ALINEA

NUTRITION

DECEMBER 2021

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Ji M, Hong X, Chen M, Chen T, Wang J, Zhang N. Dietary inflammatory index and cardiovascular risk and mortality: A meta-analysis of cohort studies. Medicine (Baltimore). 2020;99(20):e20303.

What We Know, Think We Know, or Are Starting to Know

Ah, inflammation. Has there been a bigger buzzword in the health and wellness space in the past decade? With Covid-19, we' ve obviously been inundated with "immune-boosting" and other related rhetoric, but up there with the darlings of the likes of Mark Hyman is "anti-inflammatory" foods, which he has discussed with such vaunted scientific minds as Vani Hari [of "Food Babe" infamy] and David Perlmutter [of Quack Asylum infamy].

Inflammation is an area which warrants separating facts from quacks, and it occurred that, to date, a Deepdive has not looked specifically at the main validated instrument by which we consider inflammation and diet as an exposure: the Dietary Inflammatory Index* [DII]. As a buzzword, "inflammation" often gets applied without much definition for what exactly is going on. So first, let' s define our terms by asking, to ourselves, a series of questions…

- ***"What is inflammation?"*** Inflammation is a defence mechanism to protect the body from infection and injury [(1)]. It is a normal physiological process, designed to assist repair damage to tissue and to return the body to homeostasis after infection, stress, and/or damage [(1)].
- ***"What causes inflammation?"*** There are three main triggers for inflammation [see **Figure** below]: microbial infection, tissue damage, and metabolic stress [(1)]. However, irrespective of the trigger, each of these triggers results in activation of similar pathways, and the activation of these pathways results in the production of inflammatory mediators [an array of chemical compounds, prostaglandins], generating an inflammatory response [(1)].
- ***"What are the symptoms of inflammation?"*** The inflammatory response is characterised by pain, heat, redness, swelling, and loss of function, caused by the activation of inflammatory mediators [(1)]. The extent of these processes depends on the magnitude of initial injury or infection [(1)].
- ***"What stops inflammation?"*** Inflammation is regulated as a negative feedback loop, i.e., there are several counter-processes which act to eliminate or regulate the initial trigger, initiate repair processes, and terminate the inflammatory response [(1)].
- ***"Are there different types of inflammation?"*** Yes, inflammation may be distinguished as acute or chronic. Acute inflammation is the initial response to infection/injury, characterised by increased plasma and white blood cell flow to the site of infection/injury [(1)]. Chronic inflammation describes the ongoing process of tissue breakdown and repair at the site of infection/injury, which may become excessive if the counter-regulatory processes to shut off the inflammatory response become impaired [(1)].

- ***"I've heard people talk about 'low-grade' inflammation, what is that?"*** Certain inflammatory conditions, like Rheumatoid Arthritis or Inflammatory Bowel Disease, exhibit pronounced elevations in inflammatory mediators and cells, and resulting damage to tissues: conditions like these are considered 'high-grade inflammation' [(1)]. 'Low-grade inflammation', conversely, still exhibits elevations in inflammatory markers but in the absence of overt clinical symptoms, and commonly occurs in adipose tissue with obesity [(1)].
- ***"How is inflammation measured?"*** Inflammation is measured using biomarkers, and several biomarkers may be used, including interleukins [i.e., interleukin-1 or interleukin-6], or tumour necrosis factor [TNF], or C-reactive protein [CRP] [(1)].. These may relate to each other. For example, CRP is produced in the liver in response to increased interleukin-6 released into the bloodstream from the site of inflammation [(1)]. CRP is considered one of the most accurate biomarkers of systemic inflammation and is strongly predictive of cardiovascular disease [CVD] [(2)].

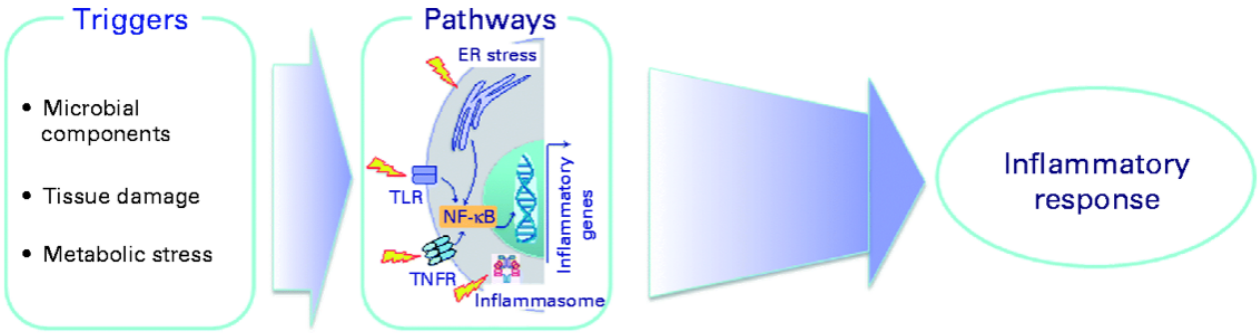


Figure *from [(1)] illustrating the processes leading to the inflammatory response: different initial triggers activate several pathways, which produce a range of inflammatory mediators that generate the inflammatory response.*

Of course, having outlined all the above, the question begs: how does inflammation and diet relate to disease risk? The DII represents a well-validated tool to assess the inflammatory potential of a dietary pattern, and has been utilised to investigate a range of health outcomes [(3)]. Because of the strong links between inflammation and CVD [(2)], investigating links between the DII and CVD has attracted interest in epidemiology. The study we Deepdive into today is the most recent meta-analysis of cohort studies investigated associations between the DII and CVD.

*Geek Box: The Dietary Inflammatory Index [DII]

The DII was first utilised in 2009 and was based on available research linking diet to one of six inflammatory biomarkers: interleukin-1β [IL-1β], interleukin-4 [IL-4], interleukin-6 [IL-6], interleukin-10 [IL-10], tumour necrosis factor alpha [TNF-α], or CRP. The DII utilised 45 food parameters based on national food data intakes from different countries across different world regions: Europe, North America, the Middle East, East Asia, South Asia, and Australia. From these data, average intakes of the various food parameters included in the DII were calculated. As an index of diet, the DII is representing the total dietary pattern. This allows for the overall inflammatory score of an individual's diet pattern to be quantified, and the overall scores in a cohort can be divided into different levels and analysed in relation to disease outcomes. In the DII, foods associated with positive influences on inflammatory markers – e.g., flavonoids and omega-3 fatty acids – are scored positively. Conversely, foods associated with negative influences on inflammatory markers – e.g., saturated fat and free sugars – are scored negatively. This is one of the great strengths of dietary indices: they are inherently adaptable to different dietary patterns. More particularly, the use of the DII as a standardised measurement instrument means that the same instrument may be applied across different studies, providing a level of consistency in measuring the exposure-outcome relationship of interest, i.e., DII and CVD or DII and cancer, which is rare for measurement instruments in nutritional epidemiology.

The Study

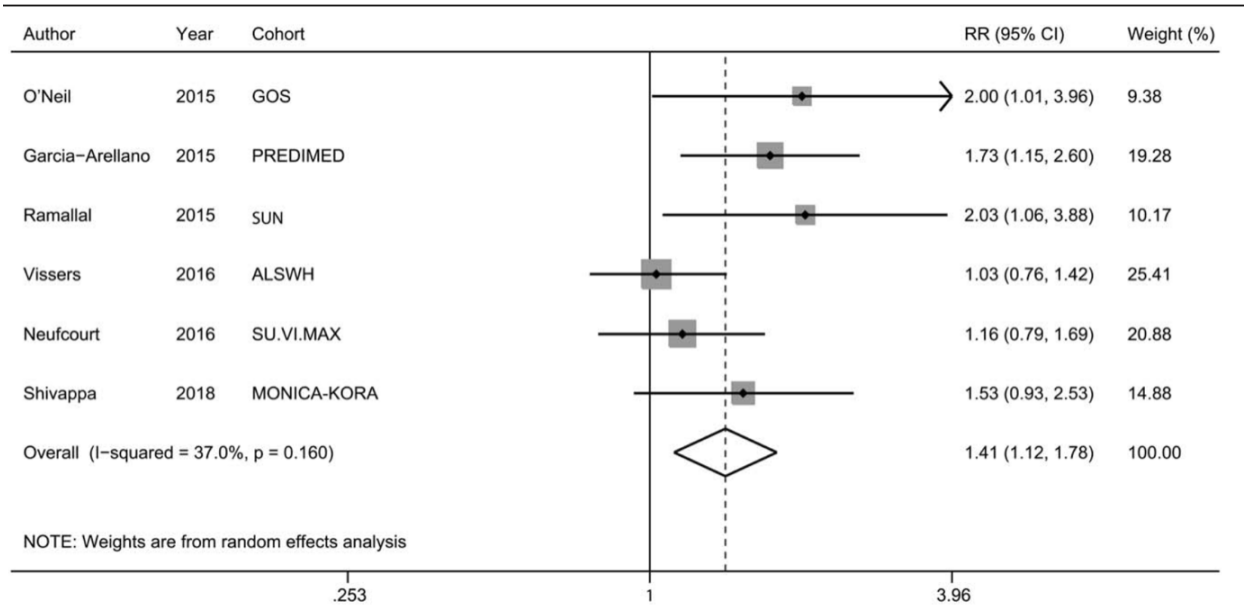
The present study was a meta-analysis of studies investigating the associations between the DII and CVD incidence and mortality. To be included in the meta-analysis, a study had to meet the following criteria:

- The DII was the exposure of interest;
- Risk of CVD events and/or CVD mortality was the outcome of interest;
- The study design was a prospective cohort or nested case-control study;
- Risk of the outcomes was reported as relative risk [RR] with accompanying 95% confidence intervals [95% CI].

The analysis compared the highest DII score against the lowest DII score, which was the reference category. Analyses were stratified by region, study quality, and number of cases of the outcomes, to see if these factors modified any associations.

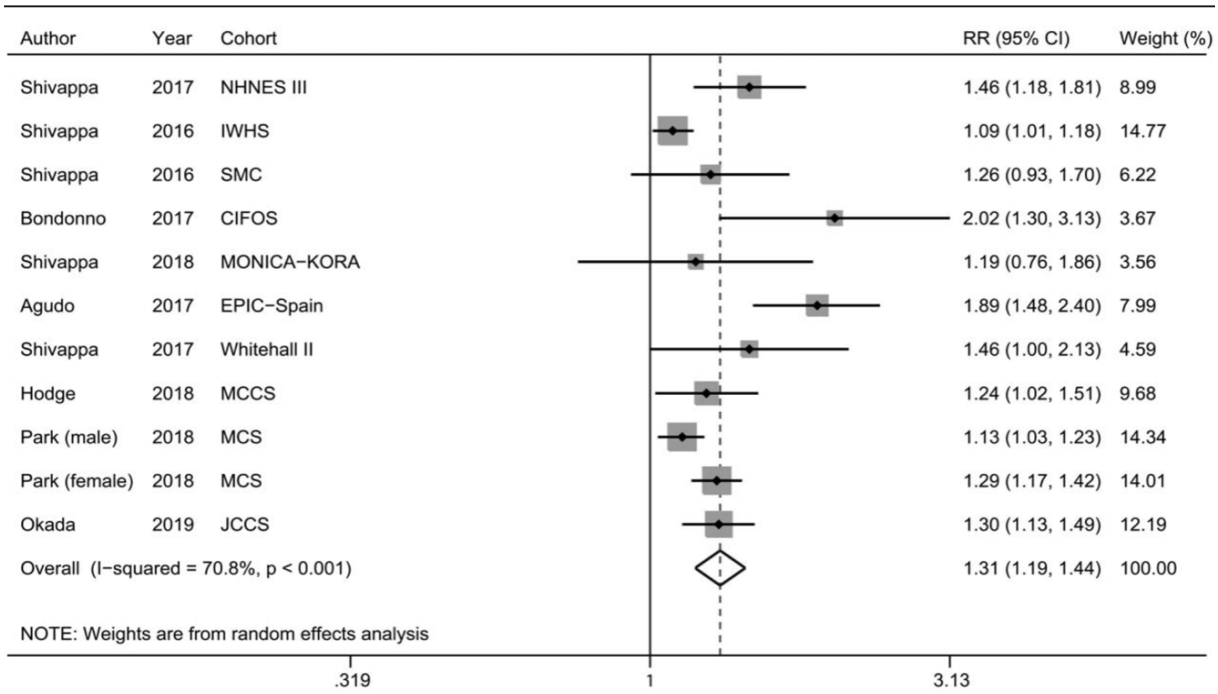
Results: 15 studies overall were included, of which nine studies reported on CVD mortality, 5 on CVD incidence [i.e., event risk], and 1 on both incidence and mortality. 3 studies were from America, 7 from Europe, 4 from Australia, and one from Asia.

- ***CVD Incidence*:** Compared to the lowest DII score, the highest DII scores were associated with a 41% [RR 1.41, 95% CI 1.12 – 1.78] increased risk for CVD events.



***Forest plot** from the paper showing the associations between high DII scores and CVD incidence. You can see that most studies showed a direction of effect toward increased risk. The I2 score of 37% would be considered moderate heterogeneity between studies.*

- ***CVD Mortality*:** Compared to the lowest DII score, the highest DII scores were associated with a 41% [RR 1.41, 95% CI 1.12 – 1.78] increased risk for CVD events.



***Forest plot** from the paper showing the associations between high DII scores and CVD incidence. You can see that most studies showed a direction of effect toward increased risk. The I2 score of 70.8% would be considered substantial heterogeneity between studies*

The Critical Breakdown

Pros: This study is the most up-to-date meta-analysis of this research question, and all included studies were published between 2015 and 2019. The quality of the included studies was assessed using the Newcastle-Ottawa Scale [NOS], which is a pragmatic 9-point scale grading tool to assess the quality of non-randomised trials included in a meta-analysis. Included studies had a NOS score of 7 or over, indicating good quality observational research. All studies used food-frequency questionnaires, and the same method to assess dietary inflammation, namely the DII, providing some degree of uniformity in the assessment of the exposure of interest.

Cons: To follow on the positive point about using the DII, however, not all included studies used the exact same food parameters to calculate their DII scores. While dietary indices tend to be flexible, if some studies used, for example, a 22-food parameter rather than 45-food parameter, this could result in meaningful differences in classification of diet and inflammation. The DII may be applied in any population, and so it will be useful in future research to see more representation from other populations and dietary patterns, while the current research only had one cohort from Japan [the remainder being Western countries]. There was also moderate to substantial heterogeneity across the included studies, seemingly due to the number of cases [which could mean smaller studies over-inflated the associations between DII and CVD]. Annoyingly, they don't actually state what "high" or "low" DII scores were in the primary included studies.

Key Characteristic

Detecting a signal in the noise can be challenging in nutritional epidemiology, where studies have used varying methodologies, designs, have varying sample sizes, and follow-up periods. The present study contained an overall sample size of 385,765 participants from the included primary studies, all of which were prospective cohorts [although they had case-control studies as an inclusion criterion, none were included]. And the shortest duration of follow-up was 13.5yrs, with a range of 13.5 up to 25.8yrs follow-up. On these levels, this study has several positive characteristics from an epidemiological quality perspective.

However, you'll note from the 'Con' above that the included studies did not calculate the DII scores from the exact same number of food parameters. When the DII is calculated from all 45-food parameters, the scores typically range from −8.87 to +7.98 [3,4]. For DII scores calculated from 25 to 30-food parameters, the range is from −5.5 to +5.5 [3,4]. In the present meta-analysis, all included studies used between 22-food parameters and 36-food parameters, and of the included studies did not report how many food parameters their calculation of the DII scores was based on. Thus, there is potential for the range of DII to have differed between studies, which may have influenced the final analysis. The authors are pretty scant on detail on this, which is a knock on an otherwise solid effort at a meta-analysis of prospective cohort studies.

Interesting Finding

Beware the small study effect! The importance of sample size and number of cases is illustrated in the present study. Recall that there was significant heterogeneity among the studies investigating CVD mortality. In investigating the source of that heterogeneity, the authors identified that number of cases was a potential source. So, let' s bring this concept to life so you can really see it.

Take a look at the table from the paper below; I've highlighted the name of the lead author on four studies, the number of participants in the study, and the number of cases [in this case, CVD deaths]. The Agudo et al. study is the largest at 41,199, but with only 722 cases. The other studies are much smaller cohorts and have 244-269 cases, but relative to their sample sizes a much greater proportion of participants have died compared to the Agudo et al. study.

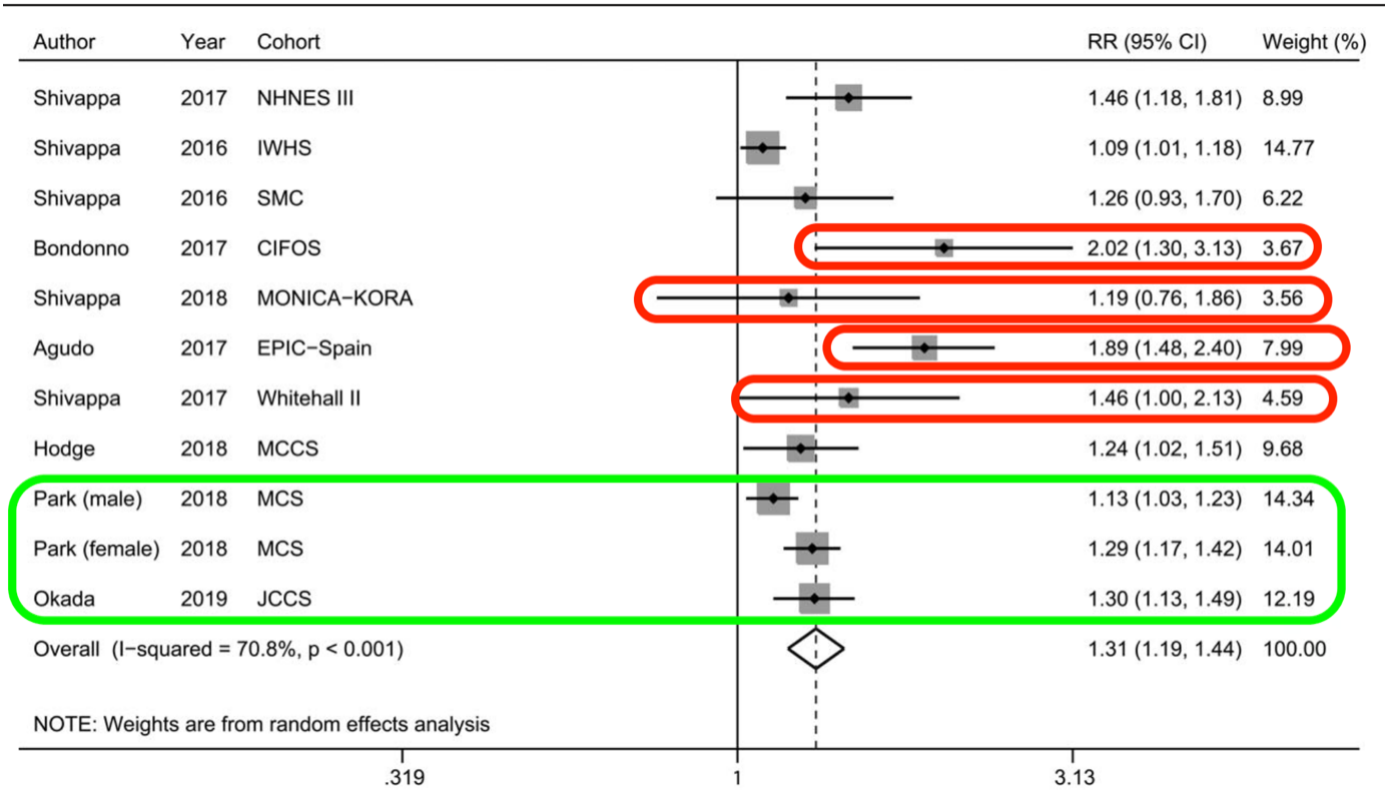
First author	Year	Region	Design	No. of Participants	No. of Cases
Shivappa	2017	USA	Cohort	12,366	1233
Shivappa	2016	USA	Cohort	37,525	6528
Shivappa	2016	Sweden	Cohort	33,747	2399
Bondonno	2017	Australia	Cohort	1304	269
Shivappa	2018	Germany	Cohort	1297	244
Agudo	2017	Spain	Cohort	41,199	722
Shivappa	2017	UK	Cohort	7627	264
Hodge	2018	Australia	Cohort	41,513	1040
Park	2018	USA	Cohort	150,405	16,212
Okada	2019	Japan	Cohort	58,782	3408

There are several potential implications for this combination of small sample size [for epidemiology!] and a low number of cases that is either low for the total sample or very high relative to a small sample size:

a) over-inflated effect sizes;

b) imprecise estimates of effect, i.e., wide confidence intervals.

Right, let' s have a look at these studies in the forest plot for the meta-analysis:



Because you' ve watched the Research Lecture on interpreting meta-analysis, you' ll see that each of these studies do not lend much statistical weight to the analysis: but added together they do comprise 19.81%. More importantly, look at the effect sizes in these studies, the Bondonno et al. relative risk is 2.02, unheard of for most nutrition exposures. And the Agudo et al. paper is 1.89, but a slightly more reliable direction of effect given the 95% CI of 1.48 to 2.40 [still not precise, but all way above 1.0]. The other papers, as you can see from the line through the box representing the study weight, are very imprecise.

Now, look at the difference when you look at the studies circled in green: the Park et al. paper is one study split by sex, and had a sample size of 150,405 participants in which 16,212 CVD deaths occurred. The Okada et al. study had a sample size of 58,782 participants and 3,408 CVD deaths. Collectively they comprise 40.54% of the statistical weight, but you' ll note that their overall relative risk is lower, and their estimate of effect more precise [narrow lines through the box for the 95% CI].

So, you can see from this example how the characteristics of the included studies can influence the outcomes. If we only had smaller studies available, we could come away thinking a high DII more than two-fold increases CVD death risk. The bigger studies, with more deaths, come to the rescue of the analysis and temper our findings, while still providing us with some confidence that high DII are scores are associated with quite a significant increase in CVD mortality.

Relevance

The present study updates the previous 2018 meta-analysis of the DII and CVD, which found a 36% [RR 1.36, 95% CI 1.19 – 1.57] increase in CVD incidence and mortality risk [5]. The present study indicates an increase in risk for CVD incidence and mortality in the magnitude of 30-40% from high DII scores, and this magnitude of risk appears to reflect the larger studies with more cases, as smaller studies may over-inflate the estimated effect of DII on CVD risk.

There is strong biological plausibility of the relationship between inflammation and CVD, evident in the relationship between CRP and LDL-C [2]. Inflammation acts as a strong modifier of effect on the processes of atherosclerosis, and is a consequence of injury in the artery from retention and oxidation of LDL-C [6,7]. Wider research shows the increasing DII scores correlate with CRP levels, particularly in men [8].

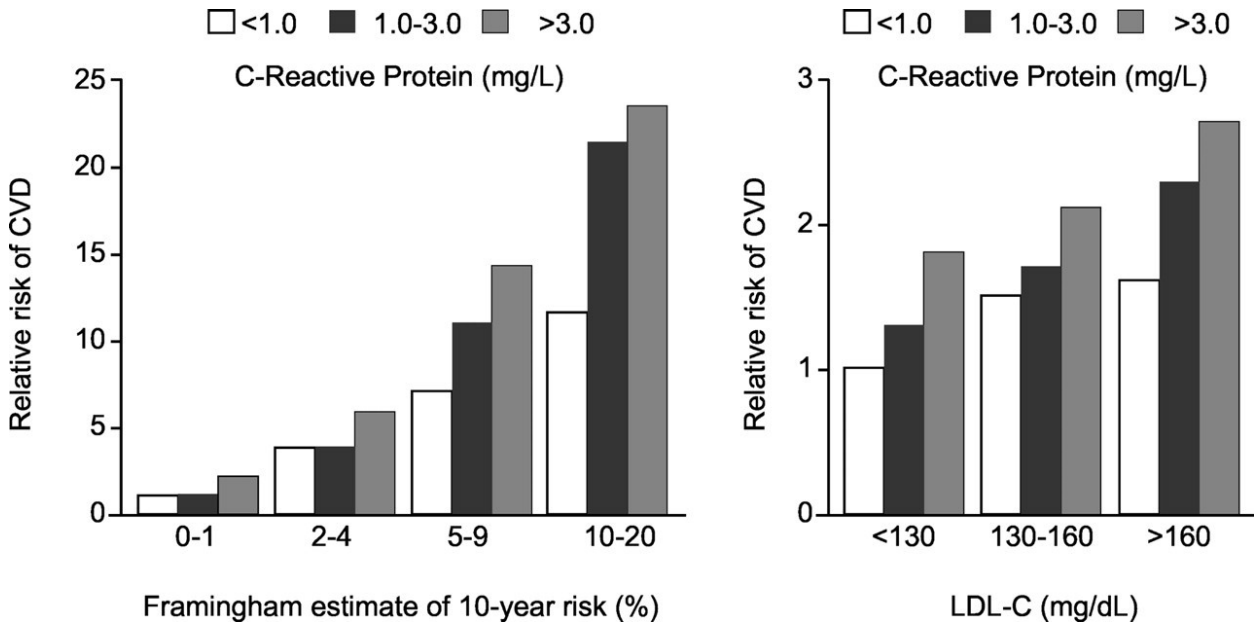


Figure *from [2], illustrating the relationship between CRP and CVD risk comparing <1.0mg/L CPR [generally a safe measure] to 1-3.0mg/L [>2.0mg/L is where significant increases in risk begin to be observed] and >3.0mgL [the Reaper beckons], and relative to LDL-cholesterol. You can see that at any given level of LDL-C, higher inflammation on top is associated with significantly greater risk of CVD.*

However, while the role of inflammation attracts a lot of the pushback for LDL-C, as we have discussed in this Exclusive Article, biomarkers of inflammation provide a general, systemic indicator for the physiological state of the body. They are highly important and informative for the total clinical picture, the level of risk in each individual, and the potential treatment options and targets available. Inflammation is therefore a systemic factor that influences CVD pathology, but is not causal in and of itself in the manner that LDL-C is.

Future research on the DII should look to conduct mediation analyses of the relationship between DII and CVD in relation to LDL-C. For now, however, we could surmise that high DII contributes to an ongoing state of low-grade, chronic inflammation, which modifies and accelerates the pathophysiology of CVD. An intervention based around the DII is overdue.

Application to Practice

One of the good things about nutrition is while the tools to investigate diet and disease must be sophisticated to capture such a complex exposure, building it back up into food-based recommendations is always simpler, thankfully. It is important to stress that with any index of diet, no conclusions may be made in relation to specific foods *per se*; it is the representation of a total dietary pattern, and at the level of isolated foods and nutrients the evidence for "pro-inflammatory" or "anti-inflammatory" effect is much more inconsistent [sorry, Dr. Hyman]. Nutrients like omega-3 fatty acids are the exception, rather than the norm. But broadly speaking, dietary patterns rich in polyphenols [flavonoids in particular], long-chain omega-3 fatty acids, olive oil [potentially related to polyphenols again!], and fibre, are associated with lower DII scores. Conversely high intakes of meat and sugar are associated with higher DII scores. This may not be rocket science.

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