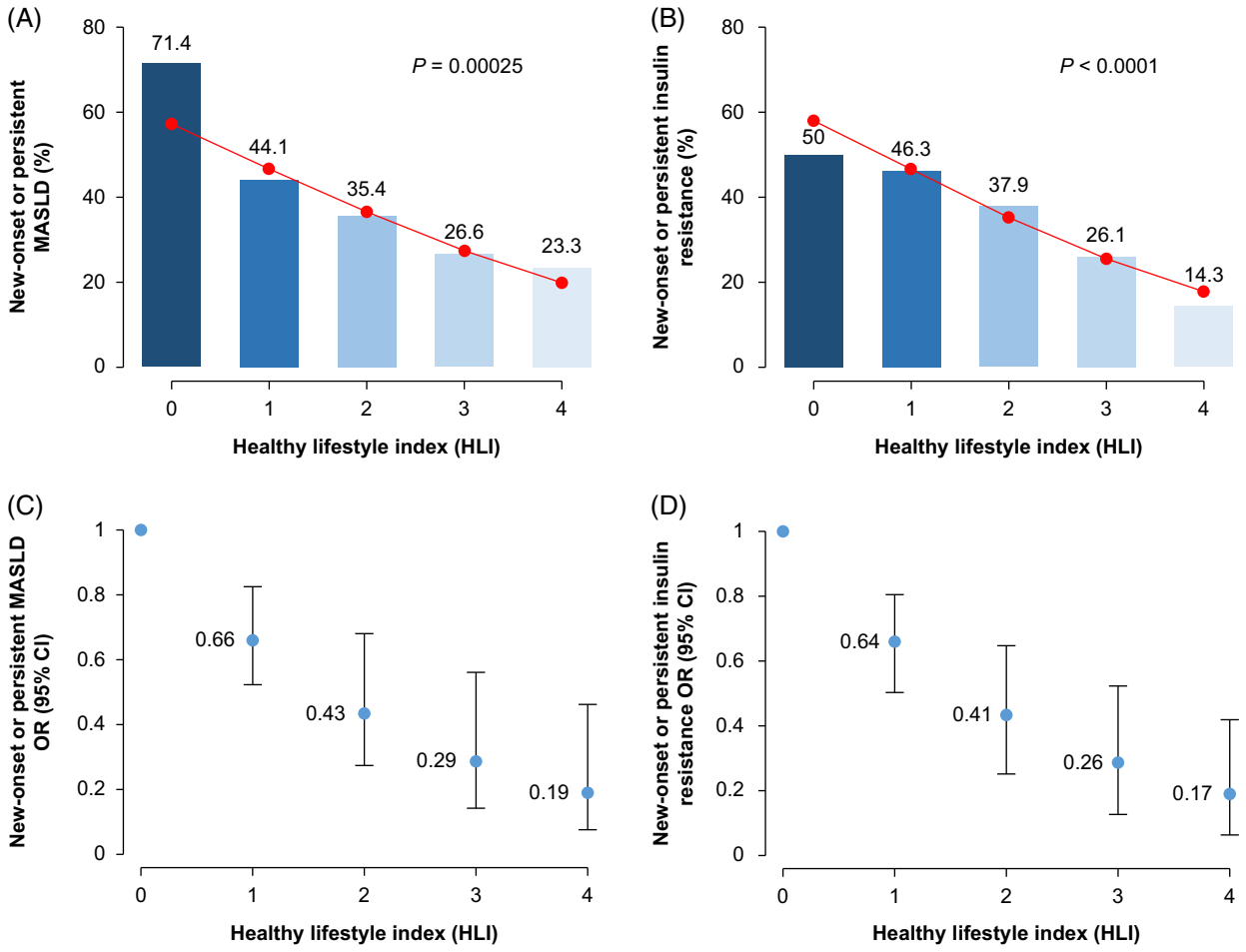

FIGURE 2 Dose-response association between HLI at baseline and new-onset or persistent metabolic dysfunction–associated steatotic liver disease or insulin resistance. Bars represent the percentage of new-onset or persistent MASLD (A) and new-onset or persistent IR (B) cases; red points are the fitted values based on univariable logistic regression with the associated *p* value. ORs and their 95% CIs (with respect to HLI = 0), based on multivariable logistic regression of new-onset or persistent MASLD (C) and new-onset or persistent IR (D), adjusted for baseline age, sex, and energy intake. N cases/n total in each category (0, 1, 2, 3, and 4): 10/14, 30/68, 34/96, 25/94, and 10/43 for new-onset or persistent MASLD and 7/14, 31/67, 36/95, 24/92, and 6/42 for new-onset or persistent IR. N cases/n total for total MASLD sample 109/315 and IR sample 104/310 (310 subjects had complete data for HOMA-IR). Abbreviations: HLI, healthy lifestyle index; HOMA-IR, homeostasis model assessment of insulin resistance; IR, insulin resistance; MASLD, metabolic dysfunction–associated steatotic liver disease.

New-onset or persistent MASLD was diagnosed in 28.7% (n = 29/101) of the subjects, with 20.4% (n = 10/49) among those with high HLI versus 36.5% (n = 19/52) among those with low HLI ($p = 0.073$). A favorable lifestyle was associated with new-onset or persistent MASLD in the fully adjusted model (OR = 0.36; 95% CI: 0.14–0.98; $p = 0.044$) (Table 3). ORs of new-onset MASLD were not analyzed because of the small sample size (n = 56 without MASLD at baseline).

In addition, a cross-sectional analysis was conducted on the baseline survey sample, in which MASLD was diagnosed only by AUS (MASLD prevalence of 38.6%, n = 304/786) to test the robustness of our findings. Similarly, the cross-sectional analysis showed that a favorable lifestyle was independently associated with lower odds for MASLD (OR = 0.41; 95% CI: 0.29–0.56; $p < 0.001$) (Table 3).

Multivariable analysis for the cross-sectional association between eating behavior habits, HLI, and liver-related outcomes

In the follow-up sample (n = 314), the prevalence of MASLD was 34.7% (n = 109/314) and 41.2% (n = 70/170) among subjects with unhealthful eating behavior habits (≥14 [sample median score]) versus 27.1% (n = 39/144) among subjects with healthful eating behavior habits (<14) ($p = 0.009$). Adjusting for potential confounders plus HLI (evaluated at the follow-up survey), unhealthful eating behavior habits were independently associated with higher odds of MASLD (OR = 1.81; 95% CI: 1.07–3.06; $p = 0.028$), IR (OR = 2.38; 95% CI: 1.37–4.13; $p = 0.002$), and MASH (OR = 2.10; 95% CI: 1.24–3.54; $p = 0.006$). In addition, a favorable lifestyle (evaluated at the follow-up

TABLE 3 Multivariable analysis for the prospective and cross-sectional association between high healthy lifestyle index at baseline and metabolic dysfunction–associated steatotic liver disease evaluated only by abdominal ultrasound

MASLD by AUS	OR (95% CI), *p*
Prospective analysis (n = 101)	New-onset or persistence (vs. never or remission)
	29/101 (n cases/n total)
High HLI[a]	
Adjusted model A[b]	0.43 (0.17–1.10), 0.077
Adjusted model B[c]	0.36 (0.14–0.98), **0.044**
Cross-sectional analysis (n = 786)	Baseline prevalence
	304/786 (n cases/n total)
High HLI[a]	
Adjusted model A[b]	0.41 (0.29–0.56), **< 0.001**
Adjusted model B[c]	0.39 (0.28–0.54), **< 0.001**

Note: *p* values < 0.05 are in boldface.
[a]HLI category definition: low HLI (unfavorable lifestyle) versus high HLI (favorable lifestyle); adherence to 0–2 versus 3–4 healthy lifestyle components, respectively.
[b]Model A: adjusted for potential confounders: baseline age (y), sex, and energy intake (kcal/d).
[c]Model B: adjusted for model A plus potential dietary confounders: cholesterol intake (mg/d), fiber intake (g/d), and sugared beverages (portions/d).
Abbreviations: AUS, abdominal ultrasound; HLI, healthy lifestyle index; MASLD, metabolic dysfunction–associated steatotic liver disease.

survey, high HLI score of 3–4) was inversely associated with the odds of these outcomes, adjusted for potential confounders plus unhealthful eating behavior habits (Figure 3).

Further examination of specific eating behavior habits revealed that 15.0% (n = 47/314) of the participants were eating mainly following urge (vs. hunger/mealtime) and that it was associated with higher odds for IR and MASH (OR: 2.51; 95% CI: 1.27–4.98; $p = 0.008$ and OR = 2.40; 95% CI: 1.21–4.74; $p = 0.012$, respectively), but not with MASLD. A fast eating pace (vs. slow/regular), reported among 33.8% (n = 108/314) of the subjects, was associated with higher odds of MASLD (OR = 1.69; 95% CI: 1.01–2.85; $p = 0.048$) (Table 4, univariable analysis is depicted in Supplemental Table S5, http://links.lww.com/HC9/B82).

DISCUSSION

The global prevalence of MASLD is increasing at an alarming rate,[2] with no current pharmaceutical treatment emphasizing the essential role of lifestyle modification interventions in prevention and treatment.[1] A combination of beneficial lifestyle components has been linked to a decreased risk of cardiovascular disease,[35] cancer,[41] as well as type 2 diabetes.[42] To our knowledge, our study is the first to test the prospective association between a healthy lifestyle and the onset of MASLD detected by imaging (vs. biomarkers) in a Western population and the only cohort to examine the association with MASLD-related presumed liver damage using markers of significant liver fibrosis and MASH. We demonstrated an independent association between a favorable lifestyle and lower odds for new-onset or persistent MASLD and IR, as well as lower odds for new-onset MASH. We also showed a dose-response association with new-onset or persistent MASLD and IR across the 4 HLI score categories. Our results are in accordance with the few studies published on this topic, including 2 large recent cohort studies conducted among the Chinese population, in which MASLD was evaluated using AUS. The first study, conducted among 5411 Chinese government employees, found that the risk of developing MASLD among subjects with a favorable lifestyle was reduced by 50% compared with subjects with an unfavorable lifestyle.[14] However, this study had a relatively short mean follow-up time of 1.1 years. The second study had a longer follow-up time of 3 years, indicating a dose-response association between HLI and the risk of developing MAFLD.[15] Our study, with a longer follow-up time of almost 7 years, confirmed a long-term association between HLI and MASLD. In addition to finding an association with MASLD evaluated by imaging, sensitivity analysis also revealed an association with FLI, a validated marker of MASLD in the general population,[43] supporting our results and previous studies using FLI.[9,13,18] Furthermore, we have shown, for the first time, an association between a favorable lifestyle and lower odds of presumed MASH. However, larger prospective studies are required to confirm these results. We could not demonstrate an independent association between a favorable lifestyle and significant liver fibrosis on its own, although a healthy lifestyle was previously shown to be inversely related to significant liver fibrosis in a large cross-sectional study (n = 3893).[11] A possible explanation for this discrepancy may be that our study had a smaller sample size and a small number of subjects with significant liver fibrosis.

In addition to the typically studied lifestyle habits included in the HLI, we further evaluated overall and specific unhealthful eating behavior habits in a cross-sectional analysis conducted in the follow-up survey. We found that overall unhealthful eating behavior habits were associated with higher odds of MASLD, IR, and MASH, as evaluated by the biomarker. These associations persisted after adjusting for HLI and energy intake. In addition, a fast eating pace was associated with higher odds of MASLD. While eating at a fast pace is the most studied topic in the field of eating behavior habits, the findings are not consistent. A Chinese cross-sectional study found no association between eating fast and increased odds of MASLD,[22] whereas a Korean cross-sectional study found that fast eating was associated with increased odds of MASLD, with more

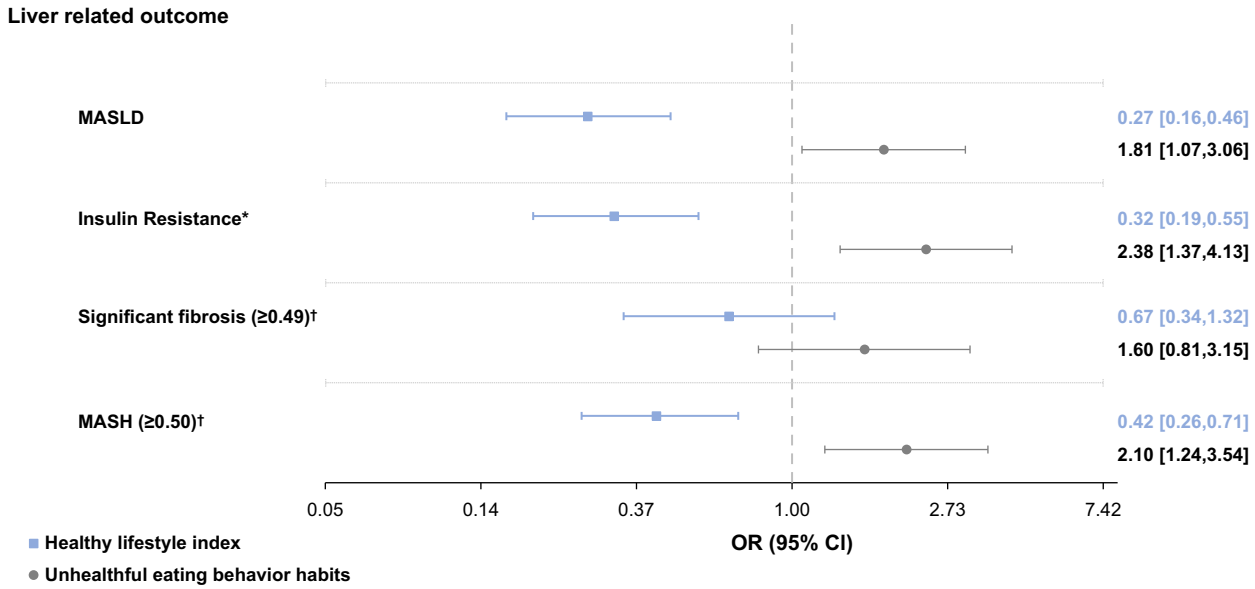

FIGURE 3 Multivariable analysis for the cross-sectional association between healthy lifestyle index, unhealthful eating behavior habits, and liver-related outcomes. ORs and their 95% CIs, based on multivariable logistic regression, adjusted for follow-up age (years), sex, follow-up energy intake (kcal/d), and for the other exposure variable; HLI or eating behavior habits accordingly (both evaluated at the follow-up survey). N cases/n total for each outcome: 109/314 for MASLD, 104/310 for IR, 51/303 for liver fibrosis, and 117/303 for MASH. HLI categories were defined as low HLI (unfavorable lifestyle) versus high HLI (favorable lifestyle); adherence to 0–2 versus 3–4 healthy lifestyle components, respectively. Eating behavior habits categories were defined as unhealthful (higher score reflects less appropriate eating behavior habits) versus healthful eating behavior habits; ≥ 14 (sample median score) versus < 14, respectively. *Insulin resistance was defined as the upper quartile (≥ Q4) of the study population's HOMA levels (corresponding to a value ≥ 3.46 at follow-up) or diabetes with no insulin resistance according to the upper quartile of HOMA levels at follow-up. †Significant liver fibrosis and MASH were evaluated noninvasively using Fibromax. Abbreviations: HLI, healthy lifestyle index; HOMA, homeostasis model assessment; IR, insulin resistance; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease.

TABLE 4 Multivariable analysis for the cross-sectional association between specific unhealthful eating behavior habits and liver-related outcomes

Liver-related outcomes	Unhealthful eating behavior habits[a]	Prevalence OR (95% CI), *p*
MASLD		109/314 (n cases/n total)
	Eating following urge[b]	1.02 (0.51–2.01), 0.964
	Eating fast[c]	1.69 (1.01–2.85), **0.048**
Insulin resistance[d]		104/310 (n cases/n total)
	Eating following urge[b]	2.51 (1.27–4.98), **0.008**
	Eating fast[c]	1.07 (0.63–1.82), 0.812
Significant liver fibrosis (≥ 0.49)[e]		51/303 (n cases/n total)
	Eating following urge[b]	1.58 (0.64–3.89), 0.319
	Eating fast[c]	0.82 (0.42–1.63), 0.576
MASH (≥ 0.50)[e]		117/303 (n cases/n total)
	Eating following urge[b]	2.40 (1.21–4.74), **0.012**
	Eating fast[c]	1.36 (0.82–2.27), 0.237

Note: *p* values < 0.05 are in boldface.
[a]ORs adjusted for potential confounders: follow-up age (y), sex, follow-up energy intake (kcal/d), and HLI (evaluated during the follow-up survey).
[b]Eating following urge was compared to eating following hunger/mealtime combined (reasons for eating categories).
[c]Fast eating pace was compared with slow/regular eating pace combined (eating pattern categories).
[d]Insulin resistance was defined as the upper quartile (≥ Q4) of the study population's HOMA levels (corresponding to a value of ≥ 3.46 at follow-up) or diabetes with no insulin resistance according to the upper quartile of HOMA levels at follow-up.
[e]Significant liver fibrosis and MASH were evaluated noninvasively using Fibromax.
Abbreviations: HLI, healthy lifestyle index; HOMA-IR, homeostasis model assessment of insulin resistance; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease.

pronounced associations in lean subjects.[23] Furthermore, a Japanese retrospective cohort study found that subjects who ate at a fast pace and before bedtime had a higher risk of probable MASLD, evaluated by FLI ≥ 60.[21] Examining unhealthful eating behavior habits, in addition to HLI, provided a holistic perspective combining well-studied lifestyle parameters with a more novel behavioral component. However, more research is needed to test whether changes in eating behavior habits should be one of the lifestyle goals of MASLD treatment.

For each of the HLI components, there is convincing evidence of an association with MASLD and, in some cases, with MASH and liver fibrosis markers.[7] Smoking has been related to MASLD, liver fibrosis, and liver cancer.[5] People with obesity have a 3.5-fold increased risk of developing MASLD compared with those with normal weight.[44] Engaging in physical activity for ≥ 150 min/wk of moderate or 75 min/wk of vigorous-intensity physical activity is protective against MASLD and liver fibrosis[45] and is the currently accepted recommendation.[46] Lastly, prospective studies repeatedly show an inverse association between MASLD development and MED or similar healthy eating dietary patterns.[47] The joint effect of these lifestyle behaviors may be synergistic, but this needs to be tested in studies with larger sample sizes. As expected, in our study, participants with a favorable lifestyle had a better metabolic profile, which could be a mediating factor, including less IR and lower serum levels of ferritin, uric acid, and triglycerides.

Worse eating behavior habits may be related to unhealthy eating or other unhealthy lifestyle behaviors or a greater caloric intake, although we adjusted for these factors, and the association persisted. There is little evidence to explain the association between eating behavior habits and MASLD. A previous randomized controlled trial showed that increased meal frequency, but not meal size, increased intrahepatic triglyceride content, independent of calorie intake and weight gain,[25] suggesting that continuous delivery of nutrients might lead to a different metabolic response compared to a pattern of fasting and feeding cycles, as in regular meals. Moreover, the timing of energy intake, including eating before bedtime, may predispose to MASLD.[21] Both continuous snacking and eating in an unorganized order due to emotional cues and eating in late evening hours are eating behaviors opposite to the concept of intermittent fasting based on a limited eating time window, which has been demonstrated to lead to increased lipolysis and reduced lipogenesis during fasting, confer overall metabolic health benefits, and be potentially protective in MASLD.[48,49]

Our study has several strengths, including its prospective design that enables temporal inference. Furthermore, a wide range of liver-related outcomes was included in our study, strengthening the robustness of our findings. The present study also has several limitations that should be addressed. First, the observational study was prone to residual confounding factors. Second, the lifestyle components in the survey, excluding body weight, were self-reported and thus susceptible to information bias. Nevertheless, several measures were taken to minimize this bias, including using structured questionnaires adapted to the Israeli population, excluding participants with unreasonable self-reported caloric intake, blinding participants, and the research team to the liver and blood test outcomes so that the bias would be nondifferential and may only lead to underestimation of the associations. Third, the diagnosis of MASLD (including its histological spectrum) and IR was not made with their gold standard diagnostic tools of liver biopsy and glucose clamp, respectively. Nevertheless, the noninvasive methods used in this study are validated and widely accepted diagnostic tools appropriate for general population-based studies. Furthermore, the main diagnostic method of MASLD was switched from AUS to FibroScan during the follow-up survey, which may have created information bias. To address this issue, we conducted a sensitivity analysis in the subsample of subjects undergoing AUS at both time points, and the associations observed corresponded with those of the entire sample. Finally, all data were collected within a single country, which may limit the generalizability of the study results.

In conclusion, adherence to a healthy lifestyle, including moderate physical activity, nonsmoking, maintaining normal body weight, and adhering to a healthy diet, was prospectively associated with lower odds of MASLD, IR, and MASH evaluated by biomarker. In particular, a dose-response association was noted between MASLD and IR. These associations were independent of potential confounding factors. Unhealthful eating behavior habits were also independently associated with various liver-related outcomes. A holistic treatment approach that simultaneously targets several lifestyle parameters may be useful in preventing MASLD and liver damage.

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CONFLICTS OF INTEREST

Oren Shibolet consults and is on the speaker's bureau for Roche. Shira Zelber-Sagi consults for Siemens. She is on the speaker's bureau for AbbVie. The remaining authors have no conflicts to report.

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