HHS Public Access

Author manuscript

J Nutr Intermed Metab. Author manuscript; available in PMC 2020 August 20.

Published in final edited form as:

J Nutr Intermed Metab. 2019 June ; 16: . doi:10.1016/j.jnim.2019.100095.

Adiposity does not modify the effect of the dietary inflammatory potential on type 2 diabetes incidence among a prospective cohort of men

Mark A. Guinter[a,*], **Anwar T. Merchant**[b], **Fred K. Tabung**[d,e], **Michael D. Wirth**[b,c,f], **Nitin Shivappa**[b,c,f], **Thomas G. Hurley**[c], **James R. Hebert**[b,c,f], **Xuemei Sui**[g], **Steven N. Blair**[b,g], **Susan E. Steck**[b,c,h]

[a]Behavioral and Epidemiology Research Group, American Cancer Society, Atlanta, GA, USA

[b]Department of Epidemiology and Biostatistics, University of South Carolina, Columbia, SC, USA

[c]Cancer Prevention and Control Program, University of South Carolina, Columbia, SC, USA

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

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

[f]Connecting Health Innovations LLC, Columbia, SC, USA

[g]Department of Exercise Science, University of South Carolina, Columbia, SC, USA

[h]Center for Research in Nutrition and Health Disparities, Arnold School of Public Health, University of South Carolina, Columbia, SC, USA

Abstract

[*]Corresponding author. 250 Williams St NW, Atlanta, GA, 30307, USA. Mark.guinter@cancer.org (M.A. Guinter).

Authorship statement

- Guinter, Merchant, and Steck conceptualized the research aims of the manuscript.
- Guinter, Merchant, Steck, Shivappa, Wirth, Hurley, and Hebert developed the methodology.
- Hurley, Steck, Hebert, Shivappa, and Wirth contributed to the development of the DII.
- Guinter, Tabung, and Hurley were responsible for the coding used.
- Blair and Sui were responsible for collection and maintenance of the data.
- All authors contributed to the writing of the manuscript.

Human subjects

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/ or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Participants provided written informed consent to participate in the examination and follow-up study. The Cooper Institute Institutional Review Board approved the study protocol annually.

Disclosures

Dr. James R. Hébert owns controlling interest in Connecting Health Innovations LLC (CHI), a company that has licensed the right to his invention of the dietary inflammatory index (DII) from the University of South Carolina in order to develop computer and smart phone applications for patient counseling and dietary intervention in clinical settings. Drs. Nitin Shivappa and Michael Wirth are employees of CHI. The subject matter of this paper will have no direct bearing on the work of CHI, nor has any CHI-related activity exerted any influence on this project. Dr. Blair has received unrestricted research grants in the past five years from The Coca-Cola Company.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jnim.2019.100095.

Purpose—Inflammatory contributions from diet and adiposity may interact with respect to the development of type 2 diabetes mellitus (T2DM). We investigated the degree to which adiposity modified the association between dietary inflammatory potential and incident T2DM.

Methods—Data from 6,016 US men in the Aerobics Center Longitudinal Study who completed a 3-day diet record were used. The inflammatory potential of diet was characterized by the Dietary Inflammatory Index (DII®), and adiposity was assessed with body mass index, waist circumference, body fat percentage (BF) and waist-to-height ratio. Inverse probability weights were used in modified Poisson regression models to examine whether adiposity modifies the relationship between the DII and T2DM, while accounting for selection bias from participants who were lost to follow-up.

Results—There were 336 incident cases of T2DM after a mean follow-up of 6.5 years. DII scores were not significantly associated with T2DM incidence in multivariable models, but point estimates were consistently elevated across increasing DII quartiles compared to the most anti-inflammatory DII quartile. In the model that evaluated BF, the term for overall effect modification was significant ($p = 0.02$), but there was no evidence of effect modification on the multiplicative and additive scales when examined further. Effect modification was not present for any other adiposity measures.

Conclusions—We did not observe evidence that a pro-inflammatory diet, as measured by the DII, is associated with incidence of T2DM, nor evidence that adiposity modifies a potential relationship. Further investigation is needed in larger cohorts with longer follow-up.

Keywords

Adiposity; Obesity; Effect modification; Dietary pattern; Epidemiology; Inflammation

1. Introduction

Chronic, low-grade inflammation is hypothesized to play an important role in the development of cardiometabolic disorders, including type 2 diabetes mellitus (T2DM) [1]. Acute-phase proteins, such as C-reactive protein (CRP), mediate biological processes leading to insulin resistance and T2DM [2]. Positive associations between inflammatory markers and T2DM have been reported in cross-sectional and prospective observational studies [3,4]. In addition, the effects of diet and adiposity on T2DM risk have been postulated to be mediated by inflammation [5].

Dietary factors can influence health through nutrients that exhibit potential anti- or pro-inflammatory properties [6]. Markers of systemic inflammation are associated with many dietary nutrients and components. For example, flavonoids from plant-based foods are inversely associated with inflammation, but long-chain saturated fatty acids exhibit a positive association [7,8]. Studying whole dietary patterns may be advantageous in evaluating the inflammatory effect of diet because such patterns can take into account individual effects of multiple nutrients or foods. The Dietary Inflammatory Index (DII®) was designed to assess the overall inflammatory potential of an individual's diet [9]. Higher, more pro-inflammatory, DII scores have been positively associated with metabolic states that precede diabetes, such as glucose intolerance, compared to more anti-inflammatory DII

scores [10–13]. Higher DII scores have been shown to increase the odds of T2DM [14] and gestational diabetes; [15] however, the relationship with the DII score has not been investigated with T2DM in a prospective study.

There is evidence that associations between diet and health outcomes vary by adiposity; [16,17] however, this relationship has not been studied extensively in relation to T2DM. More research is needed to understand the potential modifying effect of adiposity on the relationship between diet and T2DM [18]. It is possible that inflammation from adiposity or dietary sources may act synergistically, or may mask one another, with respect to the development of T2DM [5]. Understanding how the effects of diet vary across individuals at different adiposity levels will help to identify appropriate prevention strategies for population subgroups. The objective of the present study was to investigate the degree to which adiposity modified the prospective association between the DII and incident T2DM in a longitudinal cohort of adult men. We hypothesized a differential effect of the DII on T2DM risk within strata of adiposity status, using BMI, waist circumference (WC), waist-to-height ratio (WHtR) and body fat percentage (BF) as criteria to define excess adiposity.

2. Materials and methods

The Aerobics Center Longitudinal Study (ACLS) is a prospective cohort study of individuals who received preventive medical examinations at the Cooper Clinic in Dallas, Texas [19]. The present analysis includes 6,016 men aged 20–84 years at baseline who completed a clinical examination in 1987 and 1999 and who had completed 1) a comprehensive medical examination, 2) a medical survey, and 3) a 3-day diet record. Follow-up continued until T2DM onset, death, or the cut-off date of November 2003, whichever came first. All participants in the analytic sample were free of a history of cancer, cardiovascular disease (CVD), or diabetes at baseline. Due to the small number of T2DM cases (n = 62) in the ACLS cohort among women, only men were included in the present analysis. Participants were predominantly (> 95%) non-Hispanic, White, college graduates from professional or executive occupations.

2.1. Dietary inflammatory index (DII®)

Dietary assessment in this subset of ACLS participants was performed using a 3-day diet record, including two weekdays and one weekend day, which were mailed to participants prior to their medical examination. Dietitians provided participants with detailed instructions on recording intakes and portions. Nutrient values were obtained using the Food Intake Analysis System (FIAS) (versions 3.0 and 3.9) of the University of Texas-Houston School of Public Health, Houston, TX, 1996, 2000), based on the US Department of Agriculture Survey Nutrient Database.

Dietary inflammatory potential was assessed using the DII. Derivation and construct validation of the DII has been previously described [9,20]. Briefly, a literature search identified peer-reviewed original research articles investigating the association between dietary factors and six inflammatory biomarkers (IL-1β, IL-4, IL-6, IL-10, TNF-α, and CRP). This search identified 45 specific foods and nutrients that were associated with one or more of these six inflammatory markers. An inflammatory effect score was derived for

each of the 45 dietary components by assigning a score for each research article based on the association between the dietary factor and inflammatory marker. A total of 26 of the 45 components were available from the ACLS dietary database (total energy intake, alcohol, caffeine, cholesterol, fiber, protein, carbohydrates, total fat, monounsaturated fat, saturated fat, iron, magnesium, niacin, riboflavin, thiamin, vitamin A, β-carotene, vitamin B6, vitamin B12, vitamin C, vitamin E, zinc, folic acid, ω−3 fatty acids, ω−6 fatty acids, and selenium). Intake of each of the 26 components was standardized to a global intake amount, representing average intake from 11 populations across the world. The standardized dietary intake Z-score (computed as the difference between the reported amount and the standard amount divided by the standard deviation in the referent database) was then multiplied by the inflammatory effect score for each DII component. These were converted to proportions to lessen the effective right skewing. Each portion was centered on zero by doubling the value and subtracting 1. These scores were then summed to obtain an overall DII score for each subject. In the present analysis, the DII was categorized into quartiles, with the highest quartile indicative of individuals with the most pro-inflammatory dietary potential.

2.2. Measurements

Baseline examinations, including blood sample collection, took place after a 12-h overnight fast. Anthropometric measurements (height, weight, WC, and BF) were collected at the baseline and follow-up examinations by trained staff. Furthermore, BF was assessed using standardized protocols via hydrostatic weighing, skinfold measures, or both methods [21]. Using four different adiposity measures, the cut points for defining the presence of excess adiposity were as follows: 1) BMI ≥ 30 kg/m^2, 2) WC ≥ 108 cm, 3) BF ≥ 25%, or 4) WHtR ≥0.85. A self-administered questionnaire was used to collect information on other risk factors. Smoking status was categorized into current smoker and non-smoker. Drinking status was dichotomized into heavy vs. light drinkers (greater than or equal to 5 drinks per week vs. less than 5 drinks per week). Participants were categorized as inactive if they reported no participation in at least nine of ten aerobic activities in the 3 months prior to baseline.

Investigators of the Cooper Institute diagnosed incident T2DM following American Diabetes Association guidelines. A diagnosis occurred in one of three ways: 1) fasting-plasma glucose ≥7 mmol/l (126 mg/dl) measured at a clinical follow-up evaluation, 2) self-report of current hypoglycemic medication use, or 3) self-report of T2DM diagnosis by their personal physician. An agreement of 92% has been shown between self-reported diabetes and confirmation with medical records in the ACLS [22].

2.3. Statistics

Baseline comparisons of participant characteristics by DII quartiles were performed using t-tests and chi-square tests for continuous and categorical variables, respectively. Confounders included in the analysis were age, smoking status, alcohol use, family history of diabetes, physical inactivity, hypertension, and hypercholesterolemia; all measured at baseline. Inverse probability weighting (IPW) was used to control for confounding and selection bias resulting from loss to follow-up [23]. The IPW was calculated by multiplying the stabilized

exposure weight and stabilized censoring weight. The denominator of the exposure weight was the probability of being exposed given the confounders; the numerator was the probability of being exposed given the adiposity measure and the probability of being exposed for the main effect of DII on T2DM. Similarly, the denominator of the censoring weight was the probability of being censored, given the confounders; the numerator was the probability of being censored given the adiposity measure and the probability of being censored for the main effect. All probabilities were determined in logistic regression models with DII quartiles or censorship status as the dependent variables for the exposure and censor weights, respectively. More information on this method has been described elsewhere [23].

Generalized Poisson regression models with robust variance (also known as sandwich error variance), weighted by IPW, were used to calculate risk ratios (RR) and 95% confidence intervals (CI). Tests for trend were evaluated by assigning participants their quartile's median DII value. In all models, the first quartile of the DII, representing the most anti-inflammatory dietary potential, was the referent. First, the association between the DII and T2DM was evaluated in crude and multivariable-adjusted models, with and without inclusion of BF as a covariate. Since alcohol use and total energy intake are confounders in the relationship between the DII and T2DM, but are also a part of the DII calculation, we excluded these covariates from models in a sensitivity analyses to evaluate the potential bias from over-adjustment. Effect modification by adiposity was assessed in four different models for each of criteria used to define adiposity. To assess effect modification on the multiplicative scale, a multiplicative term between DII quartiles and each of the adiposity criteria was added to the fully adjusted Poisson model. These models evaluated the joint association between DII quartiles and adiposity in relation to T2DM risk, with the lowest risk category as the referent (first DII quartile; non-obese individuals).

As effect modification can be defined as departure from the additivity of absolute effects, the relative excess risk due to interaction (RERI) and corresponding 95% CIs were calculated. To calculate RERI, the RR for non-obese individuals in the fourth DII quartile and the RR for obese individuals in the first DII quartile were subtracted from the RR for obese individuals in the fourth DII quartile, plus one. A RERI < 0 indicates a reduced risk due to interaction and RERI > 0 indicates an increased risk due to interaction. A RERI = 0 suggests there is no change in risk and no effect modification on the additive scale. The delta method was used for calculation of 90% CIs for RERI estimates, as is appropriate with qualitative evidence of interaction [24]. All analyses were performed using SAS® 9.3 software (SAS Institute, Cary, NC).

3. Results

Baseline characteristics are presented in Table 1. During an average 6.5 years of follow-up, there were a total of 332 incident cases of T2DM out of 6,016 men; data from 990 participants were censored. The mean ± standard deviation (SD) DII score was −0.74 ± 1.54 with a range of −4.31 to 3.66. Although there was no significant difference in number of incident T2DM cases across DII quartiles ($p = 0.22$), the highest frequency occurred in the fourth quartile. Individuals in the fourth quartile of DII were younger, more likely to

be current smokers and physically inactive, had a lower caloric intake, had higher mean BMI/WC/BF/WHtR, higher fasting glucose levels, and had slightly shorter follow-up. Study participants lost to follow-up were less likely to have a family history of diabetes ($p = 0.30$) but more likely to have hypertension ($p < 0.01$) compared to participants who were uncensored, and were similar on all other covariates (data not shown).

Results of modified Poisson regression models for the crude (Model 1), multivariable-adjusted (Model 2), and multivariable-plus-adiposity-adjusted (Model 3) relationships for the DII and T2DM are shown in Table 2. A modest increased risk was observed between the DII and T2DM in a crude model (RR_{q4vsq1}: 1.35; 95% CI: 1.00–1.83). After adjustment for potential confounders, except adiposity, effect estimates strengthened slightly across all quartiles (RR_{q4vsq1}:1.39; 95% CI: 0.95–2.02), though confidence intervals included the null. Effect estimates were further attenuated with additional adiposity adjustment (RR_{q4vsq1}:1.29; 95% CI: 0.89–1.88). Removing covariate adjustment for alcohol use and energy intake made no substantial impact on our point estimates (Supplemental Table 1), suggesting no bias was introduced by potential over-adjustment.

The results of a potential effect modification of DII by adiposity on T2DM are presented in Table 3. The overall assessment of effect modification on the multiplicative scale, as indicated by the p-value for the interaction terms of the DII quartiles and adiposity measures, is shown in the right-hand column of Table 3. Significant effect modification was observed only when using BF ($p = 0.02$) to define excess adiposity. Individuals with a BMI < 30 kg/m^2 who were in the lowest quartile of the DII, representative of the most anti-inflammatory dietary potential, comprised the referent group. The largest estimate for the joint association between DII, adiposity, and T2DM was observed among obese individuals in the fourth DII quartile when using BMI (RR: 2.74; 95% CI: 1.65–4.56) and WC (RR: 2.18; 95% CI: 1.32, 3.60) as criteria, but in the second quartile when using BF (RR: 2.28; 95% CI: 1.47, 3.54) and WHtR (RR: 2.76; 95% CI: 1.67–4.57) as criteria.

The stratum-specific associations for the joint relationship between DII and adiposity with T2DM also are shown in the right column of Table 3, yielding no significant associations when comparing the fourth DII quartile with the first quartile within strata of adiposity. Results for the second and third quartiles can be seen in the online Supplemental Table 2.

A summary of effect modification on the multiplicative and additive scales is shown in Table 4 for individual comparisons of DII quartiles. The ratios of adiposity stratum-specific RRs are shown to assess effect modification on the multiplicative scale. None of the estimates reached significance, but results from the models for BMI, WC, and WHtR were all below the null value of 1, with BF greater than 1. Effect modification on the additive scale was assessed using RERI (Table 4), with no statistically significant results. Models using BMI and BF indicated the potential for an increase in absolute risk, whereas models using WC and WHtR indicated the potential for a decrease in absolute risk. A full summary of effect modification results for all DII quartiles can be seen in Supplemental Table 3.

4. Discussion

In this prospective cohort of men, the DII was not statistically significantly associated with T2DM incidence. However, the point estimates ranged from 1.25 to 1.39 for higher DII quartiles (more pro-inflammatory diet) compared to the lowest quartile (more anti-inflammatory diet) after controlling for multiple confounders including BF. The results did not support that there are differences in the association of the DII and T2DM by adiposity. There was some evidence of multiplicative interaction when considering BF as the criteria to define adiposity; however, the estimates for RERI and ratio of RRs made it difficult to provide a meaningful interpretation, especially considering null results when using other definitions of adiposity.

The DII was modestly related to T2DM risk, though results were not statistically significant after adjusting for multiple confounders. After including adiposity in the model (i.e., BF), associations were attenuated. If part of a potential association between DII and T2DM worked indirectly through adiposity, adjusting for adiposity may be inappropriate; for example, by mediator bias. When investigating an association between the DII within strata of adiposity, the lack of evidence of an association persisted. The joint association of DII and BF on T2DM risk suggests that there is no synergistic effect modification by adiposity on the multiplicative scale based on the confidence intervals for the ratio of the RRs comparing extreme DII quartiles across the strata of adiposity. These results suggest that consuming a pro-inflammatory diet does not have a differential relative effect in obese and non-obese individuals. Furthermore, no effect modification was observed on the additive scale, as seen by the confidence intervals for RERI estimates that contain the null value of 0 indicating no difference in excess risk due to potential interaction.

Most point estimates from Supplemental Tables 2 and 3 showed the association between DII and T2DM incidence was lower in the presence of excess adiposity, suggesting adiposity is a stronger predictor of T2DM incidence than diet quality, which is consistent with results shown in Table 3. The magnitude of the association between measures of adiposity and inflammatory biomarkers are consistently larger than those seen between dietary exposures and inflammation [25,26]. Therefore, we expected to see a diluted effect of dietary inflammatory potential in individuals whose systemic inflammation is already heightened because of increased adiposity. This needs to be studied further in a population with sufficient numbers of cases to detect a differential effect.

This is the first study, to our knowledge, to assess the joint association of the inflammatory contributions from diet and adiposity with respect to the risk of developing T2DM. In a previous investigation with the DII and metabolic syndrome, a condition that precedes diabetes, individuals in the highest DII tertile had 2 times the odds of having a fasting glucose ≥100mg/dL compared to the lowest DII tertile (odds ratio (OR): 2.03; 95% CI: 1.08, 3.82) [13]. In an investigation of T2DM among Mexican adults, those in the highest quintile of DII scores had higher odds of T2DM compared to the first quintile (OR: 3.02; 95% CI: 1.39, 6.58) [14].

Similar to our results, the use of dietary patterns derived from factor analysis showed no effect modification by BMI in relation to T2DM [27]. However, other studies reported animal protein intake interacting with BMI to increase risk of developing T2DM among women ($p < 0.001$), [28] and total protein intake interacting with BMI and waist circumference to affect T2DM risk ($p < 0.05$), supporting effect modification by adiposity in relation to T2DM [29].

There are limitations in the study that should be noted. The small sample size and inadequate numbers of cases in certain cells was a limitation that leads to insufficient statistical power to detect effect modification. The study participants were willing to participate in a cardiorespiratory fitness study and they were primarily healthy, motivated individuals. Perhaps this explains why there were relatively few obese participants. Similarly, the population was primarily comprised of White, well-educated men, limiting the generalizability of results beyond those demographics. Although diet records may be associated with less measurement error (though more prone to dietary awareness bias) than other dietary assessment methods, [30] three days may not represent usual diet in all individuals. Furthermore, the ACLS dietary database included information on only 26 of the 45 DII scoring components. However, in the original construct validation study, the DII computed based on only 28 components was essentially the same as 24-h recall-derived DII scores that included 44 parameters [20]. Both were significantly associated with concentrations of CRP in a longitudinal study with up to five measurements per individual [20]. Also, T2DM cases were ascertained, in part, by self-report. However, a 92% agreement between self-reported events and medical records review has been shown in ACLS [22].

There are several strengths in the present analysis including the prospective nature and use of multiple measures to define excess adiposity. The comprehensive evaluation of effect modification on the multiplicative and additive scales provides useful benchmarks on which future research can build. Our measure of dietary inflammatory potential, the DII, has been construct validated, showing a positive association with multiple inflammatory markers, such as CRP, IL-6, and TNF-α [20,31–37]. The use of IPW corrected for potential selection bias caused by censoring and improved model efficiency because of fewer parameters.

5. Conclusion

A more pro-inflammatory diet was only modestly associated with T2DM incidence. The use of BF as a measure of adiposity is recommended in examining the role of adiposity in modifying the effect of diet on T2DM. Larger studies in more racially diverse populations are needed to confirm this finding.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Funding

This publication was made possible in part by Grant Number T32-GM081740 from National Institute of General Medical Sciences. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Institute of General Medical Sciences or National Institutes of Health. Drs. Wirth, Shivappa and Hébert were supported by grant number R44DK103377 from the United States National Institute of Diabetes and Digestive and Kidney Diseases. Dr. Tabung was supported by National Cancer Institute grant #K99CA207736. The ACLS was supported by National Institutes of Health grants AG06945, HL62508, and DK088195.

Abbreviations

ACLS	Aerobics Center Longitudinal Study
BF	Body fat percentage
BMI	Body mass index
CI	Confidence interval
CRP	C-reactive protein
CVD	Cardiovascular disease
DII®	Dietary Inflammatory Index
FIAS	Food Intake Analysis System
IPW	Inverse probability weighting
OR	Odds ratio
RERI	Relative excess due to interaction
RR	Relative risk
SD	Standard deviation
T2DM	Type 2 diabetes mellitus
TNF-α	Tumor necrosis factor alpha
USDA	U.S. Department of Agriculture
WC	Waist circumference
WHtR	Waist-to-height ratio

References

[1]. Esser N, Legrand-Poels S, Piette J, et al. , Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes, Diabetes Res. Clin. Pract 105 (2014) 141–150. [PubMed: 24798950]

[2]. Donath MY, Shoelson SE, Type 2 diabetes as an inflammatory disease, Nat. Rev. Immunol 11 (2011) 98–107. [PubMed: 21233852]

[3]. Esser N, Paquot N, Scheen AJ, Inflammatory markers and cardiometabolic diseases, Acta Clin. Belg 70 (2015) 193–199. [PubMed: 26103538]

[4]. Lontchi-Yimagou E, Sobngwi E, Matsha TE, et al. , Diabetes mellitus and inflammation, Curr. Diabetes Rep 13 (2013) 435–444.

[5]. Gregor MF, Hotamisligil GS, Inflammatory mechanisms in obesity, Annu. Rev. Immunol 29 (2011) 415–445. [PubMed: 21219177]

[6]. Minihane AM, Vinoy S, Russell WR, et al. , Low-grade inflammation, diet composition and health: current research evidence and its translation, Br. J. Nutr 114 (2015) 999–1012. [PubMed: 26228057]

[7]. Calder PC, Long chain fatty acids and gene expression in inflammation and immunity, Curr. Opin. Clin. Nutr. Metab. Care 16 (2013) 425–433. [PubMed: 23657154]

[8]. Chun OK, Chung SJ, Claycombe KJ, et al. , Serum C-reactive protein concentrations are inversely associated with dietary flavonoid intake in U.S. adults, J. Nutr 138 (2008) 753–760. [PubMed: 18356331]

[9]. Shivappa N, Steck SE, Hurley TG, et al. , Designing and developing a literature-derived, population-based dietary inflammatory index, Publ. Health Nutr 17 (2014) 1689–1696.

[10]. Moslehi N, Ehsani B, Mirmiran P, et al. , Inflammatory properties of diet and glucose-insulin homeostasis in a cohort of Iranian adults, Nutrients 8 (2016).

[11]. Neufcourt L, Assmann KE, Fezeu LK, et al. , Prospective association between the dietary inflammatory index and metabolic syndrome: findings from the SU.VI.MAX study, Nutr. Metabol. Cardiovasc. Dis 25 (2015) 988–996.

[12]. Vahid F, Shivappa N, Karamati M, et al. , Association between Dietary Inflammatory Index (DII) and risk of prediabetes: a case-control study, Appl. Physiol. Nutr. Metabol 42 (2017) 399–404.

[13]. Wirth MD, Burch J, Shivappa N, et al. , Association of a dietary inflammatory index with inflammatory indices and metabolic syndrome among police officers, J. Occup. Environ. Med 56 (2014) 986–989. [PubMed: 25046320]

[14]. Denova-Gutierrez E, Munoz-Aguirre P, Shivappa N, et al. , Dietary inflammatory index and type 2 diabetes mellitus in adults: the diabetes mellitus survey of Mexico city, Nutrients 10 (2018).

[15]. Shivappa N, Hebert JR, Akhoundan M, et al. , Association between inflammatory potential of diet and odds of gestational diabetes mellitus among Iranian women, J. Matern. Fetal Neonatal Med 1–201 (2018).

[16]. Park YM, Steck SE, Fung TT, et al. , Mediterranean diet and mortality risk in metabolically healthy obese and metabolically unhealthy obese phenotypes, Int. J. Obes 40 (2016) 1541–1549.

[17]. Yang HK, Han K, Kwon HS, et al. , Obesity, metabolic health, and mortality in adults: a nationwide population-based study in Korea, Sci. Rep 6 (2016) 30329. [PubMed: 27445194]

[18]. Camhi SM, Whitney Evans E, Hayman LL, et al. , Healthy eating index and metabolically healthy obesity in U.S. adolescents and adults, Prev. Med 77 (2015) 23–27. [PubMed: 25937589]

[19]. Blair SN, Kohl HW 3rd, Paffenbarger RS Jr.et al. , Physical fitness and all-cause mortality. A prospective study of healthy men and women, Jama 262 (1989) 2395–2401. [PubMed: 2795824]

[20]. Shivappa N, Steck SE, Hurley TG, et al. , A population-based dietary inflammatory index predicts levels of C-reactive protein in the Seasonal Variation of Blood Cholesterol Study (SEASONS), Publ. Health Nutr 17 (2014) 1825–1833.

[21]. Lee CD, Blair SN, Jackson AS, Cardiorespiratory fitness, body composition, and all-cause and cardiovascular disease mortality in men, Am. J. Clin. Nutr 69 (1999) 373–380. [PubMed: 10075319]

[22]. Sui X, Hooker SP, Lee IM, et al. , A prospective study of cardiorespiratory fitness and risk of type 2 diabetes in women, Diabetes Care 31 (2008) 550–555. [PubMed: 18070999]

[23]. Hernan M, J.M. R, Casual Inference, Chapman & Hall/CRC, Boca Raton, 2016.

[24]. Knol MJ, VanderWeele TJ, Recommendations for presenting analyses of effect modification and interaction, Int. J. Epidemiol 41 (2012) 514–520. [PubMed: 22253321]

[25]. Barbaresko J, Koch M, Schulze MB, et al. , Dietary pattern analysis and biomarkers of low-grade inflammation: a systematic literature review, Nutr. Rev 71 (2013) 511–527. [PubMed: 23865797]

[26]. Cox AJ, West NP, Cripps AW, Obesity, inflammation, and the gut microbiota, Lancet Diabetes Endocrinol. 3 (2015) 207–215. [PubMed: 25066177]

[27]. Bauer F, Beulens JW, van der AD, et al. , Dietary patterns and the risk of type 2 diabetes in overweight and obese individuals, Eur. J. Nutr 52 (2013) 1127–1134. [PubMed: 22972436]

[28]. van Nielen M, Feskens EJ, Mensink M, et al. , Dietary protein intake and incidence of type 2 diabetes in Europe: the EPIC-InterAct Case-Cohort Study, Diabetes Care 37 (2014) 1854–1862. [PubMed: 24722499]

[29]. Sluijs I, Beulens JW, van der AD, et al. , Dietary intake of total, animal, and vegetable protein and risk of type 2 diabetes in the European Prospective Investigation into Cancer and Nutrition (EPIC)-NL study, Diabetes Care 33 (2010) 43–48. [PubMed: 19825820]

[30]. Bingham SA, Gill C, Welch A, et al. , Validation of dietary assessment methods in the UK arm of EPIC using weighed records, and 24-hour urinary nitrogen and potassium and serum vitamin C and carotenoids as biomarkers, Int. J. Epidemiol 26 (Suppl 1) (1997) S137–S151. [PubMed: 9126542]

[31]. Boden S, Wennberg M, Van Guelpen B, et al. , Dietary inflammatory index and risk of first myocardial infarction; a prospective population-based study, Nutr. J 16 (2017) 21. [PubMed: 28376792]

[32]. Shivappa N, Hebert JR, Marcos A, et al. , Association between dietary inflammatory index and inflammatory markers in the HELENA study, Mol. Nutr. Food Res 61 (2017).

[33]. Shivappa N, Hebert JR, Rietzschel ER, et al. , Associations between dietary inflammatory index and inflammatory markers in the Asklepios Study, Br. J. Nutr 113 (2015) 665–671. [PubMed: 25639781]

[34]. Shivappa N, Wirth MD, Hurley TG, et al. , Association between the dietary inflammatory index (DII) and telomere length and C-reactive protein from the National Health and Nutrition Examination Survey-1999–2002, Mol. Nutr. Food Res 61 (2017).

[35]. Tabung FK, Steck SE, Zhang J, et al. , Construct validation of the dietary inflammatory index among postmenopausal women, Ann. Epidemiol 25 (2015) 398–405. [PubMed: 25900255]

[36]. Vahid F, Shivappa N, Hekmatdoost A, et al. , Association between Maternal Dietary Inflammatory Index (DII) and abortion in Iranian women and validation of DII with serum concentration of inflammatory factors: case-control study, Appl. Physiol. Nutr. Metabol 42 (2017) 511–516.

[37]. Wirth MD, Shivappa N, Davis L, et al. , Construct validation of the dietary inflammatory index among African Americans, J. Nutr. Health Aging 21 (2017) 487–491. [PubMed: 28448077]

HIGHLIGHTS

- Diet and adiposity both contribute to chronic, systemic inflammation.
- Adiposity has been shown to modify the effect of some dietary factors.
- Diet, adiposity, and inflammation play a role in type 2 diabetes development.
- Adiposity did not modify the inflammatory effect of diet on diabetes in our study.

Table 1

Baseline descriptive statistics stratified by DII score quartiles.

		DII Quartiles[a]				*p* value[b]
		1st	2nd	3rd	4th	
N		1503	1501	1502	1503	
Type 2 diabetes		67 (5.4)	87 (6.9)	85 (6.8)	92 (7.3)	0.22
DII score		−2.60 ± 0.49	−1.41 ± 0.29	− 0.31 ± 0.36	1.36 ± 0.70	< 0.01
Age		51.0 ± 10.4	48.6 ± 10.2	47.6 ± 9.4	45.9 ± 9.1	< 0.01
BMI (kg/m^2)		25.1 ± 3.1	26.1 ± 3.3	26.4 ± 3.5	26.7 ± 3.5	< 0.01
	≥30	102 (6.8)	162 (10.8)	203 (13.5)	230 (15.3)	< 0.01
WC (cm)		90.3 ± 9.4	93.2 ± 10.1	94.4 ± 9.9	94.6 ± 10.4	< 0.01
	≥102	167 (11.5)	250 (17.3)	311 (21.5)	319 (21.8)	< 0.01
WHtR		0.51 ± 0.05	0.52 ± 0.06	0.53 ± 0.05	0.53 ± 0.6	< 0.01
	≥0.58	117 (8.1)	189 (13.1)	216 (14.9)	244 (16.7)	< 0.01
BF%		19.6 ± 6.0	21.2 ± 6.0	21.8 ± 6.0	22.6 ± 5.8	< 0.01
	≥25	254 (17.1)	374 (25.2)	428 (28.8)	503 (33.8)	< 0.01
Total energy intake (kcal/day)		2431 ± 598	2440 ± 663	2233 ± 590	1884 ± 532	< 0.01
Fasting glucose (mg/dL)		97.7 ± 8.3	98.2 ± 8.4	98.7 ± 8.6	99.0 ± 8.6	< 0.01
Current smokers		106 (7.1)	116 (7.7)	181 (12.1)	250 (16.6)	< 0.01
Heavy drinkers		174 (11.6)	147 (9.8)	164 (10.9)	142 (9.5)	0.20
Family history of diabetes		149 (9.9)	177 (11.8)	184 (12.3)	150 (10.0)	0.08
Physically inactive		155 (10.3)	284 (18.9)	372 (24.8)	501 (33.3)	< 0.01
Hypertension		403 (26.8)	439 (29.3)	469 (31.2)	437 (29.1)	0.07
Hypercholesterolemia		441 (29.3)	451 (30.1)	470 (31.3)	466 (31.0)	0.64
Average follow-up (years)		6.9 ± 4.8	6.6 ± 4.5	6.5 ± 4.5	6.1 ± 4.4	< 0.01

[a]Categorical variables are reported as counts with column percentage; continuous variables are reported as means with standard error.

[b]*P* values for categorical variables were based on chi-square/ANOVA tests and continuous measures were based on *t* tests.

Table 2

RRs and 95% CIs for the relationship between the DII and type 2 diabetes mellitus.[a].

	Type 2 diabetes cases (n)	Model 1[b]	Model 2[c]	Model 3[d]
DII (quartile)				
1st	67	1.00 (ref)	1.00 (ref)	1.00 (ref)
2nd	87	1.26 (0.92, 1.71)	1.30 (0.91, 1.87)	1.28 (0.90, 1.82)
3rd	85	1.24 (0.91, 1.69)	1.30 (0.90, 1.86)	1.25 (0.87, 1.78)
4th	92	1.35 (1.00, 1.83)	1.39 (0.95, 2.02)	1.29 (0.89, 1.88)
p_{trend}		0.23	0.13	0.45

[a] All models account for censoring through IPW.

[b] Crude model with no adjustment for confounders.

[c] Adjustment for age, energy intake, smoking status, alcohol use, family history of diabetes, physical inactivity, hypertension, and hypercholesterolemia.

[d] Same covariates as Model 2, with additional adjustment for BF.

Table 3

Relationship between DII, different measures of adiposity. and type 2 diabetes mellitus (T2DM)[a].

	DII Quartiles								RRs (95%CI) for DII within strata of obesity measure	$p_{interaction}$
	1st		2nd		3rd		4th			
	N_{cases}/ $N_{controls}$	RR (95% CI)	N_{cases}/ $N_{controls}$	RR (95% CI)	N_{cases}/ $N_{controls}$	RR (95% CI)	N_{cases}/ $N_{controls}$	RR (95% CI)	4th vs 1st DII Quartiles	
BMI (kg/m^2)										0.83
< 30	60/1096	1.00 (ref)	71/1057	1.37 (0.96, 1.97)	69/1020	1.39 (0.97, 2.00)	68/1012	1.37 (0.92, 2.03)	1.37 (0.92, 2.03)	
≥30	7/76	2.26 (0.93, 5.47)	16/124	2.57 (1.49, 4.42)	16/151	2.10 (1.21, 3.61)	24/154	2.74 (1.65, 4.56)	1.21 (0.47, 3.10)	
WC (cm)										0.79
< 102	54/1004	1.00 (ref)	65/946	1.42 (0.97, 2.07)	59/903	1.37 (0.93, 2.01)	61/909	1.37 (0.90, 2.07)	1.37 (0.90, 2.07)	
≥102	12/126	2.03 (0.98, 4.20)	18/194	1.90 (1.11, 3.25)	21/232	1.80 (1.09, 2.99)	26/231	2.18 (1.32, 3.60)	1.07 (0.49, 2.34)	
BF (%)										0.02
< 25	53/963	1.00 (ref)	51/888	1.13 (0.76, 1.69)	63/828	1.51 (1.03, 2.21)	50/788	1.21 (0.79, 1.85)	1.21 (0.79, 1.85)	
≥25	14/199	1.23 (0.61, 2.45)	34/282	2.28 (1.47, 3.54)	19/332	1.12 (0.66, 1.90)	38/372	1.91 (1.18, 3.11)	1.56 (0.75, 3.24)	
WHtR										0.17
< 0.58	58/1044	1.00 (ref)	63/1003	1.27 (0.87, 1.85)	65/979	1.35 (0.93, 1.96)	64/971	1.31 (0.87, 1.97)	1.31 (0.87, 1.97)	
≥0.58	8/86	2.31 (1.00, 5.31)	20/137	2.76 (1.67, 4.57)	15/156	1.88 (1.07, 3.31)	23/169	2.52 (1.51, 4.23)	1.09 (0.45, 2.66)	

[a]Includes IPW to account for the probability of being censored and for covariate adjustment of age, energy intake, smoking status, alcohol use, family history of diabetes, physical inactivity, hypertension, and hypercholesterolemia.

Table 4

Summary of effect modification on additive and multiplicative scales.

	Multiplicative[a]		Additive[b]	
	Ratio of RRs (95% CI)	**p value**	**RERI (90% CI)**	**p value**
BMI	0.89 (0.32, 2.46)	0.82	0.12 (−2.31, 2.54)	0.94
WC	0.79 (0.33, 1.90)	0.60	− 0.21 (−1.82, 1.40)	0.83
BF	1.29 (0.56, 3.02)	0.55	0.48 (−0.90, 1.87)	0.57
WhtR	0.84 (0.31, 2.22)	0.72	− 0.09 (−2.17, 1.98)	0.94

[a] $\text{Ratio of RRs}_{\text{4th DII vs 1st DII}}$ across strata of obesity.

[b] $\text{RERI} = \text{RR}_{\text{obese, 4th DII}} - \text{RR}_{\text{obese, 1st DII}} - \text{RR}_{\text{non-obese, 4th DII}} + 1$.