Results of the WHO public consultation on the scope of the guideline on polyunsaturated fatty acid intake

Comments were received from the following individuals and organizations

Government agencies

Hanna Eneroth	National Food Agency, Sweden
Jacinta Holdway	Australian Government Department of Health
Chantal Martineau	Health Canada
Rusidah Selemat	Nutrition Division, Ministry of Health, Malaysia

Nongovernmental and consumer organizations and associations

Asha Mettla	L V Prasad Eye Institute, India
Robert Rankin	Calorie Control Council, USA

Private sector (including industry organizations and associations)

Angelika De Bree	Unilever, Netherlands
Nathalie Lecocq	FEDIOL, Belgium
Harry Rice	Global Organization for EPA and DHA Omega-3s, USA
Anne Roulin	Nestlé, Switzerland
Laurence Rycken	International Dairy Federation, Belgium

Academic/research

William Harris	University South Dakota School of Medicine and OmegaQuant Analytics, LLC, USA
Ifeoma Uzoamaka Onoja	University of Nigeria Teaching Hospital, Nigeria
Pankaj Shah	SRMC & RI, SRU, India
Rob te Biesebeke	Tp Institute Food & Nutrition, Switzerland

Full comments on polyunsaturated fatty acids

(alphabetical by contributor)

1. Angelika De Bree

Unilever, Netherlands

Comments

Total PUFAs

Populations

Include adults with prior type 2 diabetes. Having diabetes confers a 2-fold risk for CHD and other cardiovascular complications, and is a major risk factor that is modifiable by diet and lifestyle (ref: Sattar N. Revisiting the links between glycaemia, diabetes and cardiovascular disease. Diabetologia 2013 Apr;56(4):686-95.)

Also consider to include adults with high levels of established CVD risk factors, such as plasma cholesterol and blood pressure.

Interventions

We recommend to make 'replacement' the primary intervention and to consider reports on high vs low intake in subgroup analyses. PUFA is a significant contributor to total energy intake, and there is increasing consensus that relations of a macronutrient (such as PUFA) with a certain health outcome (such as CVD) should be interpreted in comparison to another specific macronutrient that replaces the calories from the macronutrient under study (PUFA) . (Refs: Jakobsen MU, O'Reilly EJ, Heitmann BL, Pereira MA, Bälter K, Fraser GE, et al. Major types of dietary fat and risk of coronary heart disease: A pooled analysis of 11 cohort studies. American Journal of Clinical Nutrition 2009;89(5):1425-32. Siri-Tarino, P. W., Q. Sun, F. B. Hu, and R. M. Krauss. 2010. 'Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease', Am J Clin Nutr, 91: 535-46. Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. American Journal of Clinical Nutrition 1997;65(4 SUPPL.):1220S-8S)

Comparators

See our comment at Interventions.

We recommend to include both total amount and quality of carbohydrates in the replacement analyses.

Outcomes

We want to emphasize that the threshold of critical vs important outcomes is conservative as effects on CVD are established, and limited to CHD related outcomes only. The focus on these as critical outcomes does not give sufficient room for the impact of evaluation of more recent developments.

In particular, diabetes is an emerging disease, with increasing public health impact. We question whether this is sufficiently reflected in the current ratings and thresholds.

Additional Comments

No comments provided.

n-6 PUFAs

Populations

Include adults with prior type 2 diabetes. Having diabetes confers a 2-fold risk for CHD and other cardiovascular complications, and is a major risk factor that is modifiable by diet and lifestyle.

Also consider to include adults with high levels of established CVD risk factors, such as plasma cholesterol and blood pressure.

Interventions

We recommend to make 'replacement' the primary intervention and to consider reports on high vs low intake in subgroup analyses. PUFA is a significant contributor to total energy intake, and there is increasing consensus that relations of a macronutrient (such as PUFA) with a certain health outcome (such as CVD) should be interpreted in comparison to another specific macronutrient that replaces the calories from the macronutrient under study (PUFA).

The rationale for the chosen threshold levels is not clear. The most recent FAO/WHO expert consultation has set a threshold intake of 9% EI for linoleic acid/omega-6 PUFA (ref:FAO/WHO 2010. Fats and fatty acids in human nutrition. Report of an expert consultation. (FAO: Rome).

We recommend to distinguish between linoleic acid (LA) and arachidonic acid (AA) for infants. Proportions of LA in blood and adipose tissue are established biomarkers of dietary intake (ref: Hodson L, Skeaff CM, Fielding BA (2008) Fatty acid composition of adipose tissue and blood in humans and its use as a biomarker of dietary intake. Prog Lipid Res 47, 348-380). We recommend to include a subgroup analysis on the dose-response effect of LA in blood and adipose tissue.

Comparators

See our comment at Interventions.

We recommend to include both total amount and quality of carbohydrates in the replacement analyses.

Outcomes

We want to emphasize that the threshold of critical vs important outcomes is conservative as effects on CVD are established, and limited to CHD related outcomes only. The focus on these as critical outcomes does not give sufficient room for the impact of evaluation of more recent developments. In particular, diabetes is an emerging disease, with increasing public health impact. We question whether this is sufficiently reflected in the current ratings and thresholds.

The most recent FAO/WHO expert consultation concluded that there is no rationale for a specific recommendation for the omega-6/omega-3 ratio if intakes of omega-6 and omega-3 fatty acids lie within the recommendations. As the omega-6/omega-3 ratio continues to be supported (refs: Wood KE, Mantzioris E, Gibson RA, Ramsden CE, Muhlhausler BS. The effect of modifying dietary LA and ALA intakes on omega-3 long chain polyunsaturated fatty acid (n-3 LCPUFA) status in human adults: a systematic review and commentary. PLEFA. 2015;95:47-55; Simopoulos AP & DiNicolantonio JJ. The importance of a balanced ω-6 to ω-3 ratio in the prevention and management of obesity. Open Heart. 2016;3:e000385), it would be informative if the WHO committee updates its view on the omega-6/omega-3 ratio.

n-3 PUFAs

Populations

Include adults with prior type 2 diabetes. Having diabetes confers a 2-fold risk for CHD and other cardiovascular complications, and is a major risk factor that is modifiable by diet and lifestyle.

Also consider to include adults with high levels of established CVD risk factors, such as plasma cholesterol and blood pressure

Interventions

Proportions of EPA and DHA in blood and adipose tissue are established as biomarkers of dietary intake. We recommend to include a subgroup analysis on the dose-response effect of EPA and DHA in blood and adipose tissue.

Comparators

No comments provided.

Outcomes

No comments provided.

Additional Comments

The most recent FAO/WHO expert consultation concluded that there is no rationale for a specific recommendation for the omega-6/omega-3 ratio if intakes of omega-6 and omega-3 fatty acids lie within the recommendations. As the omega-6/omega-3 ratio continues to be supported, it would be informative if the WHO committee updates its view on the omega-6/omega-3 ratio.

Alpha-linolenic acid

Populations

Include adults with prior type 2 diabetes. Having diabetes confers a 2-fold risk for CHD and other cardiovascular complications, and is a major risk factor that is modifiable by diet and lifestyle.

Also consider to include adults with high levels of established CVD risk factors, such as plasma

cholesterol and blood pressure.

Interventions

Proportions of ALA in blood and adipose tissue are established as biomarkers of dietary intake. We recommend to include a subgroup analysis on the dose-response effect of ALA in blood and adipose tissue.

Comparators

No comments provided.

Outcomes

No comments provided.

Additional Comments

No comments provided.

Additional comments (covering all topics)

Many thanks for this opportunity to input into the consultation.

2. Hanna Eneroth

National Food Agency, Sweden

Comments

Total PUFAs

Populations

No comments provided.

Interventions

For infants 0-2 y only the suggested question will be probably be impossible to answer due to lack of data.

Comparators

No comments provided.

Outcomes

No comments provided.

Additional Comments

The approach seems to be to start with the current recommendations as thresholds. Would it be possible to instead investigate the health effects of PUFA and then evaluate by dose-response where the threshold (future recommendation) should be?

n-6 PUFAs

Populations

No comments provided.

Interventions

What is the reasons for including linoleic acid only?

What is the reasons for questions differing in terms of including dietary supplements or not?

Comparators

No comments provided.

Outcomes

No comments provided.

Additional Comments

No comments provided.

n-3 PUFAs

Populations

No comments provided.

Interventions

No comments provided.

Comparators

It would be interesting to compare low levels of omega 3 long chain PUFA (with or without supplements)

Outcomes

No comments provided.

Additional Comments

No comments provided.

Alpha-linolenic acid

Populations

No comments provided.

Interventions

What is the reasons for including ALA only? What about total n3 PUFA?

What is the reasons for questions differing in terms of including dietary supplements or not

Comparators

No comments provided.

Outcomes

No comments provided.

Additional Comments

No comments provided.

3. William Harris

University of South Dakota School of Med and OmegaQuant Analytics, LLC, USA

Comments

Total PUFAs

Populations

No comments provided.

Interventions

No comments provided.

Comparators

No comments provided.

Outcomes

No comments provided.

Additional Comments

No comments provided.

n-6 PUFAs

Populations

No comments provided.

Interventions

No comments provided.

Comparators

No comments provided.

Outcomes

No comments provided.

Additional Comments

No comments provided.

n-3 PUFAs

Populations

If "children >2" includes adolescents and teen agers, that's fine... but I would hope evidence for

benefits in school age kids not be ignored.

Interventions

I would recommend that in addition to "intakes" as exposures, an entire parallel section on

"circulating biomarkers" as exposures be added to this analysis. There are many studies linking blood

omega-3 levels with major clinical outcomes and I don't see a place for them to be considered. In

addition, there will be few to no studies where EPA and DHA intentionally replaced Sat or Mono... almost all the studies of interest (for interventions) will be simply n3s added to the diet as supplements. Is there a category for THAT?

Comparators

It appears that my comment above about n3's not replacing anything is sort of considered in the Comparators section. I'm surprised that something like "vegetable oil" (capsules) are not considered as comparators since they are usually the placebos in n3 trials.

Outcomes

I'm not sure it makes much difference in your analysis, but a lot of people would move cognition up the list considerably since we have therapies for CHD that work rather well but we have nothing for the scariest disease of all - losing your mind.

Additional Comments

I hope that when you consider the 4-5 most recent RCTs with n-3 LCPUFAs you also read the many papers that have been written that are critical of the designs of these studies and take that into account. It's hard, with <1 g/d x 2 years in patients in their mid 60s taking multiple other CHD drugs and consuming higher than used-to-be amounts of n3 LCPUFAs to show a benefit.

Alpha-linolenic acid

Populations

No comments provided.

Interventions

No comments provided.

Comparators

No comments provided.

Outcomes

No comments provided.

Additional Comments

I would recommend that in addition to "intakes" as exposures, an entire parallel section on "circulating biomarkers" as exposures be added to this analysis. There are many studies linking blood omega-3 levels with major clinical outcomes and I don't see a place for them to be considered.

4. Jacinta Holdway

Australian Government Department of Health, Australia

Total PUFAs

Populations

No comments provided.

Interventions

No comments provided

Comparators

No comments provided.

Outcomes

No comments provided.

Additional Comments

No comments provided.

n-6 PUFAs

Populations

No comments provided.

Interventions

No comments provided

Comparators

No comments provided.

Outcomes

No comments provided.

Additional Comments

No comments provided.

n-3 PUFAs

Populations

No comments provided.

Interventions

No comments provided.

Comparators

No comments provided.

Outcomes

No comments provided.

Additional Comments

No comments provided.

Alpha-linolenic acid

Populations

No comments provided.

Interventions

No comments provided

Comparators

No comments provided.

Outcomes

No comments provided.

Additional Comments

No comments provided.

Additional comments (covering all topics)

Australia considers the PICOs developed by WHO to be very comprehensive. We are supportive of the GRADE approach being implemented.

5. Natalie Lecocq
FEDIOL, Belgium

5. Natalie Lecocq
FEDIOL, Belgium

Comments

Total PUFAs
Populations

Consider aligning population definitions with those used by Codex (infants and young children = 0-36 months; children >3 years)

Interventions

No comments provided

Comparators

No comments provided.

Outcomes

No comments provided.

Additional Comments

No comments provided.

n-6 PUFAs
Populations

Consider aligning population definitions with those used by Codex (infants and young children = 0-36 months; children >3 years)

Interventions

Particularly for infants and young children, limiting to only linoleic acid is not sufficient. Arachidonic Acid (ARA) should be considered. Suggest adding "What is the effect of consuming ARA at or above 0.3% of total fatty acids (Total FA) compared to consuming ARA below the threshold (0.3% Total FA).

Comparators

No comments provided.

Outcomes

No comments provided.

Additional Comments

The n-6 category should be identified with specificity. More specifically, it would be better to identify as n-6 PUFA (linoleic acid and arachidonic acid), particularly since ALA is not listed in the questions below as n-3 PUFA only, but separately as ALA. As n-3 PUFA comprises not only ALA but also other long chain PUFA, this would ensure further coherence.

n-3 PUFAs

Populations

Consider aligning population definitions with those used by Codex (infants and young children = 0-36 months; children >3 years)

Interventions

When exploring effect(s) of DHA for pregnant women, consider looking at both algal DHA and DHA-rich fish oil supplementation. See Agency for Healthcare Research and Quality (AHRQ) report entitled "Omega-3 Fatty Acids and Maternal and Child Health: An Updated Systematic Review". Here's the link http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2321

10 mg/kg/day is inconsistent with the expression of n-3 LCPUFA in most studies and it is inconsistent with the units used by Codex. Suggestion: Include 0.3% n-3 LCPUFA, as %FA currently being discussed by CCNFSDU. Also, similar to what was done by the Agency for Healthcare Research and Quality in "Omega-3 Fatty Acids and Maternal and Child Health: An Updated Systematic Review" (http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2321), specifically explore DHA vs DHA+EPA.

Under "In addition, for pregnant women only", supplements are specifically excluded. We highly encourage you to include supplements and explore the benefits of omega-3s (both EPA+DHA and DHA alone)

For "Adults" and the intervention of "dementia", we suggest comparing lower DHA doses (<900-1000 mg/day) to higher DHA doses (>900-1000 mg/day). An informal evaluation of the scientific literature demonstrated cognitive benefits above a certain threshold.

For "Adults with prior event or disease" and the intervention of "dementia", we suggest comparing lower DHA doses (<900-1000 mg/day) to higher DHA doses (>900-1000 mg/day). An informal evaluation of the scientific literature has demonstrated cognitive benefits above a certain threshold.

It appears that only intervention trials are being considered? This seems very limiting, since a large body of scientific evidence is available from observational studies.

In addition to threshold levels, it may be appropriate to consider quintiles of intake.

Comparators

n-3 long-chain PUFA should be broken down into individual fatty acids. Specific to the request from the CCNFSDU, EPA+DHA should be considered. In addition, it's worth considering the effect(s) of EPA alone and DHA alone.

The general concept of competing action of n-6 vs n-3 fatty acids is being discussed frequently by scientists, so consideration should be given to looking at the n-6 to n-3 ratio.

Outcomes

For "Adults", "Neurocognition (includes dementia)" we suggest separating out "dementia"

For "Adults with prior event or disease", "Neurocognition (includes dementia), suggest separating out "dementia"

For "Adults", suggest including an additional outcome of "blood pressure"

For "Adults with prior event or disease", suggest including an additional outcome of "blood pressure"

For "Adults", suggest including an additional outcome of "cardiac/coronary mortality" in order to review the literature without vascular events

For "Adults with prior event or disease", suggest including an additional outcome of "cardiac/coronary mortality" in order to review the literature without vascular events

For "Pregnant women", in addition to "Gestation/preterm", suggest including "early preterm"

For "Pregnant women", "Neurocognition (Includes vision, IQ later in life) (infant)", the outcomes should be considered separately, particularly since vision should not be included under "Neurocognition"

For "Infants (0-2 yrs)", "Neurocognition (Includes vision, IQ later in life) (infant)", the outcomes should be considered separately, particularly since vision should not be included under "Neurocognition"

For "Children (> 2 yrs)", "Neurocognition (Includes vision, IQ later in life)", the outcomes should be considered separately, particularly since vision should not be included under "Neurocognition"

Additional Comments

Consider specifying individual fatty acids. FAO Food and Nutrition Paper 91 (Fats and fatty acids in human nutrition: Report of an expert consultation) noted "the need to focus on the roles of individual fatty acids and how requirements vary with age and physiological status" and "recognized that individual fatty acids within each broad classification of fatty acids may have unique biological properties and health effects."

Alpha-linolenic acid
Populations

Consider aligning population definitions with those used by Codex (infants and young children = 0-36 months; children >3 years)

Interventions

Thresholds for ALA in infant and child nutrition have been identified and should be considered. Suggestion: Add question related to intake above and below ALA threshold as specified in current Codex Infant Formula Standard/Follow-Up Formula Standard Revisions.

Comparators

No comments provided.

Outcomes

No comments provided.

Additional Comments

No comments provided.

6. Chantal Martineau
Health Canada, Canada

Total PUFAs
Populations

No comments provided.

Interventions

No comments provided.

Comparators

No comments provided.

Outcomes

No comments provided.

Additional Comments

No comments provided.

n-6 PUFAs
Populations

No comments provided.

Interventions

No comments provided.

Comparators

Macronutrients to which n-6 PUFA are compared:

1.1 Suggestion: perform a sub-group analysis for replacement of carbohydrates by n-6 PUFA.

The current proposal suggests doing a sub-group analysis for SFA and another one for MUFA. We know that the effects of the different types of fatty acids vary depending on the comparator. Although comparing n-6 PUFA to other fatty acid classes (such as SFA and MUFA) makes sense, there is also an important body of evidence of comparisons with carbohydrates (low-fat diets). Given that information will likely be collected from this evidence (comparison with carbohydrates), it would make sense to do a sub-group analysis for replacement of carbohydrates by n-6 PUFA in addition with the other sub-group analyses currently proposed. This approach would be consistent with the recent WHO-mandated meta-analysis by Mensink of the effects of SAFA on blood lipids in which the comparison with carbohydrates was taken into account.

1.2 Suggestion: perform a sub-group analysis for replacement of unspecified nutrients by n-6 PUFA

In some studies of low vs. high PUFA intake, calories from PUFA replace calories from unspecified nutrients. This can affect the outcomes and make them more difficult to interpret, as the subgroup of studies in which the replacement macronutrient is not specified is likely not homogenous (it may comprise different replacement macronutrients). Therefore, it would be appropriate to also perform a subgroup analysis with studies in which the replacement macronutrient was not specified, to help interpreting the outcomes of the overall meta-analysis.

2. Evidence from studies of modification of cardiometabolic disease risk markers could be included as supporting evidence

From the current proposal, it seems that the surrogate/established risk markers of cardiometabolic disease risk will not be included (only the hard endpoints). This approach is acceptable, but if the resources are available, I would suggest including also studies of established risk markers as supporting evidence. For cardiovascular diseases, the effects on blood lipids have been addressed in in the WHO-mandated meta-analysis of Mensink on the effects of (saturated) fats on blood lipids (the replacement of SAFA, MUFA, and Cabohydrates by PUFA is reported). For stroke, the effects of higher vs. lower PUFA intake on blood pressure could be considered. And for diabetes, not only diabetes per se, but effects on (fasting) blood glucose and on insulin concentrations, hemoglobin A1c concentrations as well as insulin resistance (for e.g. the index HOMA-IR) could be considered.

Outcomes

Specify more precisely the outcomes of coronary heart disease and stroke (events and mortality?) In the current proposal, cardiovascular mortality and events will be reported. Coronary heart disease and stroke are both comprised in the overall 'cardiovascular' outcomes, but will also be looked at separately, which is relevant. However, it is not clear whether 'events' and/or 'mortality' will be recorded for these two pathologies. This should be clearly defined in the analysis plan. Both CHD mortality and event would be relevant, and the same for stroke.

Additional Comments

No comments provided.

n-3 PUFAs
Populations

No comments provided.

Interventions

No comments provided.

Comparators

No comments provided.

Outcomes

No comments provided.

Additional Comments

No comments provided.

Alpha-linolenic acid

Populations

No comments provided.

Interventions

No comments provided.

Comparators

No comments provided.

Outcomes

No comments provided.

Additional Comments

No comments provided.

7. Asha Mettla

L V Prasad EyeInstitute, India

Comments

Total PUFAs
Populations

Adolescent girls -–intake of carbohydrates since the consumption during puberty and adolescence may have an impact

Interventions

A comparator study between male and female population may be useful to understand as part of the intervention

Comparators

No comments provided.

Outcomes

No comments provided.

Additional Comments

No comments provided.

n-6 PUFAs
Populations

No comments provided.

Interventions

No comments provided

Comparators

No comments provided.

Outcomes

No comments provided.

Additional Comments

No comments provided.

n-3 PUFAs
Populations

No comments provided.

Interventions

No comments provided.

Comparators

No comments provided.

Outcomes

No comments provided.

Additional Comments

No comments provided.

Alpha-linolenic acid

Populations

No comments provided.

Interventions

No comments provided

Comparators

No comments provided.

Outcomes

No comments provided.

Additional Comments

No comments provided.

8. Ifeoma Uzoamaka Onoja

University of Nigeria Teaching Hospital, Nigeria

Comments

Total PUFAs

Populations

All listed populations should be evaluated.

Interventions

Benefits of intake of total polyunsaturated fatty acid (PUFA) should be considered .

Does consumption above the threhold have any effect on immune response and bleeding time.

Does it have effect in physiologic and health outcome of infants especially in chronic diseases as fat

is the single major source of energy.

Comparators

Consumption at lower level.

Outcomes

improves neurocognition, reduces depression and improves adiposity.

Additional Comments

No comments provided.

n-6 PUFAs

Populations

all listed populations are important.

Interventions

Benefits of intake of n-6 polyunsaturated fatty acid (PUFA) should be considered .

Does consumption above the threhold have any effect on immune response and bleeding time.

Does it have effect in physiologic and health outcome of infants especially in chronic diseases as fat

is the single major source of energy.

Comparators

Consumption at lower level.

Outcomes

improves neurocognition, reduces depression and improves adiposity, reduces diabetes.

Additional Comments

No comments provided.

n-3 PUFAs

Populations

All listed populations should be evaluated.

Interventions

Benefits of intake of n-3 long chain linolenic acid should be considered .

Does consumption above the threshold have any effect on the neurocognition of thr infant

Does it have effect in physiologic and health outcome of infants especially in chronic diseases as fat

is the single major source of energy

Comparators

Consumption at lower level.

Outcomes

pregnancy outcome, measures of adiposity, breast cancer atrial fibrillation

Additional Comments

adults and children.

Alpha-linolenic acid

Populations

All listed populations are to be considered.

Interventions

Benefits of intake of alpha-linolenic acid should be considered .

Does consumption above the threhold have any effect on the neurocognition of thr infant

Does it have effect in physiologic and health outcome of infants especially in chronic diseases as fat

is the single major source of energy.

Comparators

consumption at a lower threshold.

Outcomes

neurocognition, cardiovascular risk, infant growth allergy.

Additional Comments

No comments provided.

Additional comments (covering all topics)

High intake of carbohydrates, non sugar sweeteners could lead to chronic diseases both in children

and in adults, whereas intake of high dietary fibre that is within the recommended level protects

against some diseases.

The use of polyunsaturated fatty acids equally of great importance in maintaining adequate health.

9. Robert Rankin

Calorie Control Council, United States of America

Comments

Total PUFAs

Populations

No comments provided.

Interventions

No comments provided.

Comparators

No comments provided.

Outcomes

No comments provided.

Additional Comments

No comments provided.

n-6 PUFAs

Populations

No comments provided.

Interventions

No comments provided.

Comparators

No comments provided.

Outcomes

No comments provided.

Additional Comments

No comments provided.

n-3 PUFAs

Populations

No comments provided.

Interventions

No comments provided.

Comparators

No comments provided.

Outcomes

No comments provided.

Additional Comments

The Calorie Control Council believes that the World Health Organization's Department of Nutrition for Health and Development (NHD) may want to consider that the proposed outcomes may have specific target populations. For example, the population elements considered for the outcome of dental caries may be different from those considered for obesity.

WHO defined general population as:

Adults and children (> 2 years)

Male and female

Generally healthy

Healthy BMI (18.5-24.9 kg/m2) for adults and percentile (5th – 85th) for children

Healthy metabolic parameters (such as, but not limited to, glucose, insulin, HbA1c, triglycerides, healthy BMI)

Suggested criteria specific to outcomes of overweight/obese:

Additional biological parameters for underlying co-morbidities should be adjusted or sub-grouped for:

Diabetes

Dyslipidemia

Cardiovascular disease

At-risk for unhealthy weight gain (adults, children)

Suggested criteria specific to outcome of prediabetes and type 2 diabetes:

Clearly defined clinically diagnosed prediabetes or diabetes

Glucose, insulin, HbA1c

Control groups within healthy range with no baseline differences

Suggested criteria specific to outcome of dental caries:

Sub-group analysis of adults with a) increased risk for root caries, b) xerostomia, and c) intake of medications that impact saliva production as these differences could affect the outcome

Stratification on the basis of additional socioeconomic factors, including a) geography (rural vs. urban) and b) access to medical and dental care.

Alpha-linolenic acid
Populations

No comments provided.

Interventions

No comments provided.

Comparators

No comments provided.

Outcomes

No comments provided.

Additional Comments

No comments provided.

10. Harry Rice

Global Organization for EPA and DHA Omega-3s, United States of America

Comments

Total PUFAs

Populations

No comments provided.

Interventions

No comments provided.

Comparators

No comments provided.

Outcomes

No comments provided.

Additional Comments

No comments provided.

n-6 PUFAs

Populations

Consider aligning population definitions with those used by Codex (infants and young children = 0-36 months; children >3 years).

Interventions

Particularly for infants and young children, limiting to only linoleic acid is not sufficient. Arachidonic Acid (ARA) should be considered. We suggest adding :What is the effect of consuming ARA at or above 0.3% of total fatty acids (TFA) compared to consuming ARA below the threshold (0.3% TFA).

Comparators

No comments provided.

Outcomes

No comments provided.

Additional Comments

The n-6 category should be identified with specificity. More specifically, it would be better to identify as n-6 PUFA individually (linoleic acid and arachidonic acid), particularly since ALA is not simply listed as n-3 PUFA, but rather ALA.

n-3 PUFAs

Populations

Consider aligning population definitions with those used by Codex (infants and young children = 0-36 months; children >3 years).

Interventions

When exploring effect(s) of DHA for pregnant women, consider looking at both algal DHA and DHA-rich fish oil supplementation. See Agency for Healthcare Research and Quality (AHRQ) report entitled "Omega-3 Fatty Acids and Maternal and Child Health: An Updated Systematic Review". Here's the link http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2321

10 mg/kg/day is inconsistent with the expression of n-3 LCPUFA in most studies and it is inconsistent with the units used by Codex. Suggestion: Include 0.3% n-3 LCPUFA, as %FA currently being discussed by CCNFSDU. Also, similar to what was done by the Agency for Healthcare Research and Quality in "Omega-3 Fatty Acids and Maternal and Child Health: An Updated Systematic Review" (http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2321), specifically explore DHA vs DHA+EPA.

Under "In addition, for pregnant women only", supplements are specifically excluded. We highly encourage you to include supplements and explore the benefits of omega-3s (both EPA+DHA and DHA alone).

For "Adults" and the intervention of "dementia", we suggest comparing lower DHA doses (<900-1000 mg/day) to higher DHA doses (>900-1000 mg/day). An informal evaluation of the scientific literature demonstrated cognitive benefits above a certain threshold.

For "Adults with prior event or disease" and the intervention of "dementia", we suggest comparing lower DHA doses (<900-1000 mg/day) to higher DHA doses (>900-1000 mg/day). An informal evaluation of the scientific literature has demonstrated cognitive benefits above a certain threshold. It appears that only intervention trials are being considered? This seems very limiting, since a large body of scientific evidence is available from observational studies.

In addition to threshold levels, it may be appropriate to consider quintiles of intake.

Comparators

n-3 long-chain PUFA should be broken down into individual fatty acids. Specific to the request from the CCNFSDU, EPA+DHA should be considered. In addition, it is worth considering the effect(s) of EPA alone and DHA alone.

The general concept of competing action of n-6 vs n-3 fatty acids is being discussed frequently by scientists, so consideration should be given to looking at the n-6 to n-3 ratio.

Outcomes

For 'Adults', 'Neurocognition (includes dementia)' we suggest separating out 'dementia'.

For 'Adults', we suggest adding the outcome of 'mild cognitive impairment, no dementia'.

For 'Adults with prior event or disease', 'Neurocognition (includes dementia)'we suggest separating out 'dementia'.

For 'Adults with prior event or disease', we suggest adding the outcome of 'mild cognitive impairment, no dementia'.

For 'Adults', we suggest including an additional outcome of 'blood pressure'.

For 'Adults with prior event or disease', we suggest including an additional outcome of 'blood pressure'.

For 'Adults', we suggest including an additional outcome of 'cardiac/coronary mortality' in order to review the literature without vascular events.

For 'Adults with prior event or disease', we suggest including an additional outcome of 'cardiac/coronary mortality' in order to review the literature without vascular events.

For 'Pregnant women', in addition to 'Gestation/preterm', we suggest including 'early preterm'.

For 'Pregnant women', 'Neurocognition (Includes vision, IQ later in life) (infant)', the outcomes should be considered separately, particularly since vision should not be included under 'Neurocognition'.

For 'Infants (0-2 yrs)', 'Neurocognition (Includes vision, IQ later in life) (infant)', the outcomes should be considered separately, particularly since vision should not be included under 'Neurocognition'.

For 'Children (> 2 yrs)', 'Neurocognition (Includes vision, IQ later in life)', the outcomes should be considered separately, particularly since vision should not be included under 'Neurocognition'.

Additional Comments

We suggest specifying individual fatty acids. FAO Food and Nutrition Paper 91 (Fats and fatty acids in human nutrition: Report of an expert consultation) noted the need to focus on the roles of individual fatty acids and how requirements vary with age and physiological status and recognized that individual fatty acids within each broad classification of fatty acids may have unique biological properties and health effects.

Alpha-linolenic acid
Populations

Consider aligning population definitions with those used by Codex (infants and young children = 0-36 months; children >3 years).

Interventions

Thresholds for ALA in infant and child nutrition have been identified and should be considered.

Suggestion: Add question related to intake above and below ALA threshold as specified in current Codex Infant Formula Standard/Follow-Up Formula Standard Revisions.

Comparators

No comments provided.

Outcomes

No comments provided.

Additional Comments

No comments provided.

11. Anne Roulin
Nestlé, Switzerland

Comments

Total PUFAs

Populations

- We would suggest adding the population of "Lactating women", since it is a vulnerable population with specific needs for some PUFAs

- Adults with prior CV event or disease: we suggest to clarify if it includes hypercholesterolemic subjects

- Footnote 1: does it also refer to adults with disease/history of disease and pregnant women? We would suggest adding these two populations

- Footnote 1: because this footnote refers to infants as well, we propose that it is clearly stated in the footnote: "…. apparently healthy adults, infants and children …."

- Footnote1: Can WHO clarify what is the difference between "health background" and "health status"?

- Footnote 1: in the population characteristics, we suggest adding the baseline nutritional status (vegans, usual energy intake, alcohol intake) and, when available, the FADS genotype.

- Pregnant women: we suggest adding a footnote with population characteristics, i.e. number of previous pregnancies, history of allergy

- Infant's age: it is proposed to evaluate the infants from 0-2 years in the same sub-group. Considering that the PUFA requirements of a neonate is probably not similar to those of a 1-2 year old child, we would suggest splitting the younger population of 0-2 years in different sub-groups.

- Children age: (>2yrs): the children category as proposed is thought to cover the age range 2-18 yrs. PUFA requirements for growth for younger children 2-3 years in age are higher than that of older children, where the guidelines basis is more influenced by NCD prevention. We would propose the following subgroups for the infants and children:
  0- 6months
  6 months- 3 yrs
  3-18 yrs

Interventions

- Could the WHO indicate the scientific basis for the different thresholds?

- Because all SFA have the same effects on health, we propose to add sub-groups to the 3 interventions depicted for adults, adults with prior CV events or disease, pregnant women,

infants and children:

- What is the effect of an increase in consumption of total PUFA compared to lower levels of consumption? We suggest the following:
Subgroup by: replacement of total saturated fatty acids (SFA), lauric, myristic, palmitic or stearic with PUFA.
Subgroup by: replacement of total SFA, lauric, myristic, palmitic or stearic with n-6 PUFA.
Subgroup by: replacement of total SFA, lauric, myristic, palmitic or stearic with n-3 long chain PUFA
Subgroup by: replacement of carbohydrates with PUFA

Comparators

No comments provided.

Outcomes

Adults
-Given the high number of outcomes, we would suggest to allocate the outcomes based on prior knowledge, for instance we would suggest to assess neuro-cognition and depression for alpha-linolenic acid and longer chain n-3 fatty acids, but not necessarily for total PUFA and for n-6 PUFA.
We suggest defining a priori the different cardiovascular outcomes. For instance, is "Atrial fibrillation" already included in "coronary heart disease"?
The first outcome proposed for carbohydrates review is currently "Coronary heart disease incidence, mortality, morbidity". Could the definition of these outcome be harmonized between the 3 reviews?(fat, carbohydrates and sweeteners)
We wonder if cardiovascular events include intermediate/surrogate markers of disease (i.e. blood lipids). We propose that this outcome is harmonized with the outcome proposed for non-sugar sweeteners review (which is currently "cardiovascular disease** includes intermediate/surrogate markers of disease (i.e. blood lipids)").
For the outcome on cancer, we do not understand why it is proposed to limit the assessment to (1) PUFA only; (2) breast cancer only, given the association already highlighted by FAO in his 2010 report on colorectal, breast and prostate cancer and different kinds of PUFA. Thus we would suggest to extend the assessment to at least the three cancer type and all PUFA.
Atrial fibrillation: could it be possible to clarify the parenthesis in the footnote ("n-6 PUFA also considered in the context of n-3 PUFA")
For the outcome on inflammation, we do not understand why it is proposed to limit the assessment to inflammatory bowel disease. We would suggest to extend the assessment to other inflammatory diseases such as rheumatoid arthritis and to inflammatory markers.
We propose to be more specific into the outcome "Measures of adiposity" and to harmonize as well with the outcome proposed for review on non-sugar sweeteners (which is currently "overweight/obesity").
Given the existing hypotheses linking linoleic and n-3 fatty acid intake to adiposity/ body weight, we would see this outcome as critical.
Adults with prior cardiovascular event or disease
Same comments as for adults. We propose to use the same outcomes as for "Adults"

Pregnant women

Gestation length/ preterm birth.

Could it be possible to clarify the parenthesis in the footnote ("n-6 PUFA also considered in the context of n-3 PUFA")

Infants

For the outcome on Growth, the parenthesis ("(infants)" is not necessary and should be deleted.

We suggest to consider adding the outcome "infection incidence".

Children

For CV risk, we acknowledge that the ranking depends on the nutrient assessed, however would it be possible to align more on the outcome definition used between the three reviews? The current proposed outcome is:

PUFA review, one outcome: "CV risk (including arterial wall thickening, BP, hypertension, other)"

Sweeteners, two outcomes: "Blood lipids" and "Blood pressure"

CHO, one outcome: "Cardiovascular disease** includes intermediate/surrogate markers of disease (i.e. blood lipids)"

For the outcome on Growth, the parenthesis ("infants)" is not necessary and should be deleted.

We suggest to consider adding the outcome "infection incidence".

<u>*Additional Comments*</u>

No comments provided.

n-6 PUFAs

<u>*Populations*</u>

Same comments as for total PUFA

In addition, in the "Interventions" section, it is mentioned that different children subgroups according to gender and age will be considered. Perhaps this should be indicated there.

<u>*Interventions*</u>

Adults, adults with prior event or disease, pregnant women, infants and children: What is the effect of an increase in consumption of n-6 PUFA compared to lower levels of consumption?

We propose to add a subgroup by: dose-response according to dose of n-3 PUFA, so that the concept of n-6: n-3 ratio is assessed.

In addition, for healthy adults only, for pregnant women only, for infants only, for children only. Could the WHO indicate the scientific basis for the different thresholds?

<u>*Comparators*</u>

No comments provided.

<u>*Outcomes*</u>

All comments given under the section on Total polyunsaturated fatty acids

<u>*Additional Comments*</u>

We note that it is proposed to assess n-6 PUFA as a whole. Because n-6 PUFA (e.g. LA, DGLA and ARA) have different biological effects, we would propose rather to assess linoleic acid. Indeed, some RCT

assessed specifically the effects of DGLA and ARA (fatty acids for which intake is lower than that of LA in the general population), and we would propose not to mix these studies with studies testing the effects of linoleic. Also we appreciate that it is not proposed to assess n-3 PUFA as a whole, but rather to assess separately alpha-linolenic acid and long chain n-3 PUFA.

n-3 PUFAs

Populations

Same comments as for total PUFA

Interventions

Adults; adults with prior event or disease, pregnant women, infants and children: What is the effect of an increase in consumption of n-3 long chain PUFA compared to lower levels of consumption? We propose to add a subgroup by: dose-response according to dose of n-6 PUFA, so that the concept of n-6: n-3 ratio is assessed.
Also, we suggest to specify that the effect of the ratio EPA: DPA: DHA in the different intervention will be assessed
In addition, for healthy adults only, for pregnant women only, for infants only, for children only.
Could the WHO indicate the scientific basis for the different thresholds?
Comment Pregnant women:
Could the WHO indicate why supplements are excluded.
Could the WHO expand on "Explore DHA"?
Comment Children > 10 yrs:
We suggest, as for adults, to add the threshold of 150 mg per day.
Comparators

No comments provided.
Outcomes

All comments given under the section on Total polyunsaturated fatty acids
Additional Comments

We suggest to indicate which n-3 long chain PUFA? E.g. does this include EPA, DPA and DHA?

Alpha-linolenic acid

Populations

Same comments as for total PUFA

Interventions

Adults, adults with prior event or disease, pregnant women, infants and children: What is the effect of an increase in consumption of alpha-linolenic compared to lower levels of consumption? We suggest to use the same interventions as for n-3 long chain PUFA (replacements + dose response) + add a subgroup by dose-response according to dose of n-6 PUFA, so that the concept of n-6: n-3 ratio is assessed.

In addition, for healthy adults only, for pregnant women only, for infants only, for children only. Could the WHO indicate the scientific basis for the different thresholds?

Comparators

No comments provided.

Outcomes

All comments given under the section on Total polyunsaturated fatty acids

Additional Comments

No comments provided.

Additional comments (covering all topics)

Thank you for the opportunity to contribute to this consultation.

12. Laurence Rycken

International Dairy Federation, Belgium

Comments

Total PUFAs

Populations

No comments provided.

Interventions

1. Consideration should be made on the nature of substitution, as not all SFAs are the same science shows.

What is the effect of an increase in consumption of total PUFA compared to lower levels of consumption? Subgroup by: replacement of saturated fatty acids (SFA) with PUFA.

In this PICO question it is assumed that the effects of all types of saturated fatty acids are the same. The potential impact of different saturated fats in view of their sources and chain length needs to be addressed.

As outlined below, there is clear evidence that this is not the case. Recent research has clearly indicated that dairy saturated fat consumption is associated with different health outcomes than consumption of saturated fat from other animal foods.

A 2016 pooled analysis of prospective cohort data shows dairy saturated fat is not associated with CVD and is less atherogenic than other animal fat. The Health Professionals Follow-Up study (24 years of follow-up), the Nurses' Health Study (32 years of follow-up) and the Nurses' Health Study II (20 years of follow-up) by Chen and colleagues [i] reported that dairy fat (from milk, yogurt, cheese, ice-cream, cream and butter) was not associated with risk of CVD (HR for 5% of energy 1.02; 95% CI 0.98, 1.05), CHD (HR for 5% of energy 1.03 95% CI 0.98, 1.09) or stroke (HR for 5% of energy 0.99; 95% CI 0.93, 1.05).

In addition, in this study, dairy fat consumption was associated with lower risk of CVD, CHD and stroke than other animal fat consumption. The researchers calculated that if 5% of energy from other animal fat were to be consumed in place of dairy fat:

Risk of CVD would increase by 6% (RR 1.06; 95% CI 1.02, 1.09)

Risk of CHD would increase by 6% (RR 1.06; 95% CI 1.02, 1.10)

Risk of stroke would increase by 6% (RR 1.06; 95% CI 1.00, 1.11)

These results are consistent with other recent results from prospective cohort studies:

• In 2012, researchers from the Multi-Ethnic Study of Atherosclerosis reported that consumption of different saturated fat foods was associated with different effects on CVD risk [ii]. In

this study, 5,209 adults were monitored for 10 years. A 38% lower risk of CVD was associated with consumption of 5% of energy from dairy saturated fatty acids. In contrast, consumption of saturated fatty acids from meat sources was associated with an increased risk of CVD.

•   In 2016, researchers from the Netherland EPIC cohort (which followed 36,000 adults for 12 years) reported that there was a lower IHD risk with a higher intake of saturated fat that was not dependent on the type of substituting macronutrient [iii]. Rather, it was driven by short- and medium-chain saturated fatty acids, myristic acid and the sum of pentadecylic and margaric acids and saturated fatty acids from dairy foods including butter, cheese, and milk and milk products.

•   Similarly, in a smaller study, Praagman and colleagues (2016) [iv] assessed the association between intake of saturated fatty acids from specific foods and CHD in the Rotterdam study, a cohort of 4,722 adults who were followed for 16 years. They reported that total saturated fat intake was not associated with CHD risk (HR per 5% energy 1.13; 95% CI 0.94, 1.22). In contrast, a higher intake of palmitic acid which accounts for around 50% of the total saturated fat intake was associated with a higher CHD risk (HR 1.26; 95% CI 1.05, 1.15) and meat was the top provider of palmitic acid (providing around 22% of intake).

•   In 2015, Ericson and colleagues [v] assessed the relationship between dietary fat intake and type 2 diabetes incidence in the Malmo Diet and Cancer cohort (26,930 adults were followed for 14 years) and concluded that food sources of fat may partially clarify the inconsistent role of dietary fat for risk of type 2 diabetes. Total intake of regular-fat dairy products was inversely associated with incidence of type 2 diabetes whereas intakes of both high-fat meat and low-fat meat were associated with increased risk. Intakes of short- and medium-chain saturated fatty acids and myristic acid (14:0) – the types found in dairy products – were associated with decreased risk.

Just as it is now increasingly accepted that that not all carbohydrates have the same impact on health, it should be accepted that not all saturated fats have the same impact on health.

•   A 2015 review [vi] on insights from the EPIC study on dairy product consumption and type 2 diabetes commented: 'Taken together, the findings from the EPIC study (EPIC-InterAct and EPIC-Norfolk) indicate that a public health focus solely on nutrients (e.g., SFAs) may be misplaced, and what is required is consideration of the food sources associated with those nutrients. For instance, both meat and dairy products are rich in total fat and SFAs, but their association with type 2 diabetes

is in opposite directions: a positive association has been observed between red and processed meat intake and diabetes risk, while there is now consistent evidence from EPIC and elsewhere for an inverse association between the consumption of specific types of dairy products and incident diabetes.'

Therefore, any PICO questions comparing the effects of saturated fat with those of PUFA should not consider saturated fat as one category.

2. It is food intake and dietary patterns that are important as the effects of nutrients differ according to the food matrix that they are present in.

While comparisons between, for example, vegetable oils and dairy fat are interesting, they are not very practical as they are unusual food substitutions – within meals people rarely consume four teaspoons of polyunsaturated vegetable oil instead of 2 slices of cheese. If they did, they would miss out on the important nutrients supplied by cheese such as calcium and protein, vitamin A, riboflavin, niacin, vitamin B12, vitamin K2, iodine, phosphorus, selenium and zinc.

Each food contains a unique package of nutrients and other components. These interact, so even if two foods contain exactly the same saturated fatty acids, the effects of these saturated fatty acids can differ due to the presence or absence of other nutrients and factors within in a particular food. This was demonstrated by Lorenzen and colleagues in 2014 [vii] in a highly controlled cross-over randomised controlled trial. Subjects were fed either a high-fat diet enriched with milk minerals or the same diet without the milk minerals. Both diets were consumed for 10 days. When subjects ate the high fat diet without milk minerals, there was a significant increase in both total cholesterol and LDL cholesterol. However, when the milk minerals were consumed as part of the diet the increases in total cholesterol and LDL cholesterol levels were attenuated.

It is also important to consider the impact of the whole diet as when people decrease their intake of one food, they tend to increase their intake of another food, i.e. the effect of a food depends on what it is being compared to.

References

[i] Chen M et al., (2016) Dairy fat and risk of cardiovascular disease in 3 cohorts of US adults. Am J Clin Nutr doi 10.3945/ajcn.116.134460.

[ii] De Oliveira Otto MC et al., (2012) Dietary intake of saturated fat by food source and incident cardiovascular disease: the multi-ethnic study of atherosclerosis. Am J Clin Nutr 96, 397-404.

[iii] Praagman J et al., (2016) The association between dietary saturated fatty acids and ischemic heart disease depends on the type and source of fatty acid in the European Prospective Investigation into Cancer and Nutrition-Netherlands cohort. Am J Clin Nutr 103, 356-65.

[iv] Praagman J et al., (2016) Dietary saturated fatty acids and coronary heart disease risk in a Dutch middle-aged and elderly population. Thromb Vasc Biol 36, pii: ATVBAHA.116.307578

[v] Ericson U et al., (2015) Food sources of fat may clarify the inconsistent role of dietary fat intake for incidence of type 2 diabetes. Am J Clin Nutr 101, 1065-80.

[vi] Forouhi NG (2015) Association between consumption of dairy products and incident type 2 diabetes – insights from the European Prospective Investigation into Cancer study. Nutr Rev 73, SI 15-22

[vii] Lorenzen et al., 2014 Milk minerals modify the effect of fat intake on serum lipid profile: results from an animal and human short-term study. Br J Nutr 111, 1412-20

Comparators

No comments provided.

Outcomes

1. Clarification needed regarding the outcomes chosen

In the saturated fat PICO questions outlined in Mensink, RP Effects of saturated fatty acids on serum lipids and lipoproteins: a systematic review and regression analysis[viii], there is consideration of non-communicable diseases (NCDs). Why are the outcomes more limited for PUFA? Also, in the Mensink review there was a comparison of replacing SFA with carbohydrates (refined vs unrefined). This comparison appears to be absent for PUFA and.

2. The importance given to various outcomes is not consistent

Why is coronary heart disease more important for those who already have this condition than it is for adults who do not (page 6)? Surely all-cause mortality and cardiovascular mortality are the most important outcomes for adults whether they already have this condition or not.

References:

[viii] Mensink, RP. Effects of saturated fatty acids on serum lipids and lipoproteins: a systematic review and regression analysis. Geneva: World Health Organization; 2016.

Additional Comments

No comments provided.

n-6 PUFAs

Populations

No comments provided.

Interventions

1. Consideration should be made on the nature of substitution, as not all SFAs are the same science shows.

What is the effect of an increase in consumption of n-6 PUFA compared to lower levels of

consumption? Subgroup by: replacement of SFA with n-6 PUFA.

In this PICO question it is assumed that the effects of all types of saturated fatty acids are the same. The potential impact of different saturated fats in view of their sources and chain length needs to be addressed.

As outlined below, there is clear evidence that this is not the case. Recent research has clearly indicated that dairy saturated fat consumption is associated with different health outcomes than consumption of saturated fat from other animal foods.

A 2016 pooled analysis of prospective cohort data shows dairy saturated fat is not associated with CVD and is less atherogenic than other animal fat. The Health Professionals Follow-Up study (24 years of follow-up), the Nurses' Health Study (32 years of follow-up) and the Nurses' Health Study II (20 years of follow-up) by Chen and colleagues [i] reported that dairy fat (from milk, yogurt, cheese, ice-cream, cream and butter) was not associated with risk of CVD (HR for 5% of energy 1.02; 95% CI 0.98, 1.05), CHD (HR for 5% of energy 1.03 95% CI 0.98, 1.09) or stroke (HR for 5% of energy 0.99; 95% CI 0.93, 1.05).

In addition, in this study, dairy fat consumption was associated with lower risk of CVD, CHD and stroke than other animal fat consumption. The researchers calculated that if 5% of energy from other animal fat were to be consumed in place of dairy fat:

Risk of CVD would increase by 6% (RR 1.06; 95% CI 1.02, 1.09)

Risk of CHD would increase by 6% (RR 1.06; 95% CI 1.02, 1.10)

Risk of stroke would increase by 6% (RR 1.06; 95% CI 1.00, 1.11).

These results are consistent with other recent results from prospective cohort studies:

In 2012, researchers from the Multi-Ethnic Study of Atherosclerosis reported that consumption of different saturated fat foods was associated with different effects on CVD risk [ii]. In this study, 5,209 adults were monitored for 10 years. A 38% lower risk of CVD was associated with consumption of 5% of energy from dairy saturated fatty acids. In contrast, consumption of saturated fatty acids from meat sources was associated with an increased risk of CVD.

In 2016, researchers from the Netherland EPIC cohort (which followed 36,000 adults for 12 years) reported that there was a lower IHD risk with a higher intake of saturated fat that was not dependent on the type of substituting macronutrient [iii]. Rather, it was driven by short- and medium-chain saturated fatty acids, myristic acid and the sum of pentadecylic and margaric acids and saturated fatty acids from dairy foods including butter, cheese, and milk and milk products.

Similarly, in a smaller study, Praagman and colleagues (2016) [iv] assessed the association between intake of saturated fatty acids from specific foods and CHD in the Rotterdam study, a cohort of 4,722 adults who were followed for 16 years. They reported that total saturated fat intake was not

associated with CHD risk (HR per 5% energy 1.13; 95% CI 0.94, 1.22). In contrast, a higher intake of palmitic acid which accounts for around 50% of the total saturated fat intake was associated with a higher CHD risk (HR 1.26; 95% CI 1.05, 1.15) and meat was the top provider of palmitic acid (providing around 22% of intake).

In 2015, Ericson and colleagues [v] assessed the relationship between dietary fat intake and type 2 diabetes incidence in the Malmo Diet and Cancer cohort (26,930 adults were followed for 14 years) and concluded that food sources of fat may partially clarify the inconsistent role of dietary fat for risk of type 2 diabetes. Total intake of regular-fat dairy products was inversely associated with incidence of type 2 diabetes whereas intakes of both high-fat meat and low-fat meat were associated with increased risk. Intakes of short- and medium-chain saturated fatty acids and myristic acid (14:0) – the types found in dairy products – were associated with decreased risk.

Just as it is now increasingly accepted that that not all carbohydrates have the same impact on health, it should be accepted that not all saturated fats have the same impact on health.

A 2015 review [vi] on insights from the EPIC study on dairy product consumption and type 2 diabetes commented: 'Taken together, the findings from the EPIC study (EPIC-InterAct and EPIC-Norfolk) indicate that a public health focus solely on nutrients (e.g., SFAs) may be misplaced, and what is required is consideration of the food sources associated with those nutrients. For instance, both meat and dairy products are rich in total fat and SFAs, but their association with type 2 diabetes is in opposite directions: a positive association has been observed between red and processed meat intake and diabetes risk, while there is now consistent evidence from EPIC and elsewhere for an inverse association between the consumption of specific types of dairy products and incident diabetes.'Therefore, any PICO questions comparing the effects of saturated fat with those of n-6 PUFA should not consider saturated fat as one category.

2. It is food intake and dietary patterns that are important as the effects of nutrients differ according to the food matrix that they are present in.

While comparisons between, for example, vegetable oils and dairy fat are interesting, they are not very practical as they are unusual food substitutions – within meals people rarely consume four teaspoons of polyunsaturated vegetable oil instead of 2 slices of cheese. If they did, they would miss out on the important nutrients supplied by cheese such as calcium and protein, vitamin A, riboflavin, niacin, vitamin B12, vitamin K2, iodine, phosphorus, selenium and zinc.

Each food contains a unique package of nutrients and other components. These interact, so even if two foods contain exactly the same saturated fatty acids, the effects of these saturated fatty acids can differ due to the presence or absence of other nutrients and factors within in a particular food.

This was demonstrated by Lorenzen and colleagues in 2014 [vii] in a highly controlled cross-over randomised controlled trial. Subjects were fed either a high-fat diet enriched with milk minerals or the same diet without the milk minerals. Both diets were consumed for 10 days. When subjects ate the high fat diet without milk minerals, there was a significant increase in both total cholesterol and LDL cholesterol. However, when the milk minerals were consumed as part of the diet the increases in total cholesterol and LDL cholesterol levels were attenuated.

It is also important to consider the impact of the whole diet as when people decrease their intake of one food, they tend to increase their intake of another food, i.e. the effect of a food depends on what it is being compared to.

References

[i] Chen M et al., (2016) Dairy fat and risk of cardiovascular disease in 3 cohorts of US adults. Am J Clin Nutr doi 10.3945/ajcn.116.134460.

[ii] De Oliveira Otto MC et al., (2012) Dietary intake of saturated fat by food source and incident cardiovascular disease: the multi-ethnic study of atherosclerosis. Am J Clin Nutr 96, 397-404.

[iii] Praagman J et al., (2016) The association between dietary saturated fatty acids and ischemic heart disease depends on the type and source of fatty acid in the European Prospective Investigation into Cancer and Nutrition-Netherlands cohort. Am J Clin Nutr 103, 356-65.

[iv] Praagman J et al., (2016) Dietary saturated fatty acids and coronary heart disease risk in a Dutch middle-aged and elderly population. Thromb Vasc Biol 36, pii: ATVBAHA.116.307578

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[vi] Forouhi NG (2015) Association between consumption of dairy products and incident type 2 diabetes – insights from the European Prospective Investigation into Cancer study. Nutr Rev 73, SI 15-22

[vii] Lorenzen et al., 2014 Milk minerals modify the effect of fat intake on serum lipid profile: results from an animal and human short-term study. Br J Nutr 111, 1412-20

Comparators

No comments provided.

Outcomes

1. Clarification needed regarding the outcomes chosen

In the saturated fat PICO questions outlined in Mensink, RP Effects of saturated fatty acids on serum lipids and lipoproteins: a systematic review and regression analysis[viii], there is consideration of non-communicable diseases (NCDs). Why are the outcomes more limited for PUFA? Also, in the

Mensink review there was a comparison of replacing SFA with carbohydrates (refined vs unrefined). This comparison appears to be absent for n-6 PUFA.

2. The importance given to various outcomes is not consistent

Why is coronary heart disease more important for those who already have this condition than it is for adults who do not (page 6)? Surely all-cause mortality and cardiovascular mortality are the most important outcomes for adults whether they already have this condition or not.

References:

[viii] Mensink, RP. Effects of saturated fatty acids on serum lipids and lipoproteins: a systematic review and regression analysis. Geneva: World Health Organization; 2016.

Additional Comments

No comments provided.

n-3 PUFAs

Populations

No comments provided.

Interventions

1. Consideration should be made on the nature of substitution, as not all SFAs are the same science shows.

What is the effect of increased consumption of n-3 long chain PUFA compared to decreased intake?

Subgroup by: replacement of SFA with n-3 long chain PUFA

In this PICO question it is assumed that the effects of all types of saturated fatty acids are the same. The potential impact of different saturated fats in view of their sources and chain length needs to be addressed.

As outlined below, there is clear evidence that this is not the case. Recent research has clearly indicated that dairy saturated fat consumption is associated with different health outcomes than consumption of saturated fat from other animal foods.

A 2016 pooled analysis of prospective cohort data shows dairy saturated fat is not associated with CVD and is less atherogenic than other animal fat. The Health Professionals Follow-Up study (24 years of follow-up), the Nurses' Health Study (32 years of follow-up) and the Nurses' Health Study II (20 years of follow-up) by Chen and colleagues [i] reported that dairy fat (from milk, yogurt, cheese, ice-cream, cream and butter) was not associated with risk of CVD (HR for 5% of energy 1.02; 95% CI 0.98, 1.05), CHD (HR for 5% of energy 1.03 95% CI 0.98, 1.09) or stroke (HR for 5% of energy 0.99; 95% CI 0.93, 1.05).

In addition, in this study, dairy fat consumption was associated with lower risk of CVD, CHD and stroke than other animal fat consumption. The researchers calculated that if 5% of energy from

other animal fat were to be consumed in place of dairy fat:

Risk of CVD would increase by 6% (RR 1.06; 95% CI 1.02, 1.09)

Risk of CHD would increase by 6% (RR 1.06; 95% CI 1.02, 1.10)

Risk of stroke would increase by 6% (RR 1.06; 95% CI 1.00, 1.11).

These results are consistent with other recent results from prospective cohort studies:

In 2012, researchers from the Multi-Ethnic Study of Atherosclerosis reported that consumption of different saturated fat foods was associated with different effects on CVD risk [ii]. In this study, 5,209 adults were monitored for 10 years. A 38% lower risk of CVD was associated with consumption of 5% of energy from dairy saturated fatty acids. In contrast, consumption of saturated fatty acids from meat sources was associated with an increased risk of CVD.

In 2016, researchers from the Netherland EPIC cohort (which followed 36,000 adults for 12 years) reported that there was a lower IHD risk with a higher intake of saturated fat that was not dependent on the type of substituting macronutrient [iii]. Rather, it was driven by short- and medium-chain saturated fatty acids, myristic acid and the sum of pentadecylic and margaric acids and saturated fatty acids from dairy foods including butter, cheese, and milk and milk products.

Similarly, in a smaller study, Praagman and colleagues (2016) [iv] assessed the association between intake of saturated fatty acids from specific foods and CHD in the Rotterdam study, a cohort of 4,722 adults who were followed for 16 years. They reported that total saturated fat intake was not associated with CHD risk (HR per 5% energy 1.13; 95% CI 0.94, 1.22). In contrast, a higher intake of palmitic acid which accounts for around 50% of the total saturated fat intake was associated with a higher CHD risk (HR 1.26; 95% CI 1.05, 1.15) and meat was the top provider of palmitic acid (providing around 22% of intake).

In 2015, Ericson and colleagues [v] assessed the relationship between dietary fat intake and type 2 diabetes incidence in the Malmo Diet and Cancer cohort (26,930 adults were followed for 14 years) and concluded that food sources of fat may partially clarify the inconsistent role of dietary fat for risk of type 2 diabetes. Total intake of regular-fat dairy products was inversely associated with incidence of type 2 diabetes whereas intakes of both high-fat meat and low-fat meat were associated with increased risk. Intakes of short- and medium-chain saturated fatty acids and myristic acid (14:0) – the types found in dairy products – were associated with decreased risk.

Just as it is now increasingly accepted that that not all carbohydrates have the same impact on health, it should be accepted that not all saturated fats have the same impact on health.

A 2015 review [vi] on insights from the EPIC study on dairy product consumption and type 2 diabetes commented: 'Taken together, the findings from the EPIC study (EPIC-InterAct and EPIC-Norfolk) indicate that a public health focus solely on nutrients (e.g., SFAs) may be misplaced, and what is

required is consideration of the food sources associated with those nutrients. For instance, both meat and dairy products are rich in total fat and SFAs, but their association with type 2 diabetes is in opposite directions: a positive association has been observed between red and processed meat intake and diabetes risk, while there is now consistent evidence from EPIC and elsewhere for an inverse association between the consumption of specific types of dairy products and incident diabetes.'

Therefore, any PICO questions comparing the effects of saturated fat with those of n-3 PUFA should not consider saturated fat as one category.

2. It is food intake and dietary patterns that are important as the effects of nutrients differ according to the food matrix that they are present in.

While comparisons between, for example, vegetable oils and dairy fat are interesting, they are not very practical as they are unusual food substitutions – within meals people rarely consume four teaspoons of polyunsaturated vegetable oil instead of 2 slices of cheese. If they did, they would miss out on the important nutrients supplied by cheese such as calcium and protein, vitamin A, riboflavin, niacin, vitamin B12, vitamin K2, iodine, phosphorus, selenium and zinc.

Each food contains a unique package of nutrients and other components. These interact, so even if two foods contain exactly the same saturated fatty acids, the effects of these saturated fatty acids can differ due to the presence or absence of other nutrients and factors within in a particular food. This was demonstrated by Lorenzen and colleagues in 2014 [vii] in a highly controlled cross-over randomised controlled trial. Subjects were fed either a high-fat diet enriched with milk minerals or the same diet without the milk minerals. Both diets were consumed for 10 days. When subjects ate the high fat diet without milk minerals, there was a significant increase in both total cholesterol and LDL cholesterol. However, when the milk minerals were consumed as part of the diet the increases in total cholesterol and LDL cholesterol levels were attenuated.

It is also important to consider the impact of the whole diet as when people decrease their intake of one food, they tend to increase their intake of another food, i.e. the effect of a food depends on what it is being compared to.

References

[i] Chen M et al., (2016) Dairy fat and risk of cardiovascular disease in 3 cohorts of US adults. Am J Clin Nutr doi 10.3945/ajcn.116.134460.

[ii] De Oliveira Otto MC et al., (2012) Dietary intake of saturated fat by food source and incident cardiovascular disease: the multi-ethnic study of atherosclerosis. Am J Clin Nutr 96, 397-404.

[iii] Praagman J et al., (2016) The association between dietary saturated fatty acids and ischemic heart disease depends on the type and source of fatty acid in the European Prospective Investigation

into Cancer and Nutrition-Netherlands cohort. Am J Clin Nutr 103, 356-65.

[iv] Praagman J et al., (2016) Dietary saturated fatty acids and coronary heart disease risk in a Dutch middle-aged and elderly population. Thromb Vasc Biol 36, pii: ATVBAHA.116.307578

[v] Ericson U et al., (2015) Food sources of fat may clarify the inconsistent role of dietary fat intake for incidence of type 2 diabetes. Am J Clin Nutr 101, 1065-80.

[vi] Forouhi NG (2015) Association between consumption of dairy products and incident type 2 diabetes – insights from the European Prospective Investigation into Cancer study. Nutr Rev 73, SI 15-22

[vii] Lorenzen et al., 2014 Milk minerals modify the effect of fat intake on serum lipid profile: results from an animal and human short-term study. Br J Nutr 111, 1412-20

Comment Pregnant women:

Could the WHO indicate why supplements are excluded.

Could the WHO expand on "Explore DHA"?

Comment Children > 10 yrs:

We suggest, as for adults, to add the threshold of 150 mg per day.

Comparators

No comments provided.

Outcomes

1. Clarification needed regarding the outcomes chosen

In the saturated fat PICO questions outlined in Mensink, RP Effects of saturated fatty acids on serum lipids and lipoproteins: a systematic review and regression analysis[viii], there is consideration of non-communicable diseases (NCDs). Why are the outcomes more limited for PUFA? Also, in the Mensink review there was a comparison of replacing SFA with carbohydrates (refined vs unrefined). This comparison appears to be absent for n-3 PUFA.

2. The importance given to various outcomes is not consistent

Why is coronary heart disease more important for those who already have this condition than it is for adults who do not (page 6)? Surely all-cause mortality and cardiovascular mortality are the most important outcomes for adults whether they already have this condition or not.

References:

[viii] Mensink, RP. Effects of saturated fatty acids on serum lipids and lipoproteins: a systematic review and regression analysis. Geneva: World Health Organization; 2016.

Additional Comments

No comments provided.

Alpha-linolenic acid

Populations

No comments provided.

Interventions

No comments provided.

Comparators

No comments provided.

Outcomes

No comments provided.

Additional Comments

No comments provided.

Additional comments (covering all topics)

The International Dairy Federation (IDF) would like to thank the WHO for this public call and we appreciate the opportunity to submit comments on the scope of the proposed update of WHO guidelines on the intake of carbohydrates, polyunsaturated fatty acids and non‑sugar sweeteners.

If, as stated the objective of this work is to ensure that WHO guidelines on these critical nutrients and associated dietary practices are comprehensive and informed by the most recent scientific data, we would suggest a 'whole food' and 'dietary approach', rather than an 'isolated nutrients' approach is taken.

Because:

1. Foods and diets are clearly far more than the sum of their single nutrients. Single nutrients are not consumed in isolation – many factors within a food influence the effects of a single nutrient and it is inaccurate to generalise about the effects of a single nutrient without considering the food it is present in.

2. Foods are not a matrix that we can adjust at will. Their composition is sometimes mainly defined by the raw material meaning by nature itself. Thus, in recommending decreasing or increasing the consumption of a single nutrient it will result in a modification of the diet itself. However, this major issue is not addressed if a nutrient approach is taken.

Instead of the suggested approach, the WHO evidence review should focus on foods and dietary patterns (rather than isolated nutrients) and on actual disease risk (rather than considering various markers of risk in isolation).

People eat whole foods not single nutrients in isolation and food based recommendations are more practical for the general public than nutrient-based dietary advice. We would therefore urge WHO to provide clear guidelines on how to translate these recommendations into practical advice for consumers.

Moreover, the GRADE system appears more relevant to developing guidelines for pharmaceutical drug use than for food based dietary guidelines. For example, short term randomised controlled trials measuring short term changes in a small number of indicators of risk will be given higher priority than long term observational studies assessing dietary intake over many years and risk of developing NCDs.

13. Rusidah Selemat

Nutrition Division, Ministry of Health, Malaysia

Comments

Total PUFAs

Populations

Suggest to also include elderly

Interventions

Which combination/Ratio of PUFA/MUFA and SFA that would have the best outcome?

Comparators

No comments provided.

Outcomes

No comments provided.

Additional Comments

No comments provided.

n-6 PUFAs

Populations

No comments provided.

Interventions

No comments provided

Comparators

No comments provided.

Outcomes

No comments provided.

Additional Comments

No comments provided.

n-3 PUFAs

Populations

No comments provided.

Interventions

No comments provided.

Comparators

No comments provided.

Outcomes

No comments provided.

Additional Comments

No comments provided.

Alpha-linolenic acid

Populations

No comments provided.

Interventions

No comments provided

Comparators

No comments provided.

Outcomes

No comments provided.

Additional Comments

No comments provided.

14. Pankaj Shah
SRMC & RI, SRU, India

14. Pankaj Shah
SRMC & RI, SRU, India

Comments

Total PUFAs
Populations

Great

Interventions

non question format as indicated earlier

Comparators

Great.

Outcomes

Great.

Additional Comments

No comments provided.

n-6 PUFAs
Populations

Great.

Interventions

non question format

Comparators

Great.

Outcomes

Great.

Additional Comments

No comments provided.

n-3 PUFAs
Populations

Great.

Interventions

non question format.

Comparators

No comments provided.

Outcomes

Great.

Additional Comments

No comments provided.

Alpha-linolenic acid

Populations

Great.

Interventions

non question format

Comparators

Great.

Outcomes

Great.

Additional Comments

No comments provided.

Additional comments (covering all topics)

Dear Sir/Madam,

Thank you for the opportunity provided.

I feel along with PICO methods of the systematic review and possibility of meta-analysis should be included. As this research method is also very important along with PICO. For example- method of literature review, data extraction, assessment of heterogeneity, publication bias,   independent work by review authors etc are also very important.

Also I suggest for registration of protocol with Prospero.

Thank you,

With regards,

Pankaj .

15. Rob te Biesebeke

Tp Institute Food & Nutrition, Switzerland

Comments

Total PUFAs

Populations

No comments provided.

Interventions

No comments provided.

Comparators

No comments provided.

Outcomes

No comments provided.

Additional Comments

No comments provided.

n-6 PUFAs

Populations

Different intakes for linoleic acid in men, women, boys and girls.

Interventions

In addition, for healthy adults only : subdivision in threshold for men = 17 g / day, threshold for women 12 g / day ?

What is the effect in men and woman of consuming linoleic acid above a threshold compared to consuming linoleic acid below the threshold?

In addition, for pregnant women only : threshold = 13 g / day ?

In addition, for infants (0‑2 yrs) only : What is the effect of consuming linoleic acid above a threshold compared to consuming linoleic acid below the threshold?

Comparators

Linoleic acid deficiency

Consumption of other substrates for eicosanoids production.

Outcomes

No comments provided.

Additional Comments

IOM makes subdivision in adults population:

- Men

- Women

- Elderly men

- Elderly Women.

n-3 PUFAs
Populations

Different intakes in men and women, boys and girls

Interventions

No comments provided.

Comparators

n-3 'long chain' polyunsaturated fatty acids vs n-3 'short chain' polyunsaturated fatty acids

Outcomes

n-3 long chain polyunsaturated fatty acids deficiency

Consumption of other substrates for eicosanoids production.

Additional Comments

No comments provided.

Alpha-linolenic acid
Populations

Different intakes for Alpha-linolenic acid acid in men, women, boys and girls.

Interventions

No comments provided.

Comparators

Alpha-linolenic acid deficiency

Consumption of other substrates for eicosanoids production.

Outcomes

Great.

Additional Comments

IOM makes subdivision in adults population :

- Men

- Women

- Elderly men

- Elderly Women.

Different intakes in men and women, boys and girls