Perspective: The Dietary Inflammatory Index (DII)—Lessons Learned, Improvements Made, and Future Directions

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ABSTRACT

The literature on the role of inflammation in health has grown exponentially over the past several decades. Paralleling this growth has been an equally intense focus on the role of diet in modulating inflammation, with a doubling in the size of the literature approximately every 4 y. The Dietary Inflammatory Index (DII) was developed to provide a quantitative means for assessing the role of diet in relation to health outcomes ranging from blood concentrations of inflammatory cytokines to chronic diseases. Based on literature from a variety of different study designs ranging from cell culture to observational and experimental studies in humans, the DII was designed to be universally applicable across all human studies with adequate dietary assessment. Over the past 4 y, the DII has been used in >200 studies and forms the basis for 12 meta-analyses. In the process of conducting this work, lessons were learned with regard to methodologic issues related to total energy and nutrient intake and energy and nutrient densities. Accordingly, refinements to the original algorithm have been made. In this article we discuss these improvements and observations that we made with regard to misuse and misinterpretation of the DII and provide suggestions for future developments. *Adv Nutr* 2019;10:185–195.

Introduction

Until the Dietary Inflammatory Index (DII) was created, virtually all dietary indexes used in epidemiologic research, except for the glycemic index (1, 2), had fallen into 1 of 3 categories: *1*) those based on dietary recommendations such

as the Healthy Eating Index–2010 or the Alternative Healthy Eating Index, both based on the US Dietary Guidelines (3–5) or the Dietary Approaches to Stop Hypertension (DASH) (6), which was promoted by the National Heart, Lung, and Blood Institute; *2*) those related to adherence to a particular foodway or cuisine such as the Mediterranean Dietary Index (7–9); or *3*) those derived from a particular study using some kind of regression technique such as principal components analysis or reduced rank regression (10–12). All of these approaches are appealing because of the relative ease with which an index can be created. Each, however, suffers from idiosyncrasies of the approach that include, as a common shortcoming, a narrow range of exposure variability [a common problem in nutritional epidemiology (13)]. Other, method-specific problems also arise. For example, dietary guidelines are not always based on the strongest empirical evidence and they are subject to debate, controversy, and periodic change (14–16). Although a Mediterranean dietary prescription may be healthful, there are 21 countries with Mediterranean coastlines and many cuisines are represented across these countries. In addition,

there are many healthy diets from around the world that are not at all Mediterranean [e.g., South Asian (17, 18) or East Asian (19, 20)]. Finally, because specific study- and population-derived indexes are often used in the same or a similar population (21), misleadingly high measures of association could result as a consequence of intra-method correlated errors, as we and others have reported previously (22, 23). This could, in turn, result in (incorrectly) ascribing a misleadingly large portion of the variance to the index score. By contrast, the DII was designed to reflect all evidence from a wide variety of human populations using different study designs and dietary assessment methods. In addition to the human studies, the DII also includes evidence from qualifying laboratory animal and cell culture experiments, albeit with lower weighting (24).

Background and History of Developing the DII

Rapid increases in our understanding of the role of inflammation in health (25, 26) and diet in inflammation (27, 28) led to the development of the DII, which began in 2004. The first version of the DII debuted in 2009 (29). That version was based on scoring 927 peer-reviewed articles published in the biomedical literature through 2007 linking any aspect of diet to ≥ 1 of 6 inflammatory biomarkers: IL-1β, IL-4, IL-6, IL-10, TNF-α, and C-reactive protein (CRP). Unlike the list of inflammatory biomarkers, dietary factors were not specified or constrained in advance. Although it was the first attempt to create a dietary index on the basis of empirical evidence linking diet to inflammation, an important factor in the development and progression of many chronic diseases (30–35), it did not gain traction in the biomedical community. In fact, no research study was subsequently published based on this older version of the DII by its original developers.

Although the original DII represented the successful development of a literature-derived index that could be universally applied across a wide variety of human studies, the second, improved, version (24) reflects a number of enhancements over the original. Developing the new, revised DII was based on our recognizing the limitations of the original DII, as follows:

- The arbitrariness of using raw consumption amounts that led to inherent distortion, if not outright biases, in the original scoring algorithm. Intakes of certain nutrients, such as vitamin A and β-carotene, had to be divided by 100 and others, such as ω-3 and ω-6 FAs, were multiplied by 10 in order to place them in a "reasonable" range so as not to over- or underestimate their influence on the overall score.
- As a sequela to the former, it became clear in analyses of available data that right skewing of many of the dietary parameters posed a potential problem.
- The perceived need to boost confidence in the DII by relying on the ever-expanding evidence base linking inflammation and diet.

- Flavonoids, as important modulators of systemic inflammation, should be included in the DII scoring algorithm.
- That the scoring system should to be reversed, with more anti-inflammatory scores being negative and more proinflammatory scores being positive.

Methodologic Improvements Made in the New DII

Based on work conducted subsequent to developing the first version of DII, various enhancements were made in the DII

To obviate reliance on reported raw amounts of food consumed, we decided to link reported dietary intake of the 45 parameters that comprise the DII to global norms of intake. This entailed identifying 11 data sets from around the world: Australia (National Nutrition Survey), Bahrain (National Nutrition Survey for Adult Bahrainis), Denmark (Danish National Survey of Diet and Physical Activity), India (Indian Health Study), Japan (National Nutrition Survey Report), Mexico (Mexican National Health and Nutrition Survey), New Zealand (National Nutrition Survey), South Korea (Korean NHANES), Taiwan (Nutrition and Health Survey in Taiwan), the United Kingdom (National Diet and Nutrition Survey), and the United States (NHANES). These formed the basis of a composite data set that contains means and SDs for the intakes of each of the 45 food parameters. These data are then used for comparative purposes (i.e., to compute a z score for each individual's intake of a specific food parameter relative to these global norms). To reduce the effect of right skewing, these values are then expressed as cumulative proportions (with values ranging from 0 to 1). Centering the data around zero (with approximately equal numbers of negative and positive individual scores) is achieved by multiplying each of these cumulative proportions by 2 and then subtracting 1. These steps made it possible to avoid the arbitrariness resulting from simply using raw consumption amounts (with arithmetic manipulations needed to regulate influence), as had been done previously (29). In addition to obviating the arbitrariness evident in the older method, this new scoring method also addressed the "right skewing" commonly seen in the distribution of dietary intake data (36).

We also reviewed and scored an additional 3 y of peer-reviewed publications. The original DII was based on all of the peer-reviewed published literature through 2007. The new DII reflects the accumulation of 3 additional years of evidence (i.e., through 2010). In just 3 y, the total literature size had slightly more than doubled, to 1943 qualifying articles. Although this resulted in more robust estimation, there were no major surprises. That is, nothing that was shown to be anti-inflammatory as of 2007 was found to be proinflammatory or null as of 2010 and nothing that was shown to be proinflammatory as of 2007 was found to be anti-inflammatory or null as of 2010. So, the consistency in the literature, with the evidence base more than doubling in size, was encouraging.

Recognizing the importance of flavonoids in controlling inflammation (37, 38), we added 16 different flavonoids that were grouped into 6 categories (anthocyanidins, flavan-3-ols, flavonols, flavonones, isoflavones, and flavones) and added to the list of food parameters. Finally, the DII scoring algorithm was inverted such that more anti-inflammatory scores are negative and more proinflammatory scores are positive.

Unlike the original DII, the new, revised version has quickly gained favor as a research tool for the study of diet-associated inflammation and health-related outcomes. This has resulted in >160 peer-reviewed articles in 4 y from the time of the official publication of the methods (24). To date, there also have been 12 DII-based meta-analyses published (32, 39–49). Because the computation of DII scores can become quite nuanced and complicated, our group at the University of South Carolina has been involved in the vast majority of these publications. This body of work has given us some important insights into a variety of methodologic and substantive issues that should help guide the DII as it continues to increase in popularity.

Additional insights based on collaborative work

By using the DII over the past several years, we have learned a lot about differences in dietary consumption, as they relate to inflammation, across a wide variety of populations (50–59). These studies have involved individuals of both sexes (54, 56, 60–63), varying ages (50, 64–70), different body sizes (66, 67, 71–76), and different levels of physical activity/sedentariness (71, 74, 75, 77–79). They have been conducted in >30 countries representing a wide variety of cultures from different parts of the world. Many of these studies have focused on cancers of various anatomic sites (55, 56, 59, 78, 80, 81), as well as conditions ranging from cardiovascular diseases (57, 61, 64, 82–85), depression and other mental health outcomes (58, 60, 86–90), to maternal and child health (66–70, 91) and aging (50, 92–97). Of course, the primary means through which we have learned about interpopulation differences derives from computing DII [or energy-adjusted DII (E-DII)] scores, conducting statistical analyses using these scores as covariates in analyses, and interpreting results. Although we anticipated that this would be complex, we have learned that the major complication is due to relations that we observed between energy and nutrient intakes and densities that differ greatly across populations (56, 90, 94). Underlying our observations across all of the many studies we have conducted to date using the DII are 2 countervailing effects. The first is a tendency to eat more of everything as one increases energy intake; this results in a positive correlation between energy intake and nutrient intake, as we and others have observed previously (22, 98–102). The other is what we would call the "healthy eater" effect (e.g., due to the intention of careful, health-conscious people to choose nutrient-dense, energy-sparse foods, in preference to energy-dense, nutrient-sparse foods) (103–107). Of course, its opposite (and, in some respects, corollary) is the "unhealthy eater" effect (i.e., showing a preference for energy-dense, nutrient-sparse foods), which

is becoming a more common pattern worldwide (108, 109). Both of these types of eaters produce data that result in negative correlations between energy density and nutrient density (104, 105, 107).

The relations between energy and nutrient consumption (and density) vary across age and are complicated by the fact that although children may have higher energy intakes than do larger adults, they often consume more energy relative to their total body mass. Growing children and others who are physically very active need to consume diets containing high amounts of total energy in order to ensure proper growth or energy balance (70, 110). So, they also often tend to eat energy-dense, nutrient-sparse foods. Because energy is a component of the DII (24), this is an important complication that has been addressed.

Improvements made subsequent to developing the new DII

The understanding that overall consumption of dietary energy matters with respect to determining overall inflammatory potential of the diet, and was strongly associated with DII scores in some populations, motivated us to create an E-DII. This has required that we construct a referent database of energy-adjusted nutrient scores on the basis of data from the same 11 countries used to compute the DII. Computing E-DII scores requires using this energy-adjusted data set. We have now used the E-DII in 16 publications (53, 56, 66, 87, 111–122) in which its use improved prediction in comparison to unadjusted DII scores.

This realization also led to developing a children's DII (C-DII), with funding by the USDA. The C-DII represents a major methodologic improvement in accounting for macronutrient and micronutrients that affect inflammation and in using, for comparison, a composite database consisting of 16 data sets on children's dietary intake from around the world (123).

Flaws Noted in Dietary Indexes to Quantify Inflammation

Over the past couple of years, we have seen misapplication of the DII or misunderstanding of how it works and what the scores mean. Part of the purpose of this commentary is to help individuals and research groups avoid additional errors based on faulty comprehension of how the DII is constructed and how it works.

Use of the older, now defunct version of the DII

Aside from the first methods/validation publication, we have never published a study based on the older method. However, there are a couple of instances in which researchers have used this outdated DII. A Dutch research group computed inflammatory effect ("Adapted-DII") scores based on the older DII (124). Soon after we learned of this, we published a letter to the editor in the same journal clearly delineating the superiority of the newer DII, warning of the pitfalls of using the older version of the DII, and offering technical assistance in using the new DII (125). A second instance

involved the use of the older version of the DII, without any apparent modification, by a group in Poland (126). The scores computed in both of these studies do not reflect improvements that were made in creating the new, 2014 version of the DII (as noted above). The first of these studies was published in 2013, before the authors could have known about the improvements made in creating the new DII. We wrote a letter to the editor of the *American Journal of Clinical Nutrition* pointing out the methodologic improvements entailed in the new DII compared with the older version (125). Despite this, the authors persisted in using their adaptation of the old, now defunct version of the DII in a recent study examining the association between the inflammatory potential of the diet and risk of colorectal cancer in individuals with Lynch syndrome (127). Furthermore, all of the corroborative evidence cited is based on references to the new DII, not the one on which their Adapted-DII was based (56, 128–133). When they were touting the advantage of the Adapted-DII in their own study (127), evidently they were comparing results to the old, now defunct version DII. They also arbitrarily omitted 3 of the proinflammatory parameters and 14 others that were not estimable from their FFQ. Results from these other studies produce scores that are not comparable to the large and growing body of research using DII scores based on the new, revised scoring algorithm.

Instances in which the new DII formulation has been used but results are suspect

To the best of our knowledge, there have been 5 attempts to use the new DII, which have produced suspect results (**Table 1**). In evaluating the association between the DII and serum CRP and protein energy wasting in hemodialysis patients, a group from Turkey created the DII score by simply summing all food parameter–specific inflammatory effect scores (134).

In calculating the DII score from 23 food parameters, a group from Spain found that their DII ranged from −6.7 to +7.8 in a representative sample of Spanish youth (135). The values are suspect because the range is close to the theoretical maximum range for all 45 parameters; for DII scores derived from 25–30 food parameters, scores usually range from −5.5 to +5.5.

In the ATTICA study, Georgousopoulou et al. (136) calculated a modified version of the DII and called it the Dietary Anti-Inflammation Index. In the Dietary Anti-Inflammation Index the *z* scores are not converted to centered percentiles but instead are multiplied directly by inflammatory effect scores. The scores ranged from 10 to 77 and therefore cannot be compared to DII scores from other studies.

In a report from the Spanish cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC) study, the authors modified the DII, calling it the Inflammatory Score of Diet (137). The difference here is that instead of standardizing the intake values to means and SDs from the global database, the authors have standardized the intake

values to means and SDs of the study population, thus limiting interpretation and comparability with other studies.

Finally, a group from Iran calculated DII scores to examine the relation between dietary inflammatory potential and cardiovascular disease risk factors in a cross-sectional analysis (138). The description of how they calculated the DII scores is correct. However, the range of DII scores presented (i.e., from the lower bound of the first quartile, −29.83 to +10.62) is outside of the theoretical bounds of −8.87 to +7.98. Furthermore, our previous work with Iranian data shows that the DII range is generally much narrower (i.e., from −2.2 to +3.2) in a case-control study of cataract (139), −2.3 to +3.9 in a case-control study of esophageal cancer (140), and −2.7 to +2.7 in a case-control study of ulcerative colitis (141). Other details of these studies are described in Table 1.

Using alternative indexes derived from a particular study with the use of statistical methods

We have observed that it is more common to see individuals and groups develop new indexes on the basis of analyses of existing data sets (11, 142–144). Given the relative ease with which such analyses can be undertaken, and the fact that there is a long tradition of developing indexes in this way, this should not be too surprising. However, as noted, these results reflect the idiosyncrasies of the particular populations from which these data sets derive.

A group at Harvard set out to create an empirical dietary inflammatory index (12), whose name was later changed to the Empirical Dietary Inflammatory Pattern score (145). Reduced rank regression was used to create a dietary pattern most predictive of 3 plasma inflammatory markers: IL-6, CRP, and TNF-α receptor 2 using data from Nurses' Health Study (NHS). They validated this dietary pattern with inflammatory markers in the NHS-II and Health Professionals Follow-Up Study. This approach relies on the nature of the dietary patterns within one cohort to predict outcomes in 2 other cohorts that share similar demographic characteristics (i.e., well-educated health professionals within the United States) and uses an identical dietary assessment method. This presents problems with respect to comparability to other populations, the matter of correlated error structures, and limitations with respect to homogeneity in dietary exposures. For example, the food groups that were used for the reduced rank regression in the NHS included items like processed meat, organ meat, and pizza, which are not typically consumed in populations from other parts of the world, including places like India and China where different foods are eaten and there is a tendency to consume meals that are more rice-based (146, 147). The second disadvantage is that the derivation of Empirical Dietary Inflammatory Pattern scores requires data on inflammatory markers in the target population. Hence, this pattern cannot be derived in studies that do not collect these biomarkers. Unless there is scope for re-validation, use of the index is limited to the same foods and dietary patterns as those that exist in the target population. Third, the derivation of a pattern is highly

TABLE 1 Main characteristics of the studies that have attempted to calculate DII scores[1]

First author, year (ref)	Study design	Study name/ country	Objective	Results	Issue with the index calculation
Kizil, 2016 (134)	Cross-sectional	Turkey	A group from Turkey attempted to evaluate the association between the DII and serum CRP and protein energy wasting in hemodialysis patients.	DII showed significant correlation with reliable malnutrition and inflammation indicators, including subjective global assessment ($r = 0.28$, $P < 0.01$), malnutrition inflammation score ($r = 0.28$, $P < 0.01$), and serum CRP ($r = 0.35$, $P < 0.001$) in hemodialysis patients.	The DII score is created by simply summing up all food parameter–specific inflammatory effect scores, without any regard to the need to use the scoring algorithm.
Bawaked, 2017 (135)	Cross-sectional	Spain	To examine the DII's association with diet quality indicators in a representative sample of Spanish youth	Scoring for the KIDMED and the total dietary antioxidant capacity significantly decreased ($P < 0.001$ and $P = 0.030$, respectively) across quintiles of the DII, whereas the opposite was true for energy density ($P < 0.001$).	When calculated from all the 45 food parameters, DII scores can range from −8.87 to +7.98. Usually, for DII scores derived from 25–30 food parameters, the range is from −5.5 to +5.5. This group calculated DII from just 23 food parameters, and their DII scores ranged from −6.7 to +7.8, which is inconsistent with the findings we obtained in >160 publications in the last 4 y, which indicate that the effective range rarely exceeds 11.
Georgousopoulou, 2016 (136)	Cohort	ATTICA/ Greece	To evaluate the association between anti-inflammatory diet and 10-y CVD incidence	An anti-inflammatory diet, as expressed by higher DII scores, was borderline associated with 10-y CVD incidence (OR for the third tertile vs. the first tertile: 0.98; 95% CI: 0.96, 1.01).	In this study, authors calculated a modified version of the DII and called it the D-AII. The difference between DII and D-AII is that in calculating D-AII scores, the z scores are not converted to centered percentiles and instead are multiplied directly by inflammatory effect scores. The scores ranged from 10 to 77, and therefore cannot be compared with DII scores.
Agudo, 2017 (137)	Cohort	EPIC/ Spain	To examine the association between inflammatory potential of the diet and mortality in the Spanish cohort of EPIC	There was a significant association between ISD and mortality: subjects classified in the fifth quintile of the ISD (more proinflammatory diets) had an HR of 1.42 (95% CI: 1.25, 1.60) compared with those in the first quintile; the corresponding figures were 1.89 (1.48, 2.40) for CVD mortality and 1.44 (1.22, 1.69) for death by cancer.	The difference here is that instead of standardizing the intake values to means and SD from the global database, authors have standardized the intake values to means and SDs of the study population, thus limiting interpretation and comparability with other studies.
Farhangj, 2018 (138)	Cross-sectional	Iran	To examine the relation between dietary inflammatory potential and CVD risk factors in a cross-sectional analysis	They reported that men in the third and fourth quartiles of DII scores (i.e., more proinflammatory) had higher total cholesterol, TGs, albumin, creatinine, blood urea nitrogen, and CRP.	The description of how they calculated the DII scores is correct. However, the range of DII scores presented, stated to be from −19.33 to 10.62, is outside of the theoretical bounds of −8.87 to +7.98. Furthermore, the lower bound of the first quartile was −29.83. Clearly, there was a significant miscalculation.

[1]CRP, C-reactive protein; CVD, cardiovascular disease; D-AII, Dietary Anti-Inflammation Index; DII, Dietary Inflammatory Index; EPIC, European Investigation into Cancer and Nutrition; ISD, Inflammatory Score of Diet; KIDMID, Mediterranean Diet Quality Index for children and adolescents; ref, reference.

dependent on the inflammatory markers being evaluated, so a pattern that is derived to predict CRP may be different from one to predict IL-6, IL-1β, or TNF-α. Fourth, this pattern was derived from an FFQ, which begins with a limited set of dietary questions (as opposed to the food list–unconstrained approach used in developing the DII).

A similar regression method was used by Tyrovolas et al. (148) in a study to evaluate anti-inflammatory nutrition and successful aging in elderly individuals, and they referred to this index as the Nutrition Anti-Inflammatory score. Using an entirely different method, Kaluza et al. (149), from Sweden, created an index called the Anti-Inflammatory Diet Index. From a 123-item FFQ, 20 food groups (including 62 individual food items) were determined to be significantly correlated with high-sensitivity CRP. Of these, 15 were negatively correlated and 5 were positively correlated with high-sensitivity CRP. Each of these food groups were scored based on a predetermined cutoff value; for example, if an individual consumed ≥ 6 servings total fruits and vegetables/d, then the food group would get a score of $+1$. Scores were summed across all the food groups to obtain the overall Anti-Inflammatory Diet Index score.

Challenges and Other Observations

The DII was developed to provide a summary measure of diet-associated inflammation that could be used in any human population. Furthermore, it was designed so that DII, E-DII, and now C-DII scores can be compared across populations [i.e., a score of -2.0 in Ontario (150) or Newfoundland (52), Canada, is equivalent to a score of -2.0 in Peshawar, Pakistan (151), or Bruges, Belgium (152)]. By contrast, indexes that are derived using data from a particular population cannot produce results that are quantitatively comparable to other indexes used in different populations. Virtually all population-specific indexes have used some version of the FFQ. To develop a pattern from 24-h diet recalls, which could entail several thousands of food items, would be very laborious. Furthermore, it would require identifying a sufficiently large study having such data.

The DII is universal in its applicability, because it is grounded in a large base of research, involves 6 of the most commonly studied inflammatory markers, and scores can be derived from any dietary assessment tool that can provide nutrient intake data. By its design, scores can be directly compared across studies conducted virtually anywhere in the world.

Another, indirect, benefit of the large and growing body of DII-related work is that we have now amassed a large number of data sets that can be used to answer the same question regarding the association between DII score and a particular health outcome. Thus, we know the "universe" of studies whose characteristics we can quantify. These include dietary data of sufficient quality to compute a DII score, sufficient information on a particular outcome (e.g., a cancer, including morphologic and histopathologic characteristics), and appropriate data on covariates that constitute known or suspected confounders and effect modifiers.

Typically, we can only guess at whether publication bias is driving the field's perspective on risk factor–health-outcome relations (153). Because we are starting out with a known pool of studies, we can obviate, nearly entirely, issues of publication bias. Although epidemiologists are preoccupied with the denominator (of subjects) within particular studies, they usually have no way of knowing the true denominator of studies as units of measurement. As a meta-technique that can be used across a large number of studies on a single topic, the DII has obviated concern about publication bias. This is because we can use it in numerous studies to which we have access to the raw data. These studies now represent >300 different data sets from >180 different studies in 36 countries and include many of the largest cohorts in world. This has resulted in large numbers of studies on a single subject (e.g., 18 on colorectal cancer) and >160 publications, including 12 meta-analyses (32, 39–49).

Although the DII was developed to assess diet-associated inflammation, it would be expected to map to (and be correlated with) other indicators of diet quality. Indeed, there is a moderate negative correlation between DII scores and those of other indexes such as the Healthy Eating Index and Mediterranean Dietary Index (i.e., from approximately -0.50 to -0.70) (4, 154), indicating that only 25–50% of variability in DII scores is explained by the comparison index (and vice versa). It is conceivable that the amount of variability not explained by the DII might be attributable to factors not related to inflammation. The problem with this, of course, is that inflammatory factors are highly correlated within an index such as the Alternative Healthy Eating Index or Mediterranean Diet (MED) score. So, attempting to ascribe attributable proportion of variance becomes a difficult, if interesting, statistical exercise.

One other index, the glycemic index (2, 155, 156), is not bound by the constraints noted for most other dietary indexes, which are limited to particular foodways, patterns of intake, or dietary recommendations. Although it is commendable to have created an index that links food intake to glycemic responses, we now know that the preponderance of evidence links inflammation to a wide variety of endpoints. In a recent study conducted in young-adult college students in Louisiana, DII scores were positively correlated with the glycemic index score, although the correlation was modest ($r = 0.30$, $P < 0.01$) (157). Furthermore, it also is known that glycemic response is subsumed under a large number of factors that determine chronic, systemic inflammation.

Recommendations

Future challenges include maintaining the integrity of the process of computing DII, E-DII, and now C-DII scores. Because computing DII scores is fraught with complications, errors may occur when doing so. This problem is magnified when the algorithm is altered; and, as noted, problems of this kind have been observed. It is important to note that neither the E-DII nor the C-DII can be computed without access to the unique comparative databases. The standard DII score can be computed without this; however, we have observed

instances of errors, often of large magnitude, when attempts have been made to do this.

Future work should explore interpopulation differences in dietary patterns that result in markedly different inflammatory potential. Delving into how these differences relate to variations in overall energy and nutrient consumption and nutrient density and energy density of the diet is likely to lead to both methodologic improvements in using the DII and in deepening our understanding of the role of diet-related inflammation in human health and well-being.

In solving the "total energy problem" by developing the E-DII, we made it possible to compute DII scores for menus, recipes, and even whole foods. Although we have done this within the United States, we have not attempted to do so with foods available in entirely different cultures or with international collaborators. This represents another frontier for future development, which should include expansion of dietary components [e.g., seaweed (158, 159)] to reflect scientific progress that will have occurred since the last careful literature review was completed.

Although diet is, no doubt, an important modulator of inflammation, it is by no means the only one. Other indexes, including physical activity and stress, should be derived using similar methods. If these could be integrated with the DII, then this could open a whole new era of research in nutritional epidemiology and health promotion.

Acknowledgments

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