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Keywords
Dietary fat guidelines · Systematic reviews/meta-analyses · Developing dietary guidelines

Abstract
This paper summarizes a debate on whether meta-analyses and systematic reviews are decisive in formulating guidelines for dietary fat. Held during the 12th congress of the International Society for the Study of Fatty Acids and Lipids in Stellenbosch, South Africa, September 7, 2016, the debate was hosted by the International Union of Nutritional Sciences and the International Expert Movement to Improve Dietary Fat Quality (IEM, www.theiem.org). Clemens von Schacky, Ludwig Maximilians-University, Munich, Germany, supported the statement, describing the types of weaknesses in individual studies and clinical trials. With examples of how to overcome such limitations, he concluded that nutritional guidelines on fat need a proper scientific basis in which randomized controlled trials (RCTs) with clinical endpoints and their meta-analyses are essential and decisive. In contention, Ingeborg Brouwer, Vrije Universiteit, Amsterdam, declared that recommendations on dietary fat intake should always be based on the totality of the evidence, including physiologic and biochemical knowledge and associations from observational epidemiology. RCTs and meta-analyses have their shortcomings, but well-conducted systematic reviews and meta-analyses support a transparent process for developing dietary fat guidelines. Participants agreed that evidence-based decision-making for dietary guidance should consider all the best available evidence using a transparent, systematic review.

Introduction and Proposition
To strengthen the scientific basis for dietary guidelines, the strongest types of evidence, such as meta-analyses and systematic reviews, well-designed, randomized, controlled trials (RCTs), and prospective cohort studies take precedence over weaker study designs, such as case-control and cross-sectional studies, opinions, and beliefs.
Difficulties arise when there are no RCTs, associations derived from observational studies are relatively weak or inconsistent, sample sizes are small and few studies exist. Further, the limitations of existing studies, which may be substantial, may be overlooked or minimized. Research needs for improving the evidence that supports dietary advice [1] and addresses the specific problems underlying dietary fat recommendations [2] have been identified.

Recent dietary fat guidelines have drawn withering criticism [3, 4]. The ensuing controversy and (mis)use of systematic reviews to bolster a particular position can restrain or obstruct the development of more effective public health policy [5]. Further, the “mass” production of systematic reviews and meta-analyses has reached “epidemic” proportions [6], suggesting that many are redundant, flawed, or conflicted. This raises the concern that systematic reviews may be at risk of corruption [7]. Given the importance of well conducted meta-analyses and systematic reviews in the hierarchy of scientific evidence and development of dietary guidelines, the question of whether such evidence is decisive in formulating dietary fat guidelines was forcefully contested at the 2016 congress of the International Society for the Study of Fatty Acids and Lipids (ISSFAL), Stellenbosch, South Africa, September 7, 2016. The debate was held under the auspices of the International Union of Nutritional Sciences and the International Expert Movement to Improve Dietary Fat Quality (IEM, www.theiem.org). Berthold Koletzko, Ludwig-Maximilians-University, Munich, Germany, moderated the exchange. This paper describes that forum.

**Proposition Support**

Supporting the proposition, Clemens von Schacky of Ludwig Maximilians-University, Munich, Germany, examined the evidence for the current dietary recommendations of the European Society of Cardiology and other Societies on Cardiovascular Disease Prevention in Clinical Practice [8]. One by one, von Schacky marshaled examples of the weaknesses in existing data: inability to accurately assess dietary intake in population samples [9], changes in surrogate risk markers that do not affect clinical outcomes or mortality [10, 11], insufficient evidence that omega-6 (n-6) fatty acid consumption affects clinical endpoints in cardiovascular disease (CVD) [12], and participant or response variability [13] that can obscure differences in outcomes [14]. He particularly highlighted the unexpected lack of association in Europe between intake of trans-fatty acids and increased risk of CVD mortality [15]. Taken together, weaknesses in diet assessment, surrogate endpoints, incomplete data, variabilities in participants and responses, and traditionally held beliefs conspire to weaken the scientific basis of current dietary guidelines. Moreover, many intervention trials in nutrition are not powered for clinical endpoints, and systematic reviews and meta-analyses of such trials must fill this gap. Therefore, systematic reviews and meta-analyses strengthen the scientific basis of dietary guidelines.

Drawing on methodological weaknesses in studies of long-chain omega-3 polyunsaturated fatty acids (n-3 LCPUFA) and CVD risk, von Schacky noted that failure to consider participant baseline levels of these PUFA may mask clinical effects [16]. Providing n-3 LCPUFA in a low-fat meal will also decrease their bioavailability, compromising the dose estimates [17].

Von Schacky pointed out that the common advice to eat 1–2 fish meals/week, one of which should be oily fish [18], is not supported by RCT data, but is by prospective cohort studies [19, 20] and remains a current European Society of Cardiology recommendation [8]. Von Schacky observed that the guideline is contradictory in itself by ascribing the protective effect of fish to its oil, but recommending non-oily fish, which undermines the protective effect of fish oil [8]. In his opinion, this confusion goes back to methodological issues of the original trials that are frequently incorporated uncritically into meta-analyses.

Shifting to solutions, von Schacky noted several ways to avoid many of the limitations cited in the n-3 LCPUFA studies. For example, higher doses of these PUFA compared with background levels are more likely to reveal positive outcomes if they exist [21, 22]. Selecting participants with low baseline levels of n-3 LCPUFA is important for detecting treatment effects [23] and implementing clinical conditions where fatty acid bioavailability is increased, such as during a high-fat meal, thus enhancing the likelihood that the dose given will be bioavailable [17]. Moreover, meta-analyses need expertise in the methodological issues of trials with n-3 fatty acids, and a critical approach toward these trials. Ensuring that systematic reviews and meta-analyses adhere to established standards [24, 25] and preferred reporting methods [26, 27] will lead to higher quality systematic reviews of nutritional studies.

In conclusion, von Schacky asserted that the nutritional guidelines on fat need a proper scientific basis in which RCTs with clinical and other endpoints and their meta-analyses are essential and decisive.
Proposition Contention

Contending that systematic reviews and meta-analyses are not necessarily decisive, Ingeborg Brouwer, Vrije Universiteit, Amsterdam, declared that strong recommendations on dietary fat intake should always be based on the totality of the evidence. That includes physiologic and biochemical knowledge and associations in observational epidemiology. Why should we not just use the rules for evidence-based medicine? The answer is that nutrition does not equal medicine. It concerns everyone, as everyone eats. Nutrition is more complex than medicine as nutrients are inter-related, food is changing, and food habits shift.

Discussing dietary fat means that changing one dietary macronutrient that provides energy also entails changing another – its replacement – and maintaining energy balance. One problem is that we do not have a placebo because the placebo itself would provide energy and might have its own effects. Instead, macronutrient exchange studies use a control treatment. Thus, dietary studies on fat are exceedingly complex. Consider RCTs. In spite of their vaunted esteem, RCTs are not the Holy Grail in nutrition. Their limitations include no clear exchange of macronutrients, short duration, participant compliance issues, poor measures or control of dietary intake or composition, and their detachment from real life.

Meta-analyses too have their shortfalls. Statistics are the basis for meta-analysis. Background knowledge of the topic is not required to perform a meta-analysis, but without it, inappropriate trials may be included. In one noteworthy example, a Cochrane meta-analysis on n-6 PUFA for the primary prevention of CVD [12], none of the included RCTs reported CVD clinical events and 1 of the 3 RCTs, accounting for 73% of the observations, reported supplementation with conjugated linoleic acid [28], which is not an n-6 PUFA. Such analyses, while not common, indicate that experts with knowledge of the topic should be the ones who conduct and interpret meta-analyses on dietary studies.

Further undermining meta-analyses as the apex of dietary data reviews are examples of dietary recommendations without evidence from clinical trials. Brouwer cited trans-fatty acids as an example where dietary recommendations are based on evidence with only intermediate endpoints [29, 30]. Another is obesity. As there are no good trials showing how to prevent obesity, does that mean we do not give any advice? We must use the best available evidence to provide the advice people deserve, in spite of the challenges for developing effective obesity strategies [31] and policy [32].

What, then, is the role for meta-analyses? Brouwer suggested that well-conducted meta-analyses and systematic reviews are very helpful to support a transparent process for developing dietary fat guidelines, but the process must consider all the available evidence.

Discussion Highlights

ISSFAL chair, Marius Smuts, North-West University, Potchefstroom, South Africa, asked whether the evidence on individual SAFA should be translated into a food-based approach. Von Schacky replied that data from the meeting and other work indicated that only palmitic acid had a negative effect on CHD risk [33] and CVD prognosis.

We need to ask the right question in order to understand what meta-analyses should decide. Brouwer agreed, observing also that meta-analyses are only as good as the studies that go into them. If the studies are flawed, then the results will be flawed.

The moderator noted that meta-analyses on SAFA give different answers depending on what question is asked. If you just look at dietary SAFA, they do not seem to matter [34]. But if you ask what nutrients replace them, you reach different conclusions [35]. A debater replied that in discussing energy, you cannot say SAFA are doing this or unsaturated fats are doing that. You can only say this replaced by that is giving “X” result. You always have to make a comparison.

The moderator asked whether you could develop a new guideline without a systematic review of the available studies. Brouwer replied that you could do it, but that approach would not be a transparent process. A good meta-analysis can make the process of formulating dietary guidelines more transparent.

A participant observed that in guideline development, evidence carries the same weight as chemical decision-making or expert opinion or biological insight and other factors such as the environment. That means evidence is necessary, but is not sufficient for making good decisions. Von Schacky noted that even the Cochrane meta-analyses only consider how the trial was designed, not how it was conducted. You can have a beautiful trial, conduct it miserably, and obtain worthless results, but you still have a Cochrane analysis as Brouwer cited [12]. We still need meta-analyses as a decisive element in forming dietary guidelines.

Another commented that we do not eat single fatty acids – we eat them combined in fats and oils. If you replace
one fatty acid with another, how can you solve the replacement question with RCTs? Von Schacky commented that we cannot solve every question with RCTs, but we can examine one aspect and then subject that to an RCT. Brouwer added that you can look at individual fatty acids in RCTs in the short-term, but when you know what to give and exchange, it becomes extremely complicated, if not impossible, in the long-term.

As all guidelines advise increasing PUFA intake, which type should one take? Some consider increasing only n-6 PUFA risky for CVD [36], while others have observed no adverse effects [37] or reported significantly lower CVD risk or mortality [35, 38]. Inclusion of both n-6 and n-3 PUFA consumption may be associated with the lowest risk of CVD mortality [39]. Dietary advice must include the full package of food-based guidelines, not just 1 or 2 fatty acids.

Another participant questioned whether any dietary recommendations have made a difference to the totality of public health. Von Schacky responded that from a cardiologist’s perspective, the treatment forms in cardiology, which are based on guidelines derived from controlled clinical trials, have improved the worldwide standard of care tremendously. The principle of dietary recommendations is a good one, but implementation is a huge problem. That does not mean that the guidelines themselves are not a good idea. Brouwer agreed, citing the project in North Karelia, Finland, where significant reductions in serum cholesterol were achieved largely through the reduction of dietary SAFA and increased PUFA intake [40]. Although SAFA intakes increased from 2007 to 2012 [41], 40-year CHD mortality among men of age 35–64 years declined by 82% and among women fell by 84% [42].

Conclusions

Von Schacky asserted that devising dietary guidelines has to be a transparent process that lists the evidence used, including RCTs and meta-analyses. These documents are decisive because they put together all the clinical and biomarker evidence and give a bird’s eye view of the problem being considered. Brouwer maintained that the totality of clinical, biomarker, biochemical, and physiological evidence has to be taken into account and that background knowledge is required to translate science into dietary guidelines. She urged that in the future we not only take into account our present health, but also remember that we will have to feed up to 10 billion people and take care of future generations and the planet. Striking a balance, the moderator proposed that evidence-based decision-making for any guidance, nutrition or otherwise, consider all the best available evidence and that guidelines be developed using a transparent systematic review. Where no RCTs or meta-analyses are available, as in the case of smoking, we must use the best of the available evidence.

Disclosure Statement

Financial assistance for this publication was provided to J.A.N; travel funds to attend the ISSFAL meeting and honoraria were provided to C.S., I.A.B., and B.K. or their institutions from an unrestricted educational grant from Unilever NV, under the auspices of the International Union of Nutritional Sciences and the International Expert Movement to Improve Dietary Fat Quality (IEM, www.theiem.org).

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