A new mathematical approach to improve the original dietary inflammatory index (DII) calculation

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Abstract

Accumulating evidence links dietary intake to inflammatory processes involved in non-communicable disease (NCD) development. The dietary inflammatory index (DII) designed by Shivappa et al. has been shown to capture the inflammatory potential of dietary behavior in a large number of epidemiological studies. Thus, the DII may serve as future tool to assess someone’s nutritional inflammatory capacities and hence, the individual risks for NCD development later in life. The calculation method of the DII, however, can benefit from alternative mathematical steps, particularly regarding the transformation from standardized daily food consumption to percentile scores. Here, we provide novel approaches, the scaling-formula (SF) and scaling-formula with outlier detection (SFOD) methods, with the aim to optimize the DII calculation method proposed by Shivappa and colleagues. We illustrate on simulated data specific limitations of the original DII calculation and show the benefits of the SF/SFOD by using simulated data and data from the prospective TEENDIAB study cohort, which supports the application of SF/SFOD in future epidemiological and clinical studies.

Introduction

The prevalence of non-communicable diseases (NCD) is increasing rapidly worldwide [1], accompanied by NCD-caused mortality. Hence, an estimate of around two-third of global deaths in 2017 has been attributed to NCD [2]. Although decreasing NCD death rates have been observed between 2007 and 2017 [2], great efforts are continuously needed to control and reduce NCD numbers, especially in low- and middle-income countries [3], as highlighted by the global action plan of the World Health Organization [4].

A healthy and balanced diet has been implicated as an important lifestyle factor for the prevention of NCD [5]. For example, a Westernized diet, typically rich in (animal-derived) fats and refined carbohydrates and, in parallel, poor in fiber, has been associated with an increased risk for NCD, such as cardio-vascular disease, metabolic syndrome, type 2 diabetes and certain...
In contrast, subjects consuming a Mediterranean diet, originally rich in plant-based fats, whole grains, fruits and vegetables, may be more protected against certain NCD [8,9]. One plausible explanation for this observation is the anti-inflammatory potential of a Mediterranean diet [10]. Chronic (low-grade) pro-inflammatory processes have been suggested to be causal for a number of NCD, for example, by promoting endothelial dysfunction, a significant contributor to coronary heart disease [11], or by promoting insulin resistance, a major cause for type 2 diabetes [12]. Potentially, such events could therefore be prevented by a higher consumption of foods with anti-inflammatory components, such as fiber [13], vitamin E [14] and n-3 fatty acids [15], and in parallel, lower intake of foods with pro-inflammatory components, e.g., saturated fatty acids [16]. In that sense, an easy-to-use tool to define the inflammatory potential of an individual diet appears to be beneficial to identify and reduce pro-inflammatory food items and promote nutrition with anti-inflammatory effects.

In 2014, Shivappa et al. developed the dietary inflammatory index (DII) using literature-derived information on 45 food parameters and their relation to six inflammatory blood markers, namely interleukin (IL)-1β, IL-4, IL-6, IL-10, tumor-necrosis-factor alpha (TNF)-α and C-reactive protein [17]. Based on the relations between the DII and these biomarkers, there has been a very large number of studies investigating associations between the DII and potential inflammatory-driven diseases. Remarkably, the DII has been applied in over 200 human studies, including different ethnicities and various health outcomes [18–24]. In numerous studies, associations were found between the intake of a rather pro-inflammatory diet (positive DII score) and an increased risk for certain NCD, e.g., several cancer types, cardiovascular disease or type 2 diabetes [18,25–29]. Thus, the DII has the potential to be an easy-to-use and low-cost tool, which could be globally applied, to assess someone’s ‘unhealthy’ diet and potentially prevent NCD development by guiding to a more non-/anti-inflammatory eating behavior. However, not all studies showed consistent associations between the DII and inflammatory markers or health outcomes, for example, with regard to the metabolic syndrome [30]. Moreover, associations in some studies were rather weak [31,32], or were only found in one of the sexes investigated [33–35]. Furthermore, it appears worthy to note that although the original DII is based on the associations between food parameters/nutrients and six selected inflammatory cytokines, several studies did not observe an association between the DII and those cytokines [32,35–39]. One potential reason for these observations could be that the calculation of the DII is still not precise enough to provide a clearer picture in various settings. With the attempt to further improve the DII, we noticed, by mathematically evaluating each calculation step, that the application of the standard normal distribution function in one of those steps does not optimally fit in this context, and that an alternative approach possibly provides a more accurate DII score. Thus, we propose a revised mathematical calculation of the DII, which may result in a higher potential to reveal associations with inflammatory markers and health outcomes, and therefore, may be better suitable for future epidemiological and clinical studies. Furthermore, we describe a possible harmonization approach to compare DIIs across various studies.

Original DII calculation according to Shivappa et al.

The literature-derived, population-based DII calculation by Shivappa et al. has been described elsewhere [17]. For the suggested improvements of the DII calculation, the most important assumptions and steps of Shivappa’s DII are described briefly. First, fixed relationships are assumed between the considered inflammatory markers (pro-inflammatory: IL-1β, IL-6, TNF-α, C-reactive protein; anti-inflammatory: IL-4, IL-10) and the DII. Second, the used articles containing results on the influence of food parameters on these inflammatory markers are
selected for the calculation of effect scores of the chosen inflammatory markers. Third, global values (means and standard deviations) for the considered food parameters are estimated from daily consumption data of a global database based on 11 different countries. Furthermore, $P$ is assumed as the set of food parameters (a total of 45 food parameters are used by Shivappa et al. [17]) included in the DII calculation.

**Scoring algorithm for food parameter effects**

For the scoring of selected articles with information on the influence of the 45 food parameters on the six pro-/anti-inflammatory blood markers, let $x$ be the result of an article and $a: X \rightarrow \{-1, 0, 1\}$ be defined through

$$a(x) = \begin{cases} 
-1, & x = \text{food parameter showed anti-inflammatory effect} \\
0, & x = \text{food parameter showed no inflammatory effect} \\
1, & x = \text{food parameter showed pro-inflammatory effect}
\end{cases}$$

**Raw and overall inflammatory effect scores for a single food parameter**

For a fixed food parameter $p$, the scores $a(x_{pi})$ of the selected articles $x_{pi}, i = 1, \ldots, n$ for the calculation of the effect scores are weighted with the weights $w(x_{pi})$, depending on study characteristics (study type, study design), e.g. study type human and study design prospective cohort (for more information see Table 1 in [17]). With it the raw inflammatory effect score (RIES) is calculated by

$$\text{RIES}_p = \frac{\sum_{i=1}^{n} a(x_{pi}) \times w(x_{pi})}{\sum_{i=1}^{n} w(x_{pi})} \in [-1, 1]. \quad \text{(Eq 1)}$$

The adjusted RIES, the overall inflammatory effect score (OIES), is calculated by

i) if $\sum_{i=1}^{n} w(x_{pi}) < \text{median}(\sum_{i=1}^{n} w(x_{pi}))$:

$$\text{OIES}_p = \frac{\sum_{i=1}^{n} a(x_{pi}) \times w(x_{pi})}{\text{median}(\sum_{i=1}^{n} w(x_{pi}))} \times \text{RIES}_p$$

$$= \frac{\sum_{i=1}^{n} a(x_{pi}) \times w(x_{pi})}{\text{median}(\sum_{i=1}^{n} w(x_{pi}))} \times \frac{\sum_{i=1}^{n} a(x_{pi}) \times w(x_{pi})}{\sum_{i=1}^{n} w(x_{pi})} \in (-1, 1)$$

ii) if $\sum_{i=1}^{n} w(x_{pi}) \geq \text{median}$

$$\text{OIES}_p = \text{RIES}_p. \quad \text{(Eq 2)}$$

**Global database values**

For every food parameter $p$, the global daily consumption is calculated by

$$\bar{I}_p = \frac{1}{n} \sum_{i=1}^{n} I_{pi}, \quad \text{(Eq 3)}$$

where $I_{pi}$ is the amount (in the same unit) of the daily consumption of the considered food parameter for subject $i$ from a global database generated by Shivappa et al. [17].
The according global variability is given by the standard deviation

\[ sd_p = \sqrt{\frac{1}{I-1} \sum_{i=1}^{I} (I_{p,i} - \bar{I}_p)^2}. \]  

(Eq 4)

**Final calculation steps of the DII**

The reported amount of the daily consumption \( I_{p,i} \) of a particular food parameter \( p \) and subject \( i \) for which the DII should be calculated is standardized by

\[ Z_{p,i} = \frac{I_{p,i} - \bar{I}_p}{sd_p}. \]  

(Eq 5)

The DII for a particular food parameter \( p \) and subject \( i \) results from

\[ DII_{p,i} = (2 \times \Phi(Z_{p,i}) - 1) \times OIES_p \in [-1, 1], \]  

where \( \Phi \) is the standard normal distribution function.

Finally, the DII for the \( i \)-th subject is then calculated by

\[ DII_i = \sum_{p \in P} DII_{p,i} \in [-|P|, |P|], \]  

completing the original calculation method by Shivappa et al. [17].

**Improvable steps within the original DII calculation**

In the following, \( P \) is assumed as the set of food parameters for a set of \( n \) subjects for which the DII should be calculated and \( \mathbf{I}_p \in \mathbb{R}^n_+ \) is the vector of the daily consumptions of the parameter \( p \in P \), where the entry \( I_{p,i} \) is the daily consumption of the \( i \)-th subject.

As shown above, the DII for the \( i \)-th subject according to Shivappa et al. is calculated through standardization of the daily consumption \( I_{p,i} \) of the subject of the food parameter \( p \) through first subtracting the global mean \( \bar{I}_p \) from the daily consumption \( I_{p,i} \), and then dividing by the global standard deviation \( sd_p \) of the considered food parameter. Subsequently, the standardized vector \( \mathbf{Z}_p \) (Z-scores) is transformed to percentiles of the standard normal distribution function, which are then scaled into \([-1,1]\) and multiplied with the respective effect scores of the food parameter. At last, the scaled and multiplied percentiles are summed across the available food parameter for the \( i \)-th subject. Here, we focus on the transformation of the daily consumption vector to the percentiles of the standard normal distribution function.

**Insufficient scaling to the entire unit interval**

Of note, most of the daily consumptions of a food parameter \( \mathbf{I}_p \) do not follow a normal distribution by the nature of the data and hence, are not standard normal distributed after standardization with the generated global values. For this reason, the entries of \( \mathbf{I}_p \) are not transformed through the standard normal distribution function into the entire unit interval but, as expected, in a sub-interval which lies within the entire unit interval. Hence, the unit interval is not fully exhausted through the transformation to percentiles of the standard normal distribution function. To show this effect, we transformed simulated data of the daily intake of a food parameter (Carbohydrates, Table 1) by using the standard distribution function and the resulting percentiles only scaled in the lower part \([0.003, 0.409]\) (Fig 1). All analyses were performed with R software v.4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

Through the standardization (Eq 5), the daily consumption vector of a specific food parameter is limited through \( -\frac{\bar{I}_p}{sd_p} \) to the left side and therefore, the percentiles of the standard
normal distribution function have a lower limit greater than zero. Furthermore, with increasing right-skewness of the shape of the density function of the vector $I_p$, the percentiles cluster in the lower part $[0, 0.5]$ of the standard normal distribution function. In addition, this effect is amplified if the standard deviation does not fit to the corresponding food parameter. For example, using simulated saffron data, $I_{\text{saffron}} = (0.471, 0.155, 0.109, 0.075, 0.094, 0.266, 0.747, 0.22, 0.153, 0.124, 0.745, 0.583, 0.474)$, and the values $I_{\text{saffron}} = 0.37, sd_{\text{saffron}} = 1.78$ as calculated by Shivappa et al. for the standardization (see Table 2 in [17]), the resulting percentiles $[0.434, 0.584]$ cluster in the middle part of the standard normal distribution function (Fig 2). The lower limit of percentiles of the standard normal distribution function in this example is $\Phi\left(-\frac{0.37}{1.78}\right)$.

### Table 1. Simulated data on daily consumption of food parameters and on a pro-inflammatory biomarker used for the Dietary Inflammatory Index (DII) calculation and analyses.

| Subject ID | Carbohydrates (g) | Cholesterol (mg) | Pro-inflammatory biomarker (pg/ml) |
|------------|-------------------|------------------|----------------------------------|
| 1          | 195.1469          | 185.1469         | 35.146869                        |
| 2          | 213.3806          | 203.3806         | 53.380553                        |
| 3          | 172.9380          | 162.9380         | 12.937982                        |
| 4          | 170.2502          | 160.2502         | 10.250178                        |
| 5          | 214.2499          | 204.2499         | 54.249885                        |
| 6          | 167.3584          | 157.3584         | 7.358408                         |
| 7          | 255.0185          | 245.0185         | 95.018335                        |
| 8          | 172.0676          | 162.0676         | 12.067571                        |
| 9          | 203.8999          | 193.8999         | 43.899851                        |
| 10         | 166.4904          | 156.4904         | 6.490351                         |
| 11         | 174.5276          | 164.5276         | 14.52783                        |
| 12         | 221.7369          | 211.7369         | 61.736869                        |
| 13         | 182.0337          | 172.0337         | 22.033748                        |
| 14         | 218.6789          | 208.6789         | 58.678931                        |
| 15         | 165.2294          | 155.2294         | 5.229385                         |
| 16         | 168.9255          | 158.9255         | 8.925473                         |
| 17         | 186.3684          | 176.3684         | 26.368428                        |
| 18         | 224.8152          | 214.8152         | 64.815199                        |
| 19         | 243.5497          | 233.5497         | 83.549694                        |
| 20         | 168.8521          | 158.8521         | 8.852105                         |
| 21         | 196.8460          | 186.8460         | 36.846049                        |
| 22         | 222.2546          | 212.2546         | 62.25498                         |
| 23         | 177.6297          | 167.6297         | 17.629736                        |
| 24         | 170.3257          | 160.3257         | 10.325747                        |
| 25         | 184.2279          | 174.2279         | 24.227861                        |
| 26         | 165.7956          | 155.7956         | 5.795587                         |
| 27         | 235.1728          | 225.1728         | 75.172809                        |
| 28         | 180.4476          | 170.4476         | 20.447607                        |
| 29         | 262.9943          | 252.9943         | 102.994341                       |
| 30         | 174.9587          | 164.9587         | 14.958738                        |
| 31         | 161.8330          | 151.8330         | 1.833000                         |
| 32         | 161.8340          | 151.8340         | 1.834000                         |

*All variables correlate with each other with a correlation coefficient of $r = 1$ according to Pearson.*

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The same effect occurs if the global values are estimated from the compiled data and these data contain outliers. As a consequence, the comparability of the DIIs between different studies becomes more difficult because it is assumed that the daily consumption vector is transformed to the entire unit interval but actually the interval is tighter.

Loss of proportions between subjects

The second improvable aspect is, that through the transformation of the standardized daily consumption vector $I_p$ to percentiles of the standard normal distribution function the proportions between the daily consumptions between the subjects can get lost, even if the daily consumptions $I_p$ of a food parameter would be normal distributed. This can result in unexpected differences between the DIIs for subjects with similar nutrition, as proportions should stay equal as well, independent of the amount of food parameter intake (see Table 2 as example).

As shown in Table 2, there is a greater difference (around the factor ten) in the DIIs according to Shivappa et al. (DII Shivappa) between the subjects with ID = 19 and ID = 27 ($\Delta I_{19-27} = 0.020471$) than for the subjects with ID = 1 and ID = 17 ($\Delta I_{1-17} = 0.004511$), although the difference of the food parameters between the subjects with ID = 1 and ID = 17 is similar as for the other subjects with ID = 19 and ID = 27. Of note, the within-subject difference between carbohydrates and cholesterol is always the same in this example. Despite a higher intake in subjects ID = 19 and ID = 27, the proportions between the shown subject pairs are expected to be equal. In particular, higher intake amounts can be affected by this effect as the upper scaling
interval is often not properly utilized. Like for the previously mentioned issue with different scale intervals of the DII, the effect of such differences between the DII$_{p_i}$ for subjects with similar nutrition is amplified with increasing right-skewness of the shape of the density function of I$_{p}$.  

**Improvements**

**Refined scaling methods.** To avoid these mentioned effects, we suggest a transformation which preserves the proportions between the daily consumptions of the subjects of a specific

![Figure 2](https://doi.org/10.1371/journal.pone.0259629.g002)

**Table 2. Differences in the Dietary Inflammatory Index (DII) calculated according to Shivappa et al. [17] or the Scaling-Formula With Outlier Detection (SFOD) method based on similar food consumption data between subject pairs.**

| Subject ID | Carbohydrates (g) | Cholesterol (mg) | DII Shivappa | DII SFOD |
|------------|-------------------|------------------|--------------|----------|
| 1          | 195.1469          | 185.1469         | -0.1945355   | -0.07063911 |
| 17         | 186.3684          | 176.3684         | -0.1990463   | -0.106589436 |
| ΔID1-17    | 8.778500          | 8.778500         | 0.004511     | 0.035926 |
| 19         | 243.5497          | 233.5497         | -0.12028190  | 0.127423316 |
| 27         | 235.1728          | 225.1728         | -0.14075287  | 0.093141146 |
| ΔID19-27   | 8.376900          | 8.376900         | 0.020471     | 0.034282 |

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food parameter and which scales the entries of \( I_p \) into the entire unit interval:

\[
 z_{p,i} = \frac{I_{p,i} - \min(I_p)}{\max(I_p) - \min(I_p)}. \tag{Eq 8}
\]

In the following, this formula will be referenced with scaling-formula (SF).

Indeed, the transformation with the SF depends on the minimum and maximum of \( I_p \). Hence, this transformation is more influenced by outliers. To account for outliers the SF can be modified using the interquartile range of the daily consumption vector of a food parameter instead of \( \max(I_p) \) and \( \min(I_p) \). For this, the daily consumption vector of a food parameter should be limited in the following way, where \( I_{p,q} \) is the \( q \)-th quartile of \( I_p \), \( R := I_{p.75} - I_{p.25} \) is the interquartile range, \( LL := I_{p.25} - 1.5 \times R \) is the lower limit and \( UL := I_{p.75} + 1.5 \times R \) the upper limit:

\[
 \tilde{I}_{p,i} = \begin{cases} 
 LL, & I_{p,i} < LL \\
 I_{p,i}, & LL < I_{p,i} < UL \\
 UL, & I_{p,i} > UL
\end{cases}
\]

Hence, the SF is modified to

\[
 z_{p,i} = \frac{\tilde{I}_{p,i} - LL}{UL - LL} \tag{Eq 9}
\]

and is referenced in the following as the scaling-formula with outlier detection (SFOD).

In comparison to the transformation to percentiles by the standard normal distribution function, the proportions between the daily consumptions of the subjects are preserved through the transformation with the SFOD, resulting in more similar DII\( s \) between subjects with similar nutrition (see Table 2). As mentioned above, the current calculation method according to Shivappa et al. can result in unequal proportions between subjects with comparable dietary intake. This effect is corrected by the SFOD method (DII SFOD, Table 2), resulting in similar differences (\( \Delta ID_{19-27} = 0.034282, \Delta ID_{1-17} = 0.035926 \)).

Moreover, the unit interval is fully utilized by the application of the SFOD method. Furthermore, the SFOD preserves the correlation structure between the DII and a pro-inflammatory biomarker (Table 1) with a correlation coefficient of \( r = 1 \) according to Pearson in this example, while through the transformation to percentiles of the standard normal distribution function some of the correlation structure gets lost (\( r = 0.9213171 \)) because of the above-mentioned disadvantages.

**Harmonization**

For better comparison of the individual DII\( s \) across studies, we suggest to consider the DII value for the \( i \)-th subject relative to the maximum value of the DII, which can be taken within a study

\[
 DII_{HR} := \frac{DII}{\max(DII)} \in [-1, 1]. \tag{Eq 10}
\]

**Evaluation of DII calculation methods in the TEENDIAB cohort study**

To evaluate the different calculation methods, we used data from the TEENDIAB cohort, a prospective observational cohort study in children and adolescents with at least one first-degree relative with type 1 diabetes. Details of the study have been published previously [40]. Briefly, children were enrolled in the study at the age of 8–12 years and followed until the age
of 18 years to investigate the period of puberty and adolescence in the natural course of type 1 diabetes development. The study has been approved by the ethical committee of the Technical University Munich (No. 2149/08) and the Medizinische Hochschule Hannover (No. 5644). Written informed consent was obtained from all participants.

In the current analysis, 193 children with complete data on dietary intake and blood cytokine levels were included. None of the children included was diagnosed with type 1 diabetes. Details of the study cohort are described in Table 3.

### Dietary assessment

Habitual dietary intake was assessed at first study visit using the modified computer-assisted Diet Interview Software for Health Examination Studies Junior (DISHES Junior; Robert Koch Institute, Berlin, Germany). The standardized questionnaire was performed by face-to-face interview with trained staff and collected detailed data on the consumed frequency, type and quantity of foods and beverages of the last four weeks [42]. DIIs according to Shivappa, SF and SFOD methods, as described above, were calculated using total energy intake and the following nutrients/food parameters: alcohol, vitamin B12, vitamin B6, beta-carotene, total carbohydrates, cholesterol, total fat, fiber, folic acid, iron, magnesium, mono-unsaturated fatty acids, niacin, total protein, poly-unsaturated fatty acids, riboflavin, saturated fat, thiamin, vitamin A, vitamin C, vitamin D, vitamin E and zinc. These nutrients/food parameters are the same ones used for the children/adolescent DII [43], with the exception of selenium, which was not assessed in this study.

### Cytokine measurements

To evaluate the different DII calculation methods, we assessed whether the different DIIs were associated with the pro-inflammatory TNF-α and IL-6 and the anti-inflammatory IL-10, which were used by Shivappa et al. for the development of the original DII calculation. Blood samples for analysis of these cytokines were taken at the first study visit and analyzed with Meso Scale Discovery (MSD) electrochemiluminescence assay (Meso Scale Diagnostics, Rockville, MA, USA) at the Institute of Diabetes Research as previously described [44].

| Table 3. Characteristics of TEENDIAB children/adolescents included in the present analysis. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Age (yrs)                       | 10.3 ± 1.2      | Females–N (%)   | 91 (47.2)       | BMI-SDS†         |
| BMI-SDS†                        | 0.12 ± 1.22     | Weight status†  |                 |                 |
| Underweight–N (%)              | 7 (3.6)         | Normal weight–N %| 141 (73.1)      |                 |
| Overweight–N (%)               | 32 (16.6)       | Obese–N (%)     | 13 (6.7)        |                 |
| Tumor-necrosis factor alpha (pg/ml) | 2.76 ± 1.0     | Interleukin-6 (pg/ml) | 0.54 ± 2.0       |                 |
| Interleukin-10 (pg/ml)         | 0.48 ± 0.60     |                 |                 |                 |

†BMI: Body-mass-index; SDS: Standard deviation score.

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Statistical analyses
Cytokine levels were log-transformed for statistical analyses [44,45]. Linear regression analyses, adjusted for sex and age, were performed to study the associations between DII and cytokine levels.

Results
The distribution of the DII according to the three different calculation methods is shown in Fig 3. The variation of the DII values calculated by the SF and SFOD methods was smaller than the variation of the DII calculated according to Shivappa, while the SF-derived DII showed the smallest variation. Moreover, the median DII score was higher (more pro-inflammatory) when calculated with the revised methods SF and SFOD (Fig 3). While the majority of subjects remained in the same category, i.e., pro- or anti-inflammatory DII, independent of the original or SFOD method, a substantial fraction of 18.1% (n = 35) children changed from a negative DII score according to Shivappa to a positive DII score according to the SFOD method. There was no subject changing from a positive DII score calculated by Shivappa’s method to a negative DII score following the SFOD method. Overall, more children had a proinflammatory DII score according to the SFOD method (n = 132) compared to the method by Shivappa (n = 97).

As shown in Table 4, no significant association was observed between any of the three DII scores (calculated acc. to Shivappa, SF and SFOD, respectively) and TNF-α or IL-6 levels. The DII score, calculated with the SF or SFOD method, was significantly inversely associated with IL-10 levels (Table 4). The same trend was observed when using the DII calculation method proposed by Shivappa et al., although not significant (Table 4).

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**Fig 3.** Boxplots of the dietary inflammatory index (DII) scores between the three different calculation methods. Nutritional data from n = 193 subjects participating in the TEENDIAB study were used to calculate the DIIs according to the original method from Shivappa et al. [17] or the revised methods scaling-formula (SF) and scaling-formula with outlier detection (SFOD), respectively.

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Discussion

The application of the DII in a large number of studies in the past years yielded promising results, that this index could be used in the future to estimate the inflammatory potential of someone’s diet and thus, individual risks for several inflammatory-associated diseases [18]. The inventors of the DII already improved the original DII calculation by including energy-adjustment [46] and made it more specific for the application in children [43]. Here, we presented alternative mathematical approaches to further optimize the original DII calculation by Shivappa et al. [17], which also serves as basis for the energy-adjusted and children DII.

With regard to the transformation from standardized Z-scores to percentiles, we demonstrated that using the standard normal distribution function can lead to an incomplete distribution across the whole unit interval and that proportions between the daily food consumptions of different subjects can disappear. Overall, this possibly affects association analyses between the DII and health outcomes in epidemiological and clinical studies. To circumvent these issues, we presented the methods SF/SFOD which capture the lacks of using the standard normal distribution function to scale into the entire unit interval, keep the proportions between subjects and solve the dependency on the global values for the standardization. Simultaneously, a dependency to the used dataset arises and therefore, it would not make sense to calculate the DII with the described SF/SFOD method for a single person. However, this could be easily achieved by using the reference values developed by Shivappa et al. [17], or alternative (e.g., country-specific) reference values, for the interquartile range (lower and upper limits). An additional benefit of the SFOD method is that any reference data, e.g., age-/sex-/country-specific, can be used. As the DII is usually applied in epidemiological or clinical studies to assess associations between the DII and health outcomes in a defined cohort, the SFOD method should be preferred because of the above described benefits.

While the application of the DII is currently mostly restricted to epidemiological/clinical studies, one aim will be to develop personalized guidelines/recommendations. It remains to be defined what units/cutoffs of the DII will be applied in guidelines/recommendations in the future. There might be more than just the two categories pro- and anti-inflammatory, such as DII scores ranging from +8 to -8, or the categories high and low pro-inflammatory or anti-inflammatory. Therefore, a more accurate calculation of the individual DII score, as provided by the SFOD method, seems to be more applicable, for example, when monitoring changes of the DII over time.

The comparison of the three different DII calculation methods using data of the TEENDIAB study yielded higher DII scores using the improved SF and SFOD methods, indicating a more pro-inflammatory diet, which is consistent with the previously published observation that dietary patterns in the TEENDIAB cohort were rather “unhealthy” [42].

Table 4. Associations between the Dietary Inflammatory Index (DII) calculated according to Shivappa, the Scaling-Formula (SF) and Scaling-Formula With Outlier Detection (SFOD) methods and cytokine levels.*

*Data are presented as unstandardized regression coefficients of linear regression analyses adjusted for age and sex in n = 193 subjects of the TEENDIAB study. Cytokine levels were log-transformed.

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of the TEENDIAB cohort consumed higher amounts of meat and meat products, sweets, snacks and sweetened beverages and lower amounts of fruits and vegetables than recommended by the optimal mixed diet guidelines [42]. We observed negative associations between the DIIs and the anti-inflammatory cytokine IL-10, as proposed by Shivappa et al. [17]. The observation that the association between DII and IL-10 was stronger when applying the revised DII calculation methods supports the proposed modification of the DII calculation.

Furthermore, no associations were observed between the DIIs and the pro-inflammatory cytokines TNF-α and IL-6 in the TEENDIAB cohort, independent of the applied DII calculation method. Previous studies on the effect of the DII on blood TNF-α/IL-6 levels yielded inconsistent results for children/adolescents; some studies also reported no association [35,38], while another study showed significant associations between the DII and IL-6 [47]. Additional analyses in larger cohorts across all age groups are warranted to validate our findings and show the improvements by the SFOD method.

The evaluation of the three methods in the TEENDIAB cohort has some limitations. First, we used the original DII calculation method instead of the children DII as the global food parameter database for children, that has been used for the calculation method by Shivappa et al., has not been provided with the publication [43]. Still, to calculate the children DII as close as possible, we used the same inflammatory effect scores, which are the same for all DII versions, and the same food parameters that have been suggested for the calculation of the children DII [43], with the exception of selenium intake since it was not assessed in the TEENDIAB cohort. Of note, the original DII has been successfully applied in children/adolescents by the inventors [38,48,49], indicating that the original DII should also be an appropriate measure at young age. Thus, the applied DIIs in the evaluation appear to be valid. Second, C-reactive protein levels, a pro-inflammatory marker used for the validation of the children DII [43], was not available in the TEENDIAB cohort. Therefore, our evaluation is restricted to the provided cytokines.

With the aim to further improve the DII, we focused here on the primary mathematical calculation steps which were made accessible by the inventors in previous publications. The proposed mathematical improvements will affect the calculation of DII at the global level, meaning that they are applicable regardless of age, socio-demographic, or cultural characteristics of the cohort studied. Further improvements may include a weighting algorithm, which bears in mind the influence of the most important food parameters, as the DII according to Shivappa’s calculation does so far not differ between the relevance of the food parameters, i.e., all of them are integrated with the same weight in the DII calculation. For now, we can only speculate if the application of the revised DII calculation would have strongly influenced the findings in the large number of previous publications using the original DII by Shivappa et al., but we think that most of the significant findings might have been stronger/clearer and some findings with borderline significance might have become non-significant. Overall, the revised DII method may provide clearer results in many upcoming analyses.

In summary, we showed a novel approach to improve the DII calculation by Shivappa et al. and provided further steps and suggestions for its optimization. Ultimately, this may increase the potential to identify associations in epidemiological/clinical settings between the DII and inflammatory markers and health outcomes, respectively.

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References

1. Bennett JE, Stevens GA, Mathers CD, Bonita R, Rehm J, Kruk ME, et al. NCD Countdown 2030: worldwide trends in non-communicable disease mortality and progress towards Sustainable Development Goal target 3.4. Lancet. 2018; 392:1072–88. https://doi.org/10.1016/S0140-6736(18)31992-5 PMID: 30264707
2. Roth GA, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018; 392:1736–88. https://doi.org/10.1016/S0140-6736(18)32203-7 PMID: 30496103
3. Ezzati M, Pearson-Stuttard J, Bennett JE, Mathers CD. Acting on non-communicable diseases in low- and middle-income tropical countries. Nature. 2018; 559:507–16. https://doi.org/10.1038/s41586-018-0306-9 PMID: 30046068
4. WHO. Global action plan for the prevention and control of NCDs 2013–2020. [cited 2021 Jan 14]. Available from: https://www.who.int/nmh/publications/ncd-action-plan/en/
5. WHO. Diet, nutrition and the prevention of chronic diseases: report of a joint WHO/FAO expert consultation, Geneva, 28 January—1 February 2002. [cited 2021 Jan 14]. Available from: https://www.who.int/publications/i/item/924120916X
6. Stoeckli R, Keller U. Nutritional fats and the risk of type 2 diabetes and cancer. Physiol Behav. 2004; 83 (4):611–5. https://doi.org/10.1016/j.physbeh.2004.07.030 PMID: 15621066
7. Kopp W. How western diet and lifestyle drive the pandemic of obesity and civilization diseases. Diabet Metab Syndr Obes. 2019; 12:2221–36. https://doi.org/10.2147/DMSO.S216791 PMID: 31695465
8. Galbete C, Kröger J, Jannasch F, Iqbal K, Schwingshackl L, Schwedhelm C, et al. Nordic diet, mediterranean diet, and the risk of chronic diseases: The EPIC-Potsdam study. BMC Med. 2018; 16(1):99. https://doi.org/10.1186/s12916-018-1082-y PMID: 29945632
9. Schwingshackl L, Schwedhelm C, Galbete C, Hoffmann G. Adherence to mediterranean diet and risk of cancer: An updated systematic review and meta-analysis. Nutrients. 2017; 9(10):1063. https://doi.org/10.3390/nu9101063 PMID: 28954418
10. Tsigalou C, Konstantinidis T, Paraschaki A, Stavropoulou E, Voidarou C, Bezirtzoglou E. Mediterranean diet as a tool to combat inflammation and chronic diseases. An overview. Biomedicines. 2020; 8(7):291. https://doi.org/10.3390/biomedicines8070201 PMID: 32650619
11. Zhang C. The role of inflammatory cytokines in endothelial dysfunction. Basic Res Cardiol. 2008; 103 (5):396–406. https://doi.org/10.1007/s00395-008-0733-0 PMID: 1860364
12. Shoelison SE, Lee J, Goldfine AB. Inflammation and insulin resistance. J Clin Invest. 2006; 116 (7):1793–801. https://doi.org/10.1172/JCI29069 PMID: 16823477
13. Bartolomeus H, Balogh A, Yakoub M, Homann S, Markò L, Höges S, et al. Short-chain fatty acid propionate protects from hypertensive cardiovascular damage. Circulation. 2019; 139(11):1407–21. https://doi.org/10.1161/CIRCULATIONAHA.118.036652 PMID: 30586752
14. Jiang Q. Natural forms of vitamin E: Metabolism, antioxidant, and anti-inflammatory activities and their role in disease prevention and therapy. Free Radic Biol Med. 2014; 72:76–90. https://doi.org/10.1016/j.freeradbiomed.2014.03.035 PMID: 24704972
15. Wall R, Ross RP, Fitzgerald GF, Stanton C. Fatty acids from fish: The anti-inflammatory potential of long-chain omega-3 fatty acids. Nutr Rev. 2010; 68(5):280–9. https://doi.org/10.1111/j.1753-4887.2010.00287.x PMID: 20500789

16. Rocha DM, Caldas AP, Oliveira LL, Bressan J, Hermsdorff HH. Saturated fatty acids trigger TLR4-mediated inflammatory response. Atherosclerosis. 2016; 244:211–5. https://doi.org/10.1016/j.atherosclerosis.2015.11.015 PMID: 26687466

17. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hébert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. Public Health Nutr. 2014; 17(8):1689–96. https://doi.org/10.1017/S1368980013002115 PMID: 23941862

18. Phillips CM, Chen LW, Heude B, Bernard JY, Harvey NC, Duijts L, et al. Dietary inflammatory index and non-communicable disease risk: A narrative review. Nutrients. 2019; 11(8):1873. https://doi.org/10.3390/nu11081873 PMID: 31408965

19. Kotemori A, Sawada N, Iwasaki M, Yamaji T, Shivappa N, Hebert JR, et al. Dietary inflammatory index is associated with inflammation in Japanese men. Front Nutr. 2021; 8:604296. https://doi.org/10.3389/fnut.2021.604296 PMID: 33898494

20. Matsumoto Y, Shivappa N, Sugiyoka Y, Tada M, Okano T, Mamoto K, et al. Change in dietary inflammatory index score is associated with control of long-term rheumatoid arthritis disease activity in a Japanese cohort: the TOMORROW study. Arthritis Res Ther. 2021; 23(1):105. https://doi.org/10.1186/s13075-021-02478-y PMID: 33832530

21. Abdurahman AA, Bule M, Azadbakhht L, Faliyeyekta M, Parouhan A, Qorbani M, et al. The association between diet quality and obesity-related metabolic risks. Hum Antibodies. 2020; 28(1):1–9. https://doi.org/10.3233/HAB-190387 PMID: 31282409

22. Saghafi-Asl M, Mirmajidi S, Asghari Jafarabadi M, Vahid F, Shivappa N, Hébert JR, et al. The association of dietary patterns with dietary inflammatory index, systemic inflammation, and insulin resistance, in apparently healthy individuals with obesity. Sci Rep. 2021; 11(1):7515. https://doi.org/10.1038/s41598-021-86993-7 PMID: 33824355

23. Ghazizadeh H, Yaghooti-Khorasani M, Asadi Z, Zare-Feyzabadi R, Saeidi F, Shabani N, et al. Association between diet quality and obesity-related metabolic risks. Hum Antibodies. 2020; 28(1):1–9. https://doi.org/10.3233/HAB-190387 PMID: 31282409

24. Asadi Z, Yaghooti-Khorasani M, Ghazizadeh H, Sadabadi F, Mosa-Far khany E, Darroud i S, et al. Association between dietary inflammatory index and risk of cardiovascular disease in the Mashhad stroke and heart atherosclerotic disorder study population. IUBMB Life. 2020; 72(4):706–15. https://doi.org/10.1002/iub.2172 PMID: 31617677

25. Vitale M, Calabrese I, Massimino E, Shivappa N, Hebert JR, Auciello S, et al. Dietary inflammatory index score, glucose control and cardiovascular risk factors profile in people with type 2 diabetes. Int J Food Sci Nutr. 2020 Oct 13;1–9. https://doi.org/10.1080/09637486.2020.1832054 PMID: 33053468

26. da Silva A, Felício MB, Caldas APS, Miranda Hermsdorff HH, Torreglosa CR, et al. Pro-inflammatory diet is associated with a high number of cardiovascular events and ultra-processed foods consumption in patients in secondary care. Public Health Nutr. 2020 Nov 5;1–10. https://doi.org/10.1017/S136898002000378X PMID: 33148359

27. Tabung FK, Steck SE, Ma Y, Liese AD, Zhang J, Lane DS, et al. Changes in the inflammatory potential of diet over time and risk of colorectal cancer in postmenopausal women. Am J Epidemiol. 2017; 186(5):514–23. https://doi.org/10.1093/aje/kwx115 PMID: 28486621

28. Paquet M, Shivappa N, Hébert JR, Baron-Dubourdieu D, Boustron-Ruault M-C, Guénel P, et al. Dietary inflammatory index and differentiated thyroid carcinoma risk: A population-based case-control study in New Caledonia. Am J Epidemiol. 2020; 189(2):95–107. https://doi.org/10.1093/aje/kwz192 PMID: 31509174

29. Ramallah R, Toledo E, Martínez-González MA, Hernández-Hermández A, García-Arellano A, Shivappa N, et al. Dietary inflammatory index and incidence of cardiovascular disease in the SUN Cohort. PLOS ONE. 2015; 10(9):e0135221. https://doi.org/10.1371/journal.pone.0135221 PMID: 26340022

30. Namazi N, Larijani B, Azadbakhht L. Dietary inflammatory index and its association with the risk of cardiovascular diseases, metabolic syndrome, and mortality: A systematic review and meta-analysis. Horm Metab Res. 2018; 50(5):345–358. https://doi.org/10.1055/a-0596-8204 PMID: 29723899

31. Corley J, Shivappa N, Hébert JR, Starr JM, Deary IJ. Associations between dietary inflammatory index scores and inflammatory biomarkers among older adults in the Lothian Birth Cohort 1936 Study. J Nutr Health Aging. 2019; 23(7):628–36. https://doi.org/10.1007/s12603-019-1221-y PMID: 31367727

32. Shivappa N, Hebert JR, Marcos A, Diaz LE, Gomez S, Nova E, et al. Association between dietary inflammatory index and inflammatory markers in the HELENA study. Mol Nutr Food Res. 2017; 61(6): https://doi.org/10.1002/mnfr.201600707 PMID: 27981781
33. Ryu I, Kwon M, Sohn C, Shivappa N, Hébert JR, Na W, et al. The association between dietary inflammatory index (DII) and cancer risk in Korea: A prospective cohort study within the KoGES-HEXA study. Nutrients. 2019; 11(11):2560.

34. Kotemori A, Sawada N, Iwasaki M, Yamaji T, Shivappa N, Hebert JR, et al. Validating the dietary inflammatory index using inflammatory biomarkers in a Japanese population: A cross-sectional study of the JPHC-FFQ validation study. Nutrition. 2020; 69:110569. https://doi.org/10.1016/j.nut.2019.110569 PMID: 31574409

35. Barragán-Vázquez S, Ariza AC, Silva IR, Pedraza LS, Rivera Dommarco JA, Ortiz-Panozo E, et al. Pro-inflammatory diet is associated with adiposity during childhood and with adipokines and inflammatory markers at 11 years in Mexican children. Nutrients. 2020; 12(12):1–18. https://doi.org/10.3390/nu12123658 PMID: 33261143

36. Wirth MD, Shivappa N, Davis L, Hurley TG, Ortaglia A, Drayton R, et al. Construct validation of the dietary inflammatory index among African Americans. J Nutr Health Aging. 2017; 21(5):487–491. https://doi.org/10.1007/s12603-016-0775-1 PMID: 28448077

37. Vahid F, Shivappa N, Faghihoori Z, Khodabakhshi A, Zayeri F, Hebert JR, et al. Validation of a Dietary Inflammation Index (DII) and association with risk of gastric cancer: a case-control study. Asian Pac J Cancer Prev. 2018; 19(6):1471–77. https://doi.org/10.22034/APJCP.2018.19.6.1471 PMID: 29936717

38. Coheley LM, Shivappa N, Hebert JR, Lewis RD. Dietary inflammation index® and cortical bone outcomes in healthy adolescent children. Osteoporosis Int. 2019; 30(8):1645–54.

39. Mayr HL, Thomas CJ, Tierney AC, Kucianski T, George ES, Ruiz-Canela M, et al. Randomization to 6-month Mediterranean diet compared with a low-fat diet leads to improvement in dietary Inflammatory Index scores in patients with coronary heart disease: the AUSMED Heart Trial. Nutr Res. 2018; 55:94–107. https://doi.org/10.1016/j.nutres.2018.04.006 PMID: 29754829

40. Ziegler AG, Meier-Stiegen F, Winkler C, Bonifacio E. Prospective evaluation of risk factors for the development of islet autoimmunity and type 1 diabetes during puberty—TEENDIAB: Study design. Pediatri Diabetes. 2012; 13:419–24. https://doi.org/10.1111/j.1399-5448.2011.00763.x PMID: 21446926

41. de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. Bull World Health Organ. 2007; 85(9):660–7. https://doi.org/10.2471/blt.07.043497 PMID: 18026621

42. Weber KS, Raab J, Haupt F, Aschemeier B, Wosch A, Ried C, et al. Evaluating the diet of children at increased risk for type 1 diabetes: First results from the TEENDIAB study. Public Health Nutr. 2015; 18:50–8. https://doi.org/10.1017/S1368980013003406 PMID: 24476676

43. Khan S, Wirth MD, Ortaglia A, Alvarado CR, Shivappa N, Hurley TG, et al. Design, development and construct validation of the children’s dietary inflammatory index. Nutrients. 2018; 10(8):993. https://doi.org/10.3390/nu10080993 PMID: 30061487

44. Ungethum K, Jolink M, Hippich M, Lachmann L, Haupt F, Winkler C, et al. Physical activity is associated with lower insulin and C-peptide during glucose challenge in children and adolescents with family background of type 2 diabetes. Diab Med. 2019; 36:366–75. https://doi.org/10.1111/dme.13819 PMID: 30242901

45. Schotthoefer AM, Schrodi SJ, Meece JK, Fritsche TR, Shukla SK. Pro-inflammatory immune responses are associated with clinical signs and symptoms of human anaplasmosis. PLoS ONE. 2017; 12(6). https://doi.org/10.1371/journal.pone.0179655 PMID: 28628033

46. Peres LC, Bandera E., Qin B, Guertin KA, Shivappa N, Hebert JR, et al. Dietary inflammatory index and risk of epithelial ovarian cancer in African American women. Int J Cancer. 2017; 140(3):535–43. https://doi.org/10.1002/ijc.30467 PMID: 27727481

47. Almeida-De-Souza J, Santos R, Barros R, Abreu S, Moreira C, Lopes L, et al. Dietary inflammatory index and inflammatory biomarkers in adolescents from LabMed physical activity study. Eur J Clin Nutr. 2018; 72:710–19. https://doi.org/10.1038/s41430-017-0013-x PMID: 29277838

48. Aslani Z, Qorbani M, Hébert JR, Shivappa N, Motlagh ME, Asayesh H, et al. Association of dietary inflammatory index with anthropometric indices in children and adolescents: The weight disorder survey of the childhood and adolescence surveillance and prevention of adult non-communicable disease (CASPIAN)-IV study. Br J Nutr. 2019; 121:340–50. https://doi.org/10.1017/S0007114518003240 PMID: 30507370

49. Rahbarinajad P, Asghari G, Yuzbashian E, Djazayery A, Dehghan P, Moslehi N, et al. Dietary inflammatory index in relation to carotid intima media thickness among overweight or obese children and adolescents. Ann Nutr Metab. 2019; 75(3):179–86. https://doi.org/10.1159/000502330 PMID: 31743894