Published in final edited form as:

Cancer Epidemiol Biomarkers Prev. 2021 April ; 30(4): 789–796. doi:10.1158/1055-9965.EPI-20-1329.

Association of Inflammatory and Insulinemic Potential of Diet and Lifestyle with Risk of Hepatocellular Carcinoma

Wanshui Yang^{*,1,2}, Jing Sui^{*,1,3}, Longgang Zhao⁴, Yanan Ma^{1,5}, Fred K. Tabung^{6,7,8}, Tracey G. Simon^{9,10,11}, Dong Hoon Lee⁶, Xufen Zeng², Long H. Nguyen^{10,11,12}, Jeffrey A. Meyerhardt¹³, Andrew T. Chan^{1,10,11}, Edward L. Giovannucci^{1,6,14}, Xuehong Zhang^{1,6}

¹Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

²Department of Nutrition, School of Public Health, Anhui Medical University, Hefei, Anhui, P.R. China

³Research Institute for Environment and Health, School of Law and Public Affairs, Nanjing University of Information Science and Technology, Nanjing, Jiangsu, P.R. China

⁴Department of Epidemiology & Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, SC, USA

⁵School of Public Health, China Medical University, Shenyang, Liaoning, P.R. China

⁶Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA

⁷Division of Medical Oncology, Department of Internal Medicine, The Ohio State University College of Medicine, Columbus, OH, USA

⁸The Ohio State University Comprehensive Cancer Center - Arthur G. James Cancer Hospital and Richard J. Solove Institute, Columbus, OH, USA

⁹Liver Center, Division of Gastroenterology, Department of Medicine, Massachusetts General Hospital, Boston, MA, USA

¹⁰Division of Gastroenterology, Department of Medicine, Massachusetts General Hospital

¹¹Clinical and Translational Epidemiology Unit (CTEU), Massachusetts General Hospital, Boston, MA, USA

¹²Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA, USA

¹³Department of Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, Massachusetts, USA

¹⁴Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA.

Abstract

Correspondence: Xuehong Zhang, MD, ScD, Brigham and Women's Hospital and Harvard Medical School; 181 Longwood Avenue, Room 453, Boston, MA 02115, USA; Telephone: +1-617-525-0342; Fax: +1-617-525-2008, xuehong.zhang@channing.harvard.edu.

*These authors contributed equally as first co-authors.

Disclosure of Potential Conflicts of Interest: The authors declare no potential conflicts of interest

Background—We prospectively examined the extent to which greater inflammatory and insulinemic potential of diet and lifestyle are associated with the risk of developing hepatocellular carcinoma (HCC) in two nationwide cohorts.

Methods—Five kinds of pattern scores including the empirical dietary inflammatory pattern (EDIP), empirical dietary index for hyperinsulinemia (EDIH) and insulin resistance (EDIR), empirical lifestyle pattern score for hyperinsulinemia (ELIH) and insulin resistance (ELIR) were calculated. Multivariable hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox regression.

Results—After an average follow-up of 25.6 years among 119,316 participants, 142 incident HCC cases were documented. Higher adherence to EDIP (HR by comparing extreme tertiles: 2.03, 95% CI: 1.31–3.16, $P_{\text{trend}} = 0.001$), EDIH (HR=1.61, 95% CI: 1.06–2.43, $P_{\text{trend}} = 0.02$), and EDIR (HR=1.62, 95% CI: 1.08–2.42, $P_{\text{trend}} = 0.02$) were associated with increased risk of HCC. Likewise, participants with higher scores of ELIH (HR=1.89, 95% CI: 1.25–2.87, $P_{\text{trend}} = 0.001$) and ELIR (HR=2.05, 95% CI: 1.34–3.14, $P_{\text{trend}} = 0.0004$) had higher risk of developing HCC. Additional adjustment for diabetes mellitus and/or body mass index attenuated the magnitude of the associations, indicating that diabetes and/or adiposity may partly mediate the association of these patterns with HCC risk.

Conclusions—Our findings suggest that inflammation and insulin resistance/hyperinsulinemia are potential mechanisms linking dietary or lifestyle factors and HCC development.

Impact—Inflammation and insulin resistance/hyperinsulinemia may partly mediate the association of diet and other lifestyles with HCC development, and interventions to reduce the adverse effect of pro-inflammatory and hyperinsulinemic diet and lifestyle may reduce HCC risk.

Keywords

Diet; inflammation; Insulin resistance; Hepatocellular carcinoma; Cancer prevention

INTRODUCTION

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide (1). In the United States, although the population seroprevalence of hepatitis B virus (HBV) (2) and hepatitis C virus (HCV) (3) continues to decline, the HCC incidence rate has tripled since 1980s (4). Most HCC patients are diagnosed at a late stage and are fatal within 1 year of diagnosis (5), thereby making primary prevention a key priority. However, well-established risk factors only include HBV and HCV infections, heavy alcohol drinking, aflatoxin contamination. About 35% of HCC cannot be explained by these factors (6).

In addition to chronic hepatitis virus infections, HCC risk is consistently increased with obesity (7–9) and type 2 diabetes mellitus (T2D) (8–11), suggesting an important role of inflammatory and insulinemic pathways in hepatocarcinogenesis. Also, epidemiological studies have consistently reported positive associations between pre-diagnostic circulating levels of biomarkers of inflammation or insulin response such as C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor (TNF)-alpha, and C-peptide and HCC risk (12–15). Furthermore, several studies (16,17) have shown that the use of anti-inflammatory

medications, such as aspirin, was associated with lower risk of HCC. In addition, individuals with higher adherence to the T2D prevention diet had lower risk of developing HCC (18). Taken together, modifiable factors that modulate inflammatory and insulinemic pathways may influence HCC development and might be crucial for HCC prevention. Previous studies have shown that diet and other lifestyle factors such as physical activity may modulate inflammation (19–21) and insulin response (20–22). We thus hypothesized that greater inflammatory and insulinemic potential of diet and lifestyle are associated with increased risk of HCC.

To test this hypothesis, we used validated empirical hypothesis-oriented dietary patterns including the food-based empirical dietary inflammatory pattern (EDIP) (23) and empirical dietary index for hyperinsulinemia (EDIH) and insulin resistance (EDIR) (24) to assess the ability of long-term dietary patterns to contribute to chronic systemic inflammation and sustained insulin hypersecretion. Likewise, empirical lifestyle patterns for hyperinsulinemia (ELIH) and insulin resistance (ELIR) that evaluate the insulinemic potential of usual lifestyle were also derived. In this study, we investigated the association of the EDIP, EDIR, EDIH, ELIR, and ELIH with risk of developing HCC using data from two large prospective cohort studies, the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS).

MATERIALS and METHODS

Study Population

The participants in the study were selected from the NHS and HPFS. The rationale, design, and methodology of these 2 cohorts were described elsewhere (25,26). Briefly, the NHS cohort was established in 1976 with enrollment of 121,700 female registered nurses aged 30–55 years. The HPFS cohort was established in 1986 with enrollment of 51,529 male health professionals aged 32–87 years. In the 2 cohorts, validated questionnaires were administered biennially to collect and update information on medical history, lifestyle, and incidence of chronic diseases, with a response rate of over 90% in each cohort. In this analysis, we excluded individuals who had missing values in any dietary or lifestyle pattern scores (i.e., EDIP, EDIR, EDIH, ELIR, and ELIH), or who had cancer (except nonmelanoma skin cancer) or implausible energy intake (<600 or >3,500 kcal/day for women; <800 or >4,200 kcal/day for men) at baseline. Overall, a total of 70,055 women and 49,261 men were included in the final analysis. The Institutional Review Board at the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health approved this study, and those of participating registries as required.

Assessments of Diet, EDIP, EDIH, and EDIR scores

A validated food frequency questionnaire (FFQ) (25,26) was sent in 1980, 1984, 1986, and every 4 years thereafter in the NHS. Likewise, dietary information was collected in 1986 and every 4 years thereafter using similar FFQs in the HPFS. In the NHS, compared with multiple weeks of weighed diet records, the mean of correlation coefficients of 55 specific foods and beverages assessed on the FFQ was 0.52 (27). In the HPFS, the correlation

coefficients between the FFQ and food records were 0.59 for red meats, 0.52 for processed meats, 0.67 for fruit, 0.26–0.55 for vegetables, and 0.27 for whole grains (28).

EDIP and EDIR/EDIH scores were developed and validated to reflect the long-term effects of diet on inflammation and insulin response (insulin resistance/hyperinsulinemia), respectively (23,24). Briefly, EDIP was derived based on 39 pre-defined food groups from FFQs using reduced-rank regression followed by stepwise linear regression models to identify a dietary pattern most predictive of 3 inflammatory biomarkers (i.e., IL-6, C-reactive protein, and TNF-alpha receptor-2). Likewise, EDIH and EDIR was derived based on 39 pre-defined food groups using stepwise linear regression to identify a dietary pattern most predictive of C-peptide (an indicator of insulin secretion) and the triglyceride to high density lipid-cholesterol (HDL-C) ratio (an indicator of insulin resistance), respectively. A total of 18 foods and food groups were included in each dietary pattern (Table S1), which were weighted by the regression coefficients derived from the final model and then summed to constitute the 3 dietary pattern scores. Higher scores (more positive) indicate more pro-inflammatory or higher insulinemic potential while lower (more negative) scores indicate anti-inflammatory or lower insulinemic potential of diets.

Assessments of Body Mass Index (BMI), Physical Activity, ELIH, ELIR, and Other Covariates

BMI was calculated from each questionnaire using weight in kilograms divided by height (collected in 1986) in square meters (kg/m^2). Self-reported weight was first collected in 1986 and updated every 2 years thereafter. The correlation between self-reported and measured weights was 0.97 both for women and men (29). Physical activity was collected through biennial questionnaires in both cohorts, and was expressed in metabolic equivalent (MET)-h/week, by summing the average MET-h/week for the following activities: tennis/squash/racquet ball, rowing, calisthenics, walking, jogging, running, bicycling, and swimming. The correlation between physical activity as reported in four 1-week recalls and that reported on the questionnaires was 0.62 in NHS and 0.65 in HPFS (30,31).

The development of ELIH and ELIR has been previously described (24). Briefly, 39 pre-defined food groups as well as 2 lifestyle factors (BMI and physical activity) were entered into stepwise linear regression (24). The ELIH score is a weighted sum of 14 components: 7 components including BMI were positively while the remaining 7 including physical activity were inversely associated with circulating C-peptide levels. The ELIR had 17 components: 11 including BMI were positively while the remaining 6 including physical activity were inversely associated with the ratio of triglyceride to HDL-C (Table S1).

We also collected information on age, race, smoking status, aspirin use, and T2D at baseline and updated during follow-up except for race.

Ascertainment of HCC

In each cohort, participants were asked for written permission to obtain their medical records and/or pathological reports if they reported liver cancer on biennial questionnaires. All possible cancer cases were further confirmed by a study physician who was blinded to exposure data and extracted information from the medical or pathological reports regarding

the histological subtypes of the cancer (e.g., HCC versus intrahepatic cholangiocarcinoma), the presence of HBV or HCV infections, and the presence of underlying cirrhosis. Additional data on HBV/HCV infection status were also available from a nested case-control study of HCC in the NHS/HPFS (26 cases and 78 controls), which were derived from laboratory blood tests (32).

Statistical Analyses

Person-time was calculated from baseline (1984 for women; 1986 for men) until the date of diagnosis of HCC, date of death, loss to follow-up, or June 1, 2012 for the NHS and January 31, 2012 for the HPFS, whichever came first. We calculated the cumulative average of dietary and lifestyle pattern scores by averaging these variables over time from 1984 in the NHS and 1986 in the HPFS to the current questionnaire cycle and updating data when information was updated. Similarly, the cumulative average intake of other covariates, when appropriate, was created to best reflect long-term food intake and lifestyle, and to minimize within-person variation (33). Age-adjusted and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using time-varying Cox regression model. The model was stratified simultaneously by age and year of questionnaire return, enabling the finest possible control of confounding for age and secular trends. To maximize the statistical power, results from the 2 cohorts were combined because we did not detect any significant heterogeneity between two cohorts ($P>0.05$ for all heterogeneity in cohort-specific associations). We found no violation of proportionality of hazards in Cox model by testing an interaction term between each pattern score and follow-up time ($P>0.05$ for all tests). The trend tests were conducted using the median of each category of pattern scores as a continuous variable.

The adjusted covariates in the multivariable model included age, race, smoking, physical activity, total energy intake, and aspirin use (categorizations see footnote in the tables). We did not adjust for intake of coffee and alcohol in the main analyses because these factors are important components in the 5 patterns, but these factors were additionally controlled in the sensitivity analysis. Similarly, we did not control for physical activity and BMI when evaluating the ELIH and ELIR in relation to HCC risk, although these factors were further adjusted in the sensitivity analyses. Because T2D and BMI are potential intermediates in the association of inflammatory and insulinemic potential of diet and lifestyle with HCC risk, we did not adjust for in the main analyses but further adjusted for these two covariates in sensitivity analyses (only for the three dietary patterns). Since BMI is a component of ELIH and ELIR, we did not adjust for BMI in sensitivity analyses when examining these two lifestyle patterns. Moreover, we adjusted for baseline T2D, BMI or waist circumference or metabolic comorbidities (i.e., T2D, obesity (BMI >30), hypertension, and dyslipidemia) to evaluate whether these variables at baseline mediate the associations of dietary and lifestyle patterns with HCC risk.

In secondary analyses, to evaluate the extent to which observed associations might be confounded by HBV/HCV infection status, we evaluated the correlation between HBV/HCV infection status and each pattern score among participants with available data on chronic HBV/HCV infections. Considering a potential difference in etiology, we evaluated the

associations between each pattern score and HCC risk according to HBV/HCV infection status (viral vs. non-viral HCC) and history of pre-existing cirrhosis (cirrhotic vs. non-cirrhotic HCC). In addition, to evaluate the independent associations of inflammatory and insulinemic potential of diet and overall lifestyle with the risk of HCC development, we further mutually adjusted for EDIP and EDIH in the analysis. Similarly, we further adjusted for EDIP when assessing associations for ELIR, EDIR, and ELIH. No mutual adjustments for EDIR and EDIH were conducted given a high correlation between the two patterns (Table S2). Lastly, we examined joint associations between EDIP and EDIH and between EDIP and EDIR. These indexes were dichotomized into low (the first and second tertile categories) versus high (the highest tertile category), resulting in four mutually exclusive groups (low-low, low-high, high-low, and high-high). These four groups were then evaluated in relation to HCC risk.

We also conducted an exploratory subgroup analyses by age, BMI, smoking status (never vs. ever), T2D, alcohol intake, physical activity, and regular aspirin use. All statistical tests were 2-sided and performed using SAS (version 9.4, SAS Institute Inc, Cary, NC).

RESULTS

After an average follow-up of 25.6 years among 119,316 participants (70,055 women and 49,261 men), we confirmed 142 incident HCC (67 women and 75 men). Participants with higher EDIP, EDIR, EDIH, ELIR, or ELIH scores reported lower physical activity, had higher BMI, and were more likely to have T2D (Table 1). Similar patterns were observed in women and men separately (Table S3 and Table S4).

In the multivariable-adjusted analyses, compared to participants in the lowest EDIP tertile, those in the highest EDIP tertile had 2.03 times higher risk of HCC (95% CI: 1.31–3.16, $P_{\text{trend}}=0.001$). Similarly, diets with higher insulinemic potential were associated with increased risk of HCC, with HRs of 1.61 (95% CI: 1.06–2.43, $P_{\text{trend}}=0.02$) for EDIH, and 1.62 (95% CI: 1.08–2.42, $P_{\text{trend}}=0.02$) for EDIR (Table 2). In the joint analysis of EDIP and EDIH, the HRs for HCC were 1.93, 1.24, 1.48, 1 (reference) for high/high, high/low, low/high, and low/low group, respectively. Likewise, individuals with high scores of both EDIP and EDIR had the highest risk of developing HCC (Figure 1). Generally, associations for the lifestyle pattern score with HCC risk seemed stronger than the diet-only pattern score. Participants with higher scores of ELIH (HR=1.89, 95% CI: 1.25–2.87, $P_{\text{trend}}=0.0001$) and ELIH (HR=2.05, 95% CI: 1.34–3.14, $P_{\text{trend}}=0.0004$) had higher risk of developing HCC (Table 3). Although we found no statistical heterogeneity in sex (cohort)-specific associations, the associations for each pattern score appeared stronger in women than those in men.

In sensitivity analysis, further adjustments for coffee and alcohol intakes for all 5 patterns and further adjustments for physical activity and BMI for lifestyle patterns did not substantially change the results. Additional adjustments for BMI and T2D attenuated the magnitude of the associations, although the strong positive association for EDIP remained (HR=1.71, 95% CI: 1.09–2.69), indicating that obesity and diabetes may partly mediate the associations of the dietary and lifestyle patterns with HCC risk (Table S5). However,

adjustments for T2D at baseline or metabolic comorbidities (excluding obesity) at baseline did not appreciably change the results. Further mutual adjustments for EDIP and EDIH in the same analysis did not appreciably alter the associations.

Among 75 HCC cases with known information on chronic HBV or HCV infection, 25 infected and 50 not. We did not detect any statistically significant differential associations of dietary or lifestyle patterns with the risk of viral and non-viral HCC (all $P_{\text{heterogeneity}} > 0.20$), despite the insufficient statistical power due to the limited number of HCC cases. Similarly, when separately examining the associations with cirrhotic (30 cases) and non-cirrhotic (54 cases) HCC, there was no difference in the associations (all $P_{\text{heterogeneity}} > 0.10$). There was no correlation between any pattern scores and HBV/HCV infection status (the Spearman correlation coefficients ranged from 0.03 to 0.15) in a subset of participants with HBV/HCV data (n=208).

In subgroup analysis, although the statistical power was limited due to limited number of cases, the association between EDIP and HCC risk appeared stronger in diabetics (HR=9.48, no. of cases=99) than those of non-diabetics (HR=1.39, no. of cases=43). In addition, the associations of EDIP and ELIR with HCC risk appeared stronger in never smokers (HR>3, no. of cases=68) than those in ever smokers (HR≈1, no. of cases=74). We did not find any statistically significant interactions with other risk factors (Tables S6–S10).

DISCUSSION

In these two large prospective US cohorts, we investigated the associations of dietary (EDIP, EDIH, and EDIR) and lifestyle (ELIH and ELIR) pattern scores reflecting the potential of habitual diets and lifestyles to contribute to chronic systemic inflammation, hyperinsulinemia and insulin resistance, with risk of developing HCC. Our findings suggested that diets or lifestyle behaviors with pro-inflammatory or hyperinsulinemic potential are associated with increased risk of developing HCC.

Few studies have examined the associations of various dietary patterns with risk of HCC (34–36). These studies suggested that better adherence to ‘healthy’ dietary patterns including Alternative Healthy Eating Index-2010 (AHEI-2010) (34,35), Alternate Mediterranean Diet (AMED) (34,35), and a vegetable-based dietary pattern (36) were associated with lower risk of incident HCC. Inflammation and insulin resistance/hyperinsulinemia are hypothesized as major biological pathways by which these dietary patterns influence HCC (37). However, no studies to date have comprehensively assessed inflammatory or insulinemic potential of whole diet or lifestyle and their associations with HCC risk. In the current study, we used validated empirical hypothesis-oriented dietary or lifestyle patterns to capture inflammatory and insulinemic potential of diet and lifestyle behaviors, and found significant positive associations with risk of HCC.

Observational studies suggested that higher concentrations of CRP, IL-6, and TNF-alpha were associated with elevated risk of HCC, indicating an important role of inflammation in hepatocarcinogenesis (12–15). Animal studies showed that estrogen may mediate inhibition of IL-6 production by Kupffer cells in females, which could partly explain the sex disparity

in HCC incidence (2–3 times higher in men than in women) (38,39). In contrast, a cohort study (13) of 330 participants between 52–65 years and with chronic HCV infection showed that high circulating levels of IL-6 was associated with higher HCC risk only in women but not in men. In addition, higher circulating levels of estradiol seemed not a protective factor for HCC, but a risk factor for intrahepatic cholangiocarcinoma in post-menopausal women (40). These results align with our findings showing that associations for inflammatory dietary pattern as well as other patterns appeared stronger in women than in men although the sex heterogeneity was not statistically significant. The underlying mechanism for the aforementioned potential sex difference remains unclear and needs to be elucidated in future research. Alternatively, the difference could be due to chance.

Previous studies have used food glycemic index (GI) and glycemic load (GL) as indicators of an immediate insulin response by assessing the influence of carbohydrate-containing foods on postprandial blood glucose, and evaluated their role in HCC development. (41–46) Findings from these studies were inconclusive, varying from positive (42,44,45), null (41,43,46), to inverse (42) associations. A possible reason for such discrepancy is that GI and GL have limited capacity to account for non-carbohydrate factors that may influence insulin response, and they do not incorporate effects of diet on insulin resistance, which is a major determinant of insulin response. Although insulinemic index (II) and insulinemic load (IL) have been developed to directly quantify the postprandial insulin response to foods independent of insulin resistance (47), there have been little study on the association of II and IL with HCC risk. Moreover, II may not reflect but be inversely associated with long-term insulin exposure (24,48,49). In contrast to using the II and IL which are based on acute insulin responses to foods independent of insulin resistance, we used the empirical hypothesis-oriented pattern score for insulin resistance/hyperinsulinemia which was based on usual diet and lifestyle behaviors and strongly predictive of C-peptide concentrations (indicator of long-term endogenous insulin) (24). Generally, associations for the lifestyle patterns (ELIH and ELIR) were slightly stronger than for the diet-only patterns (EDIH and EDIR), which was in line with the explanation that in general, lifestyle is a stronger predictor of insulin response than diet alone.

Our subgroup analysis suggested a possible interaction between T2D and EDIP in HCC development with a stronger positive association in diabetics ($P_{\text{interaction}} = 0.06$). These results indicated cross-talk between diet, inflammation, and insulin-IGF-glucose axis in hepatocarcinogenesis (20). In our previous study, we showed that adherence to a T2D prevention dietary pattern was associated with lower HCC risk, particularly among non-diabetics (18), which somewhat contradicts the current observations. Different dietary patterns with different components may partly explain such controversy. Alternatively, the findings could be due to chance given limited cancer cases. It is unclear why EDIH and ELIR showed a stronger positive association with HCC risk in never smokers (all $P_{\text{interaction}} = 0.01$). Although the reasons for these significant interactions are not clear, these findings suggest that insulinemic potential of diet and lifestyle may be a stronger predictor of HCC in never smokers. Alternatively, the results might be due to chance. Future studies are warranted to confirm these findings and elucidate the underlying mechanisms.

Interestingly, further adjustment for BMI and T2D attenuated the associations, suggesting that adiposity and diabetes may mediate the association of these dietary and lifestyle patterns with HCC risk. Of note, only the association for EDIP remained statistically significant after additional adjustments. Similarly, the association between EDIP and risk of colorectal cancer was somewhat diluted but remained statistically positive when additionally controlling for BMI and diabetes in the NHS and HPFS (50). These results indicated that other factors may mediate the association between EDIP and cancer risk except for obesity and diabetes.

Our study has several limitations. An important limitation to this study is the lack of complete data on chronic HBV/HCV infection status in the full cohorts. However, among a subset of participants who provided such data, virus infection status was not correlated with dietary or lifestyle pattern scores. These participants with available HBV/HCV data were comparable with all participants in our cohorts with regard to a number of demographic, diet and lifestyle factors. Therefore, our findings seem unlikely to be substantially confounded by HBV/HCV infection status. Second, self-reported diet and other lifestyle factors from questionnaires have measurement errors. However, questionnaires used in the 2 cohorts have showed good reproducibility and validity for assessing dietary intake and other lifestyle such as physical activity (27,28,30,31). In addition, use of cumulative average of repeated measures in the current study can decrease the measurement error of long-term diets and other lifestyles. Third, although our results showed no evidence of the differential association of dietary or lifestyle pattern scores with the risk of viral and non-viral HCC, the statistical power was limited due to the small number of HCC cases. In addition, given multiple exposures and limited HCC cases, results should be interpreted with caution, particularly for findings from interaction analysis. However, multiple testing is less of a concern because this is a hypothesis-driven study. Last, our study population consisted largely of white, educated health professionals, which may limit the generalizability of our findings to other racial or ethnic groups.

In conclusion, we found that diet and lifestyle with higher inflammatory or insulinemic potential were associated with higher risk of HCC in US adults. These findings provide strong evidence that inflammation and insulin resistance/hyperinsulinemia may partially mediate the association of diet and lifestyle behaviors with HCC development. Guidelines and interventions highlighting the importance of reducing or avoiding pro-inflammatory and insulinemic diet or lifestyle patterns may have significant potential for the primary prevention of HCC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

We would like to thank the participants and staff of the Nurses' Health Study and the Health Professionals Follow-up Study for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY. The authors assume full responsibility for analyses and interpretation of these data.

Grant Support:

This work was supported by UM1 CA186107 (Nurses' Health Study infrastructure grant, to MJS), P01 CA87969 (Nurses' Health Study program grant for cancer research, to MJS), U01 167552 (Health Professionals Follow-up Study infrastructure grant, to WCW). Dr. Tabung is supported by R00 CA207736. Dr. Chan is supported by NIH K24 DK098311. Dr. Zhang is supported by NIH K07 CA188126, R21CA238651, and American Cancer Society Research Scholar Grant (RSG NEC-130476). ATG is a Stuart and Suzanne Steele MGH Research Scholar. The funders had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Abbreviations:

AHEI-2010	Alternative Healthy Eating Index-2010
AMED	Alternate Mediterranean Diet
BMI	body mass index
CI	confidence interval
CRP	C-reactive protein
EDIP	Empirical dietary inflammatory pattern
EDIH	Empirical dietary index for hyperinsulinemia
EDIR	Empirical dietary index for insulin resistance
ELIH	Empirical lifestyle pattern score for hyperinsulinemia
ELIR	Empirical lifestyle pattern score for insulin resistance
FFQ	food frequency questionnaire
GI	glycemic index
GL	glycemic load
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HPFS	Health Professionals Follow-up Study
HR	hazard ratio
II	insulinaemic index
IL	insulinaemic load
IL-6	interleukin-6
METS	metabolic equivalent tasks
NHS	Nurses' Health Study

PUFAs	polyunsaturated fatty acids
SFAs	saturated fatty acids
TNF	tumor necrosis factor
T2D	type 2 diabetes

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394–424 [PubMed: 30207593]
2. Ioannou GN. Hepatitis B virus in the United States: infection, exposure, and immunity rates in a nationally representative survey. *Ann Intern Med* 2011;154:319–28 [PubMed: 21357909]
3. Denniston MM, Jiles RB, Drobeniuc J, Klevens RM, Ward JW, McQuillan GM, et al. Chronic hepatitis C virus infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010. *Ann Intern Med* 2014;160:293–300 [PubMed: 24737271]
4. Ryerson AB, Ehemann CR, Altekruse SF, Ward JW, Jemal A, Sherman RL, et al. Annual Report to the Nation on the Status of Cancer, 1975–2012, featuring the increasing incidence of liver cancer. *Cancer* 2016;122:1312–37 [PubMed: 26959385]
5. Jemal A, Ward EM, Johnson CJ, Cronin KA, Ma J, Ryerson B, et al. Annual Report to the Nation on the Status of Cancer, 1975–2014, Featuring Survival. *J Natl Cancer Inst* 2017;109
6. Makarova-Rusher OV, Altekruse SF, McNeel TS, Ulahannan S, Duffy AG, Graubard BI, et al. Population attributable fractions of risk factors for hepatocellular carcinoma in the United States. *Cancer* 2016;122:1757–65 [PubMed: 26998818]
7. Sun B, Karin M. Obesity, inflammation, and liver cancer. *J Hepatol* 2012;56:704–13 [PubMed: 22120206]
8. Campbell PT, Newton CC, Freedman ND, Koshiol J, Alavanja MC, Beane Freeman LE, et al. Body Mass Index, Waist Circumference, Diabetes, and Risk of Liver Cancer for U.S. Adults. *Cancer Res* 2016;76:6076–83 [PubMed: 27742674]
9. Simon TG, King LY, Chong DQ, Nguyen LH, Ma Y, VoPham T, et al. Diabetes, metabolic comorbidities, and risk of hepatocellular carcinoma: Results from two prospective cohort studies. *Hepatology* 2018;67:1797–806 [PubMed: 29152763]
10. Petrick JL, Freedman ND, Demuth J, Yang B, Van Den Eeden SK, Engel LS, et al. Obesity, diabetes, serum glucose, and risk of primary liver cancer by birth cohort, race/ethnicity, and sex: Multiphasic health checkup study. *Cancer Epidemiol* 2016;42:140–6 [PubMed: 27148890]
11. Yang WS, Shu XO, Gao J, Li HL, Cai H, Yang G, et al. Prospective evaluation of type 2 diabetes mellitus on the risk of primary liver cancer in Chinese men and women. *Ann Oncol* 2013;24:1679–85 [PubMed: 23406734]
12. Ohishi W, Cologne JB, Fujiwara S, Suzuki G, Hayashi T, Niwa Y, et al. Serum interleukin-6 associated with hepatocellular carcinoma risk: a nested case-control study. *Int J Cancer* 2014;134:154–63 [PubMed: 23784949]
13. Wong VW, Yu J, Cheng AS, Wong GL, Chan HY, Chu ES, et al. High serum interleukin-6 level predicts future hepatocellular carcinoma development in patients with chronic hepatitis B. *Int J Cancer* 2009;124:2766–70 [PubMed: 19267406]
14. Nakagawa H, Maeda S, Yoshida H, Tateishi R, Masuzaki R, Ohki T, et al. Serum IL-6 levels and the risk for hepatocarcinogenesis in chronic hepatitis C patients: an analysis based on gender differences. *Int J Cancer* 2009;125:2264–9 [PubMed: 19585572]
15. Aroucha DC, do Carmo RF, Moura P, Silva JL, Vasconcelos LR, Cavalcanti MS, et al. High tumor necrosis factor-alpha/interleukin-10 ratio is associated with hepatocellular carcinoma in patients with chronic hepatitis C. *Cytokine* 2013;62:421–5 [PubMed: 23602201]

16. Simon TG, Ma Y, Ludvigsson JF, Chong DQ, Giovannucci EL, Fuchs CS, et al. Association Between Aspirin Use and Risk of Hepatocellular Carcinoma. *JAMA Oncol* 2018;4:1683–90 [PubMed: 30286235]
17. Lee TY, Hsu YC, Tseng HC, Yu SH, Lin JT, Wu MS, et al. Association of Daily Aspirin Therapy With Risk of Hepatocellular Carcinoma in Patients With Chronic Hepatitis B. *JAMA Intern Med* 2019;179:633–40 [PubMed: 30882847]
18. Luo X, Sui J, Yang W, Sun Q, Ma Y, Simon TG, et al. Type 2 Diabetes Prevention Diet and Hepatocellular Carcinoma Risk in US Men and Women. *Am J Gastroenterol* 2019;114:1870–7 [PubMed: 31688024]
19. Due A, Toubro S, Stender S, Skov AR, Astrup A. The effect of diets high in protein or carbohydrate on inflammatory markers in overweight subjects. *Diabetes Obes Metab* 2005;7:223–9 [PubMed: 15811138]
20. Asgharpour A, Cazanave SC, Pacana T, Seneshaw M, Vincent R, Banini BA, et al. A diet-induced animal model of non-alcoholic fatty liver disease and hepatocellular cancer. *J Hepatol* 2016;65:579–88 [PubMed: 27261415]
21. Kerr J, Anderson C, Lippman SM. Physical activity, sedentary behaviour, diet, and cancer: an update and emerging new evidence. *Lancet Oncol* 2017;18:e457–e71 [PubMed: 28759385]
22. Yki-Jarvinen H Nutritional Modulation of Non-Alcoholic Fatty Liver Disease and Insulin Resistance. *Nutrients* 2015;7:9127–38 [PubMed: 26556368]
23. Tabung FK, Smith-Warner SA, Chavarro JE, Wu K, Fuchs CS, Hu FB, et al. Development and validation of an empirical Dietary Inflammatory Index. *The Journal of nutrition* 2016;146:1560–70 [PubMed: 27358416]
24. Tabung FK, Wang W, Fung TT, Hu FB, Smith-Warner SA, Chavarro JE, et al. Development and validation of empirical indices to assess the insulinaemic potential of diet and lifestyle. *British Journal of Nutrition* 2016;116:1787–98
25. Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol* 1985;122:51–65 [PubMed: 4014201]
26. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. *Am J Epidemiol* 1992;135:1114–26; discussion 27–36 [PubMed: 1632423]
27. Salvini S, Hunter DJ, Sampson L, Stampfer MJ, Colditz GA, Rosner B, et al. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. *Int J Epidemiol* 1989;18:858–67 [PubMed: 2621022]
28. Hu FB, Rimm E, Smith-Warner SA, Feskanich D, Stampfer MJ, Ascherio A, et al. Reproducibility and validity of dietary patterns assessed with a food-frequency questionnaire. *Am J Clin Nutr* 1999;69:243–9 [PubMed: 9989687]
29. Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC. Validity of self-reported waist and hip circumferences in men and women. *Epidemiology* 1990;1:466–73 [PubMed: 2090285]
30. Chasan-Taber S, Rimm EB, Stampfer MJ, Spiegelman D, Colditz GA, Giovannucci E, et al. Reproducibility and validity of a self-administered physical activity questionnaire for male health professionals. *Epidemiology* 1996;7:81–6 [PubMed: 8664406]
31. Wolf AM, Hunter DJ, Colditz GA, Manson JE, Stampfer MJ, Corsano KA, et al. Reproducibility and validity of a self-administered physical activity questionnaire. *Int J Epidemiol* 1994;23:991–9 [PubMed: 7860180]
32. Petrick JL, Campbell PT, Koshiol J, Thistle JE, Andreotti G, Beane-Freeman LE, et al. Tobacco, alcohol use and risk of hepatocellular carcinoma and intrahepatic cholangiocarcinoma: The Liver Cancer Pooling Project. *Br J Cancer* 2018;118:1005–12 [PubMed: 29520041]
33. Hu FB, Stampfer MJ, Rimm E, Ascherio A, Rosner BA, Spiegelman D, et al. Dietary fat and coronary heart disease: a comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. *Am J Epidemiol* 1999;149:531–40 [PubMed: 10084242]

34. Li WQ, Park Y, McGlynn KA, Hollenbeck AR, Taylor PR, Goldstein AM, et al. Index-based dietary patterns and risk of incident hepatocellular carcinoma and mortality from chronic liver disease in a prospective study. *Hepatology* 2014;60:588–97 [PubMed: 24715615]
35. Ma Y, Yang W, Simon TG, Smith-Warner SA, Fung TT, Sui J, et al. Dietary Patterns and Risk of Hepatocellular Carcinoma Among U.S. Men and Women. *Hepatology* 2019;70:577–86 [PubMed: 30506561]
36. Zhang W, Xiang YB, Li HL, Yang G, Cai H, Ji BT, et al. Vegetable-based dietary pattern and liver cancer risk: results from the Shanghai women's and men's health studies. *Cancer Sci* 2013;104:1353–61 [PubMed: 23841909]
37. AlEsa HB, Malik VS, Yuan C, Willett WC, Huang T, Hu FB, et al. Dietary patterns and cardiometabolic and endocrine plasma biomarkers in US women. *Am J Clin Nutr* 2017;105:432–41 [PubMed: 27974312]
38. Sander LE, Trautwein C, Liedtke C. Is interleukin-6 a gender-specific risk factor for liver cancer? *Hepatology* 2007;46:1304–5 [PubMed: 17896415]
39. Naugler WE, Sakurai T, Kim S, Maeda S, Kim K, Elsharkawy AM, et al. Gender disparity in liver cancer due to sex differences in MyD88-dependent IL-6 production. *Science* 2007;317:121–4 [PubMed: 17615358]
40. Petrick JL, Florio AA, Zhang X, Zeleniuch-Jacquotte A, Wactawski-Wende J, Van Den Eeden SK, et al. Associations between Prediagnostic Concentrations of Circulating Sex Steroid Hormones and Liver Cancer Among Post-Menopausal Women. *Hepatology* 2019
41. Fedirko V, Lukanova A, Bamia C, Trichopolou A, Trepo E, Nothlings U, et al. Glycemic index, glycemic load, dietary carbohydrate, and dietary fiber intake and risk of liver and biliary tract cancers in Western Europeans. *Ann Oncol* 2013;24:543–53 [PubMed: 23123507]
42. George SM, Mayne ST, Leitzmann MF, Park Y, Schatzkin A, Flood A, et al. Dietary glycemic index, glycemic load, and risk of cancer: a prospective cohort study. *Am J Epidemiol* 2009;169:462–72 [PubMed: 19095757]
43. Hu J, La Vecchia C, Augustin LS, Negri E, de Groh M, Morrison H, et al. Glycemic index, glycemic load and cancer risk. *Ann Oncol* 2013;24:245–51 [PubMed: 22831983]
44. Lagiou P, Rossi M, Tzonou A, Georgila C, Trichopoulos D, La Vecchia C. Glycemic load in relation to hepatocellular carcinoma among patients with chronic hepatitis infection. *Ann Oncol* 2009;20:1741–5 [PubMed: 19528361]
45. Rossi M, Lipworth L, Maso LD, Talamini R, Montella M, Polesel J, et al. Dietary glycemic load and hepatocellular carcinoma with or without chronic hepatitis infection. *Ann Oncol* 2009;20:1736–40 [PubMed: 19549710]
46. Vogtmann E, Li HL, Shu XO, Chow WH, Ji BT, Cai H, et al. Dietary glycemic load, glycemic index, and carbohydrates on the risk of primary liver cancer among Chinese women and men. *Ann Oncol* 2013;24:238–44 [PubMed: 22898034]
47. Holt S, Miller J, Petocz P. An insulin index of foods: the insulin demand generated by 1000-kJ portions of common foods. *The American journal of clinical nutrition* 1997;66:1264–76 [PubMed: 9356547]
48. Nimptsch K, Brand-Miller JC, Franz M, Sampson L, Willett WC, Giovannucci E. Dietary insulin index and insulin load in relation to biomarkers of glycemic control, plasma lipids, and inflammation markers-. *The American journal of clinical nutrition* 2011;94:182–90 [PubMed: 21543531]
49. Tabung FK, Nimptsch K, Giovannucci EL. Postprandial Duration Influences the Association of Insulin-Related Dietary Indexes and Plasma C-peptide Concentrations in Adult Men and Women. *J Nutr* 2019;149:286–94 [PubMed: 30590589]
50. Tabung FK, Wang W, Fung TT, Smith-Warner SA, Keum N, Wu K, et al. Association of dietary insulinemic potential and colorectal cancer risk in men and women. *Am J Clin Nutr* 2018;108:363–70 [PubMed: 29901698]

Figure 1.

Joint association of empirical dietary inflammatory pattern (EDIP) and empirical dietary index for hyperinsulinemia (EDIH)/ empirical dietary index for insulin resistance (EDIR) with risk of hepatocellular carcinoma (HCC). Scores of EDIP, EDIR, and EDIH were dichotomized into low (the first and second tertile categories) versus high (the highest tertile categories), resulting in four mutually exclusive groups (i.e., low-low, low-high, high-low, and high-high). These four groups were evaluated in relation to HCC risk using Cox regression. All models were stratified for age and year of questionnaire return with further adjustment for age (months), sex (women, men), race (white, non-white), physical activity (<3, 3-<27, ≥27 METS-hours/week), smoking status (never, past, current smoking), aspirin use (no, yes), and total energy intake (kcal/day, tertile). **A**, the joint association of EDIP and EDIH with HCC risk; **B**, the joint association of EDIP and EDIR with HCC risk. CI, confidence interval; HR, hazards ratio.

Age-adjusted characteristics of participants according to scores of EDIP, EDIH, EDIR, ELIH, and ELIR in the Nurses' Health Study and the Health Professionals Follow-up Study

	EDIP			EDIH			EDIR			ELIH			ELIR		
	Tertile 1	Tertile 3		Tertile 1	Tertile 3		Tertile 1	Tertile 3		Tertile 1	Tertile 3		Tertile 1	Tertile 3	
Age ^a , years	63.6 (11.0)	64.1 (11.6)		66.1 (11.2)	61.9 (11.3)		64.6 (11.1)	63.5 (11.6)		63.7 (11.7)	64.8 (10.9)		63.7 (11.5)	64.7 (11.3)	
White, %	98.3	95.5		96.9	97.2		97.7	96.7		97.0	97.1		97.1	97.2	
Body mass index, kg/m ²	24.6 (3.5)	26.4 (4.6)		24.4 (3.5)	26.4 (4.6)		24.5 (3.5)	26.4 (4.6)		22.3 (2.0)	29.3 (4.1)		23.0 (2.4)	28.4 (4.7)	
Physical activity, METS-hours/week	23.8 (23.9)	20.1 (22.9)		23.9 (24.4)	20.5 (23.2)		22.3 (23.1)	21.4 (24.0)		27.0 (27.6)	17.1 (18.9)		24.5 (25.9)	19.0 (21.1)	
Type 2 diabetes mellitus, %	2.8	8.2		2.9	8.0		2.5	8.5		1.5	10.5		1.5	10.3	
Regular aspirin use ^b , %	38.2	37.3		36.0	38.5		36.4	38.6		34.8	40.1		34.7	40.3	
Past smoking, %	44.6	34.0		43.4	34.7		44.7	33.8		39.4	38.6		42.0	36.3	
Current smoking, %	11.1	8.5		9.5	9.8		12.6	7.3		10.4	8.4		12.5	6.9	
Alcohol, g/day	12.6 (14.2)	5.0 (9.1)		10.0 (12.5)	7.2 (11.6)		14.4 (15.5)	4.0 (6.3)		8.6 (11.0)	8.1 (13.2)		12.6 (14.5)	4.8 (8.3)	
Total coffee intake, cups/day	2.5 (0.7)	1.7 (0.7)		2.2 (0.8)	1.9 (0.8)		2.3 (0.7)	1.8 (0.8)		2.2 (0.8)	1.9 (0.8)		2.2 (0.8)	1.9 (0.8)	
Total energy, kcal/day	1780 (480)	1912 (522)		1594 (421)	2098 (506)		1667 (459)	2025 (505)		1796 (487)	1852 (515)		1660 (446)	1994 (523)	

Values were means (SD) or percentages and were standardized to the age distribution of the study population.

EDIP, Empirical dietary inflammatory pattern; EDIH, Empirical dietary index for hyperinsulinemia; EDIR, Empirical dietary index for insulin resistance; ELIH, Empirical lifestyle index for insulin resistance; ELIR, Empirical lifestyle index for insulin resistance.

^aValue was not age adjusted.

^bRegular aspirin use was defined as the consumption of aspirin at least 2 times/week.

Table 2.

HRs and 95% CIs for hepatocellular carcinoma by tertiles of EDIP, EDIH and EDIR in the Nurses' Health Study (1984–2012) and the Health Professionals Follow-up Study (1986–2012)

	HR (95% CI)			<i>P</i> _{trend}
	Tertile 1	Tertile 2	Tertile 3	
EDIP				
NHS				
Number of cases	10	25	32	
Model 1 ^a	1 (Reference)	2.27 (1.09–4.74)	3.51 (1.71–7.18)	<0.01
Model 2 ^b	1 (Reference)	2.28 (1.09–4.78)	3.53 (1.71–7.30)	<0.01
HPFS				
Number of cases	21	25	29	
Model 1 ^a	1 (Reference)	1.08 (0.60–1.94)	1.36 (0.77–2.39)	0.28
Model 2 ^b	1 (Reference)	1.10 (0.61–1.98)	1.34 (0.76–2.38)	0.31
Pooled				
Number of cases	31	50	61	
Model 1 ^a	1 (Reference)	1.46 (0.93–2.29)	2.01 (1.30–3.10)	<0.01
Model 2 ^b	1 (Reference)	1.49 (0.95–2.34)	2.03 (1.31–3.16)	<0.01
EDIH				
NHS				
Number of cases	22	20	25	
Model 1 ^a	1 (Reference)	1.11 (0.60–2.04)	1.84 (1.02–3.32)	0.04
Model 2 ^b	1 (Reference)	1.14 (0.61–2.11)	1.97 (1.06–3.66)	0.03
HPFS				
Number of cases	24	22	29	
Model 1 ^a	1 (Reference)	1.00 (0.56–1.79)	1.44 (0.83–2.48)	0.18
Model 2 ^b	1 (Reference)	0.98 (0.55–1.77)	1.35 (0.77–2.36)	0.28
Pooled				
Number of cases	46	42	54	
Model 1 ^a	1 (Reference)	1.02 (0.67–1.55)	1.58 (1.06–2.36)	0.02
Model 2 ^b	1 (Reference)	1.03 (0.67–1.57)	1.61 (1.06–2.43)	0.02
EDIR				
NHS				
Number of cases	21	19	27	
Model 1 ^a	1 (Reference)	0.96 (0.52–1.80)	1.64 (0.92–2.93)	0.09
Model 2 ^b	1 (Reference)	1.00 (0.53–1.88)	1.80 (0.99–3.28)	0.05
HPFS				
Number of cases	22	20	33	

	HR (95% CI)			<i>P</i> _{trend}
	Tertile 1	Tertile 2	Tertile 3	
Model 1 ^a	1 (Reference)	0.89 (0.49–1.64)	1.47 (0.85–2.54)	0.14
Model 2 ^b	1 (Reference)	0.93 (0.50–1.71)	1.45 (0.83–2.53)	0.16
Pooled				
Number of cases	43	39	60	
Model 1 ^a	1 (Reference)	0.92 (0.59–1.41)	1.54 (1.04–2.29)	0.02
Model 2 ^b	1 (Reference)	0.95 (0.61–1.47)	1.62 (1.08–2.42)	0.02

EDIP, Empirical dietary inflammatory pattern; EDIH, Empirical dietary index for hyperinsulinemia; EDIR, Empirical dietary index for insulin resistance; NHS, the Nurses' Health Study; HPFS, the Health Professionals Follow-up Study; CI, confidence interval; HR, hazard ratio.

^aCox model was stratified for age and year of questionnaire return with further adjustment for age (months) and total energy intake (kcal/day, tertile).

^bCox model was stratified for age and year of questionnaire return with further adjustment for age (months), sex (women, men, pooled analysis only), race (white, non-white), physical activity (<3, 3–<27, ≥27 METS-hours/week), smoking status (never, past, current smoking), aspirin use (no, yes), and total energy intake (kcal/day, tertile).

Table 3.

HRs and 95% CIs for hepatocellular carcinoma by tertiles of ELIR and ELIH in the Nurses' Health Study (1984–2012) and the Health Professionals Follow-up Study (1986–2012)

	HR (95% CI)			<i>P</i> _{trend}
	Tertile 1	Tertile 2	Tertile 3	
ELIH				
NHS				
Number of cases	16	18	33	
Model 1 ^a	1 (Reference)	1.07 (0.55–2.11)	1.94 (1.06–3.53)	0.02
Model 2 ^b	1 (Reference)	1.08 (0.55–2.13)	1.98 (1.08–3.61)	0.01
HPFS				
Number of cases	18	22	35	
Model 1 ^a	1 (Reference)	1.19 (0.63–2.22)	1.86 (1.05–3.29)	0.03
Model 2 ^b	1 (Reference)	1.19 (0.64–2.24)	1.86 (1.05–3.30)	0.03
Pooled				
Number of cases	34	40	68	
Model 1 ^a	1 (Reference)	1.13 (0.71–1.79)	1.87 (1.24–2.83)	<0.01
Model 2 ^b	1 (Reference)	1.14 (0.72–1.80)	1.89 (1.25–2.87)	<0.01
ELIR				
NHS				
Number of cases	12	24	31	
Model 1 ^a	1 (Reference)	1.86 (0.93–3.73)	2.62 (1.34–5.12)	<0.01
Model 2 ^b	1 (Reference)	2.00 (0.99–4.02)	2.96 (1.50–5.84)	<0.01
HPFS				
Number of cases	21	18	36	
Model 1 ^a	1 (Reference)	0.80 (0.42–1.51)	1.54 (0.89–2.65)	0.07
Model 2 ^b	1 (Reference)	0.80 (0.42–1.52)	1.52 (0.88–2.65)	0.08
Pooled				
Number of cases	33	42	67	
Model 1 ^a	1 (Reference)	1.19 (0.75–1.88)	1.94 (1.28–2.95)	<0.01
Model 2 ^b	1 (Reference)	1.23 (0.78–1.95)	2.05 (1.34–3.14)	<0.01

ELIR, Empirical lifestyle index for insulin resistance; ELIH, Empirical lifestyle index for hyperinsulinemia; NHS, the Nurses' Health Study; HPFS, the Health Professionals Follow-up Study; CI, confidence interval; HR, hazard ratio

^aCox model was stratified for age and year of questionnaire return with further adjustment for age (months) and total energy intake (kcal/day, tertile).

^bCox model was stratified for age and year of questionnaire return with further adjustment for age (months), sex (women, men, pooled analysis only), race (white, non-white), smoking status (never, past, current smoking), aspirin use (no, yes), and total energy intake (kcal/day, tertile).