Launch of the public consultation on the WHO draft guideline on use of non-sugar sweeteners

World Health Organization

Opening remarks

Dr Francesco Branca

Director

Department of Nutrition and Food Safety

World Health Organization

Background

Dr Chizuru Nishida

Unit Head

Safe, Healthy and Sustainable Diet Unit

Department of Nutrition and Food Safety

World Health Organization

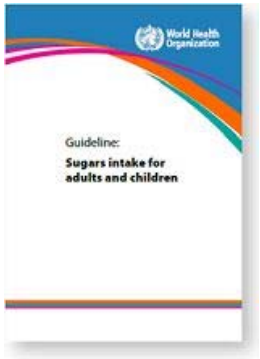
Summary history of WHO guidance on sugars intake

- 1988 Joint FAO/WHO Expert Consultation on Recommended Allowances of Nutrients for Food Labelling Purposes (Helsinki NRV meeting)
  → **< 10% of *sugars***
- 1989 WHO Working Group on Diet, Nutrition and the Prevention of Chronic Diseases (TRS 797, 1990)
  → **0 - 10% of *free sugars***
- 1997 Joint FAO/WHO Expert Consultation on Carbohydrates in Human Nutrition (1998)
- 2002 Joint WHO/FAO Expert Consultation on Diet, Nutrition and the Prevention of Chronic Diseases (TRS 916, 2003)
  → **< 10% of *free sugars***
- 2007 Joint FAO/WHO Scientific Update on Carbohydrates in Human Nutrition (EJCN 2008)
- **2015 WHO guideline on sugars intake in adults and children**

WHO Guideline on sugars intake in adults and children (April 2015)

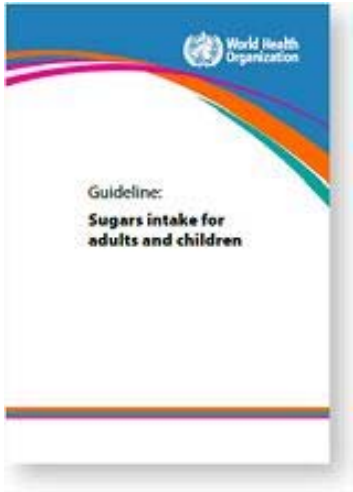
Recommendations:

- WHO recommends a reduced intake of free sugars throughout the lifecourse (*strong recommendation*)
- In both adults and children, WHO recommends reducing the intake of free sugars to less than 10% of total energy intake (*strong recommendation*)
- WHO suggests a further reduction of the intake of free sugars to below 5% of total energy intake (*conditional recommendation*)



Questions arising after the launching of WHO Guideline on sugars intake in adults and children (April 2015)

- Use of non-sugar sweeteners (NSS)
- Fruit juice consumption
- Economic implications of implementing the guideline



A surge of Member States' public health actions

Following release of the WHO guideline on sugars intake (2015)

- Revision of national dietary guidelines

Use of NSS to replace or reduce sugars intake ?

On 17 July 2015:
The Scientific Advisory Committee on Nutrition (SACN) report on Carbohydrates and Health was issued

- Recommending that population average intake of free sugars should not exceed 5% of total energy intake for age groups from 2 years upwards.
- This advice is based on SACN's assessment of evidence on the effect of free sugars on the risk of dental caries and on total energy intake. A higher sugars intake increases the risk of higher energy intakes - the higher the consumption of sugars, the more likely people are to exceed their estimated average requirement (EAR) for energy. Therefore, if intakes of free sugars are lowered, the more likely it is that the EAR for energy will not be exceeded, and this could go some way to addressing the significant public health problem of obesity.

2002 IOM report:
- Added sugars should comprise no more than 25 percent of total calories consumed.

It was not a recommendation for a desirable/acceptable sugar intake, but was a suggested maximum intake based on the decreased intake of some micronutrients of American subpopulations. But "25%" figure was misused by sugar industries to criticize WHO's TRS 916. Dr Harvey Fineberg (President of IOM) therefore sent a letter to Mr Tommy Thompson (Secretary of Health and Human Services), indicating IOM's intent to clarify it before the report it was published in final text.

Healthy eating patterns limit added sugars to less than 10 % of calories per day. This recommendation is a target to help the public achieve a healthy eating pattern, which means meeting nutrient and food group needs through nutrient-dense food and beverage choices and staying within calorie limits. When added sugars in foods and beverages exceed 10 % of calories, a healthy eating pattern may be difficult to achieve.

A surge of Member States' public health actions

Following release of the WHO guideline on sugars intake (2015)

- Taxation of SSB

Increasing numbers of countries implementing SSB taxation to reduce free sugars consumption

(85 countries are implementing SSB taxation *at national level*, May 2022)

1. Albania
2. Argentina
3. Bahrain
4. Bangladesh
5. Barbados
6. Belgium
7. Belize
8. Benin
9. Bolivia
10. Brazil
11. Brunei Darussalam
12. Brundi
13. Chad
14. Chile
15. Cook Islands
16. Costa Rica
17. Croatia
18. Cote d'Ivoire
19. Democratic Republic of Congo
20. Dominica
21. Ecuador
22. El Salvador
23. Ethiopia
24. Fiji
25. Finland
26. France
27. Guatemala
28. Honduras
29. Hungary
30. India
31. Iran
32. Ireland
33. Israel
34. Kenya
35. Kiribati
36. Latvia
37. Liberia
38. Madagascar
39. Malaysia
40. Mali
41. Mauritania
42. Mauritius
43. Mexico
44. Monaco
45. Montenegro
46. Morocco
47. Mozambique
48. Nepal
49. Nicaragua
50. Niger
51. Nigeria
52. Oman
53. Pakistan
54. Panama
55. Paraguay
56. Peru
57. Philippines
58. Poland
59. Portugal
60. Qatar
61. Rwanda
62. Saint Kitts & Nevis
63. Saint Vincent & the Grenadines
64. Samoa
65. Sao Tome & Principe
66. Saudi Arabia
67. Senegal
68. Seychelles
69. South Africa
70. Sri Lanka
71. Suriname
72. Tajikistan
73. Thailand
74. Togo
75. Tonga
76. Tunisia
77. Turkey
78. Tuvalu
79. Uganda
80. United Arab Emirates
81. UK
82. United Republic of Tanzania
83. Uruguay
84. Vanuatu
85. Zambia

- Denmark & Norway (repealed)
- Micronesia (subnational level)
- Spain (subnational level)
- US (municipality level)

Beverages with NSS should also be taxed ?

A surge of Member States' public health actions

Following release of the WHO guideline on sugars intake (2015)

- Regulating marketing of food and non-alcoholic beverages high in fats, sugars and salt
  - Despite numerous calls to action at global & regional levels, limited country implementation of policies to restrict food marketing – only 60 countries have adopted policies that restrict food marketing (May 2022) – Of these only one third have mandatory policies
  - Development of policy implementation tools
    - Regional nutrient profile model for regulating the marketing of foods and non-alcoholic beverages to children: EURO (2013 - 2015), EMRO (2014 - 2015), AMRO/PAHO (2015), WPRO (2015 - 2015), SEARO (2016 - 2017), AFRO (2018 – 2019)

2.3.1 Conditions for general exclusion from marketing

Marketing is systematically prohibited for the following:

(a) Food products that contain >1% of total energy in the form of industrially produced trans-fatty acid (1% of energy = 20 kcal = 2.2 g trans-fat).

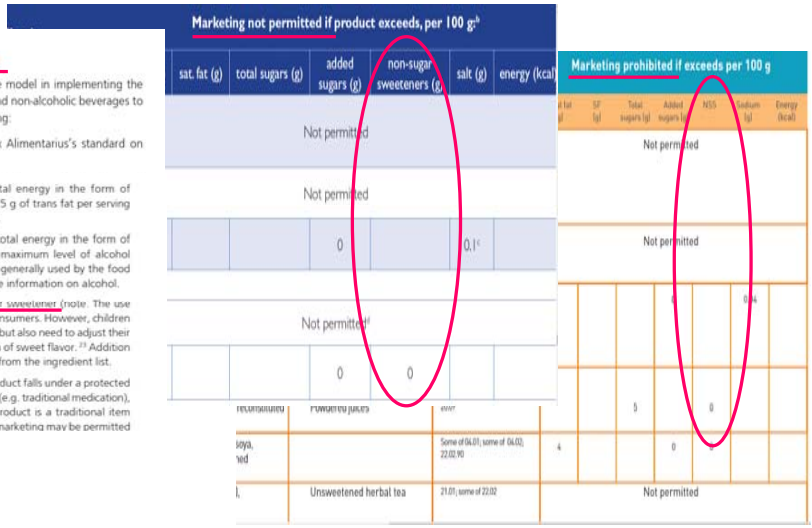
(b) Food products with non-sugar sweeteners. While the use of non-sugar sweeteners may be safe for consumers, the concern for children in their formative years is both to avoid excessive sugar intake and to reduce the risk of acquiring the taste preference for sweet flavours (34). The presence of non-sugar sweeteners can be determined from the ingredient list.

Marketing of food & beverages with NSS not permitted ?

2.3 Conditions for general exclusion

Exclusion criteria related to the application of the model in implementing the set of recommendations on marketing of foods and non-alcoholic beverages to children. Marketing is not allowed for the following:

1. Food products that do not pass Codex Alimentarius's standard on uses of food additives.
2. Food products that contain >1% of total energy in the form of industrially produced trans-fatty acid or 0.5 g of trans fat per serving (1% of energy = 20 kcal = 2.2g trans fat).
3. Food products that contains > 0.5% of total energy in the form of alcohol. This content aims to allow for maximum level of alcohol from the alcohol-based flavouring agents generally used by the food industry.[1] The ingredient panel will provide information on alcohol.
4. Food products with added with non-sugar sweetener (note. The use of non-sugar sweetener may be safe for consumers. However, children should not only reduce their energy intake but also need to adjust their eating behaviour on habitual consumption of sweet flavor.[23] Addition of non-sugar sweetener can be obtained from the ingredient list.
5. Subject to the exclusionary criteria, if a product falls under a protected geographical or quality designation regime (e.g. traditional medication), then marketing may be permitted; if a product is a traditional item associated with a celebratory event, then marketing may be permitted



A surge of Member States' public health actions

Following release of the WHO guideline on sugars intake (2015)

- Removal of sugary drinks from public institutions (including schools, hospitals, government offices, workplace)

Removal of SSB in WHO HQ

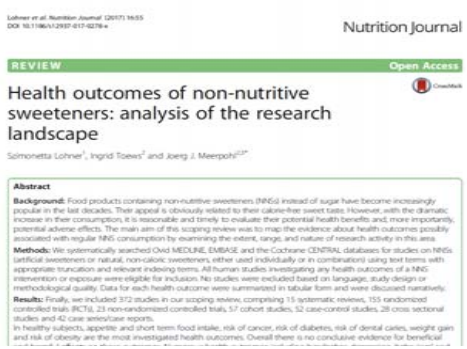
- January 2016 – Launching of ***"Walk the Talk"*** initiative
- Dialogue/consultation with Staff Association, Building Management and vendors to assess feasibility and modality of implementation
- April 2016 – Removal of 13 SSB with ≥ 50g sugars per serving (i.e. ≥ 10% of total energy intake) for 1 week
- Staff survey to get feedback and assess interest in implementing permanent removal (80% supported)
- **On 11 October 2016** (World Obesity Day) – Launching of removal of SSB in WHO HQ
  - Further consultation with Staff Association, Building Management, vendors
  - Consultation with UNAIDS

WPRO Regional Committee: 10 – 14 October 2016

World Health Organization

But diet and zero calorie drinks were not removed
when removal of SSB was implemented in 2016

- WHO had no nutrition-related guidance on the consumption of NNS
  - In the process of conducting systematic evidence review on health impacts of NSS as part of guideline development process


Nutrition Journal

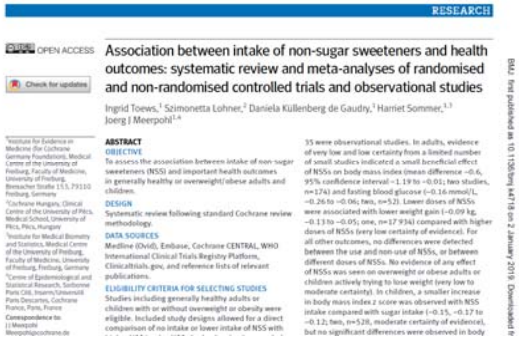
REVIEW Open Access

Health outcomes of non-nutritive sweeteners: analysis of the research landscape

Solmonetta Lohner, Ingrid Toews and Joerg J. Meerpohl

Abstract

Scoping review:
- Conducted 2015 – 2016
- Published 2017


RESEARCH

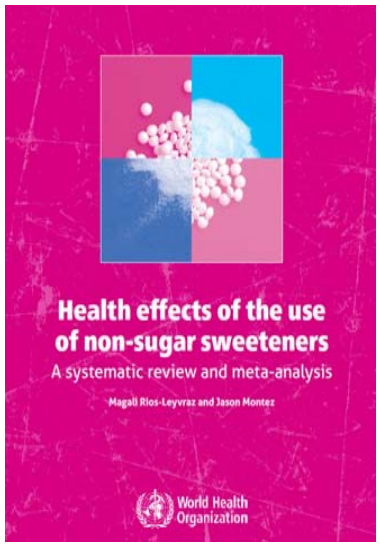
OPEN ACCESS

Association between intake of non-sugar sweeteners and health outcomes: systematic review and meta-analyses of randomised and non-randomised controlled trials and observational studies

Ingrid Toews, Szimonetta Lohner, Daniela Küllenberg de Gaudry, Harriet Sommer, Joerg J Meerpohl

ABSTRACT

Initial systematic review:
- Conducted 2017 – 2018
- Published 2019



Updated systematic review:
- Conducted 2020 – 2021
- Published 2022

Scope of the WHO guideline on the use of NSS

- Not a reassessment of safety of NSS
  - The recommendation of the draft guideline is based on evidence of health effects of NSS use at levels already considered safe by the Joint FAO/WHO Expert Committee on Food Additives (JECFA)
  - It is not intended to provide updated or alternative guidance on safe or maximal levels of intake.
  - Safe levels of intake are based on toxicological assessments of individual NSS, and such assessments are completed by authoritative bodies (i.e. JECFA).

WHO guideline development

Dr Nathan Ford

Chair, WHO Guidelines Review Committee
World Health Organization

Why does WHO develop guidance?

To provide policy makers, practitioners and patients with clear guidance..

..based on best available evidence that has been critically appraised..

..and transparent consideration of other relevant variables..

.. to guide decisions on an appropriate course of action (whether an intervention, practice, policy, medical device, diagnostic).

“It’s not very efficient, or a good use of people's time for 194 countries to all be starting from a blank piece of paper.”

“So WHO provides guidelines and recommendations on all the elements that have to be thought about and the decisions that have to be made.”


WHO GUIDELINE
RECOMMENDATIONS ON DIGITAL INTERVENTIONS FOR HEALTH SYSTEM STRENGTHENING
EVIDENCE AND RECOMMENDATIONS
World Health Organization
World Health Organization
INTERIM GUIDELINES
UPDATED RECOMMENDATIONS ON FIRST-LINE AND SECOND-LINE ANTIRETROVIRAL REGIMENS AND POST-EXPOSURE PROPHYLAXIS AND RECOMMENDATIONS ON EARLY INFANT DIAGNOSIS OF HIV
SUPPLEMENT TO THE 2016 CONSOLIDATED GUIDELINES ON THE USE OF ANTIRETROVIRAL DRUGS FOR TREATING AND PREVENTING HIV INFECTION
DECEMBER 2018
HIV TREATMENT
GUIDELINES ON PHYSICAL ACTIVITY, SEDENTARY BEHAVIOUR AND SLEEP FOR CHILDREN UNDER 5 YEARS OF AGE
World Health Organization
World Health Organization
WHO HOUSING AND HEALTH GUIDELINES
WHO recommendations non-clinical interventions to reduce unnecessary caesarean sections
World Health Organization
RISK REDUCTION OF COGNITIVE DECLINE AND DEMENTIA
WHO GUIDELINES
World Health Organization
Child Maltreatment
Worldwide, 1 in 4 adults were physically abused as children.
The Health Sector Responds
World Health Organization
WHO interim guidelines for the treatment of gambiense human African trypanosomiasis
August 2019
World Health Organization

Guideline development principles:

Guideline development processes must be…

- ❑ Explicit and transparent.
- ❑ Have a well-described scope, objectives and target audience;
- ❑ Be multidisciplinary and include all relevant expertise and perspectives
- ❑ Include detailed funding sources
- ❑ Adhere to WHO reporting standards

Relevant contributors must:

- ❑ Disclose relevant interests and conflicts must be appropriately managed.

Recommendations should be:

- ❑ Informed by best available evidence.
- ❑ Be accompanied by a rationale, an assessment of the certainty of the evidence, the strength of the recommendation, and any differences in opinion among the guideline development group.
- ❑ Be clearly articulated and precise.

Pre-2007: Use of evidence in WHO recommendations…GOBSAT

"….Systematic reviews rarely used. Processes rely heavily on experts not on representatives of those who will have to live with the recommendations. Little attention given to effective dissemination, implementation and rigorous evaluation.."

Interpretation Progress in the development, adaptation, dissemination, and implementation of recommendations for member states will need leadership, the resources necessary for WHO to undertake these processes in a transparent and defensible way, and close attention to the current and emerging research literature related to these processes.

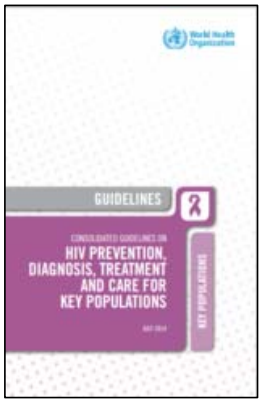
(J N Lavis MD)
Correspondence to:
Dr Andy Oxman
oxman@online.no

Types of WHO guidelines

- Standard guideline

Full systematic review and guideline development process

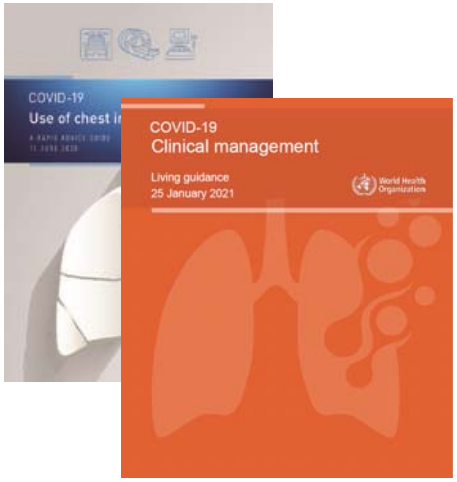
Timeframe: 6 months - 2 yrs



- Rapid advice guidelines

Compressed and abbreviated process in response to public health emergency

Timeframe: 1 - 3 months

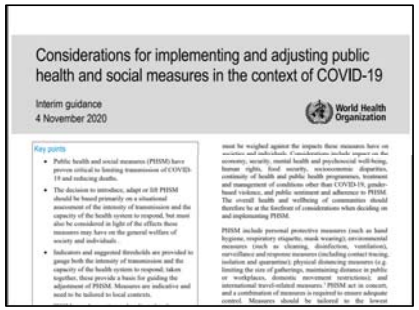


Emergency interim guidelines

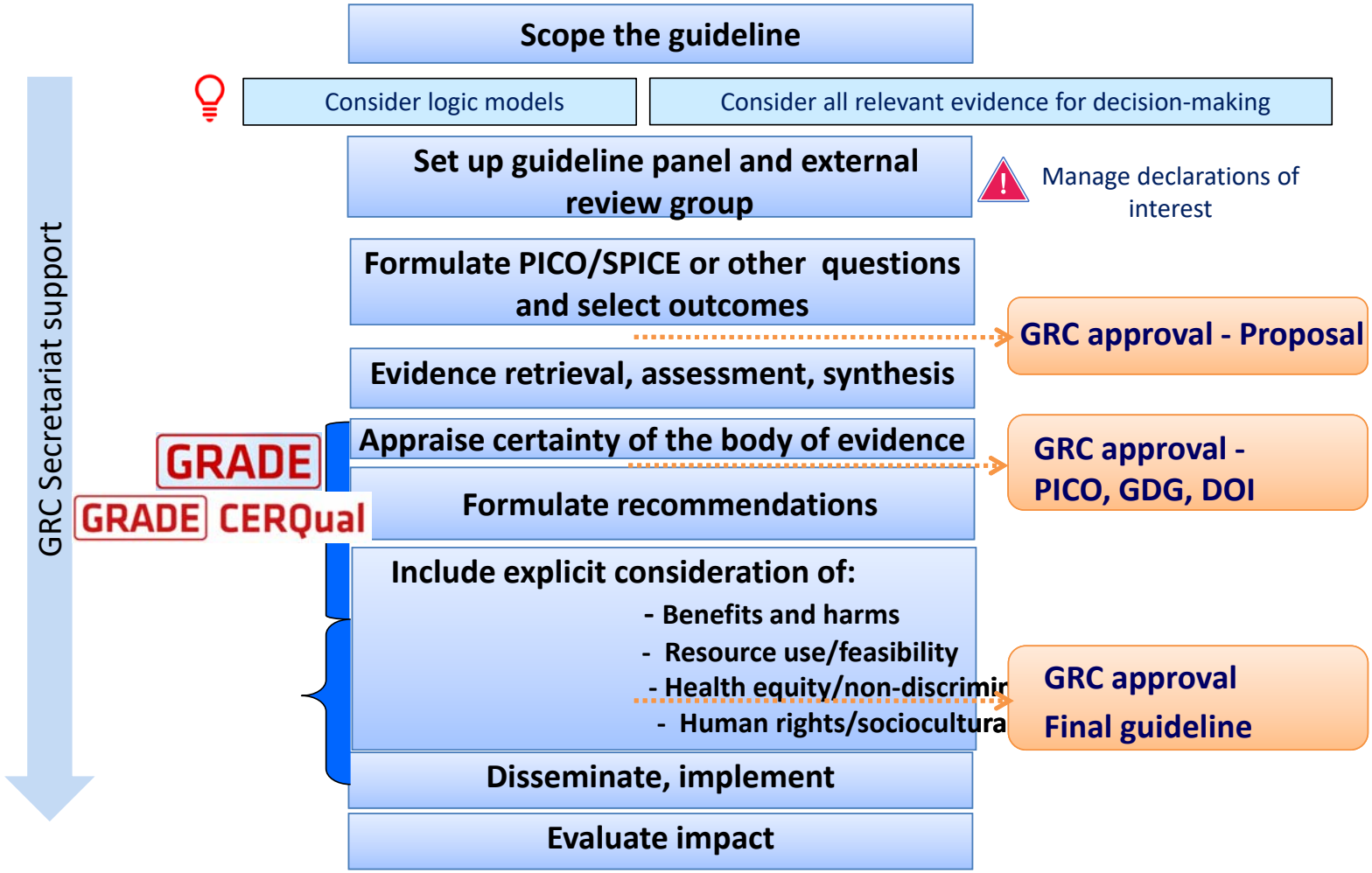
Narrow scope, short shelf-life

Can be based on indirect evidence, existing WHO guidelines or expert opinion

Timeframe: days - weeks



Guideline development process



Contributors to WHO guidelines

WHO Steering Group

- **Support** development of recommendations by the GDG

Guideline Development Group

- **Formulate** recommendations; approve the final guideline
- COI assessed and managed
- Participate as individuals; do not represent institutions
- Balanced in terms of gender, geographically, and perspective

Guideline methodologists

- **Help** the GDG to develop recommendations

+

- Meeting Observers
- External review team
- Systematic review team

Declaration of interests (DoI) of external contributors

WHO revised policy in 2014

- Employment, consulting
- Research support
- Investment interests
- Intellectual property
- Intellectual interests
- Public statements and positions

DoI required from

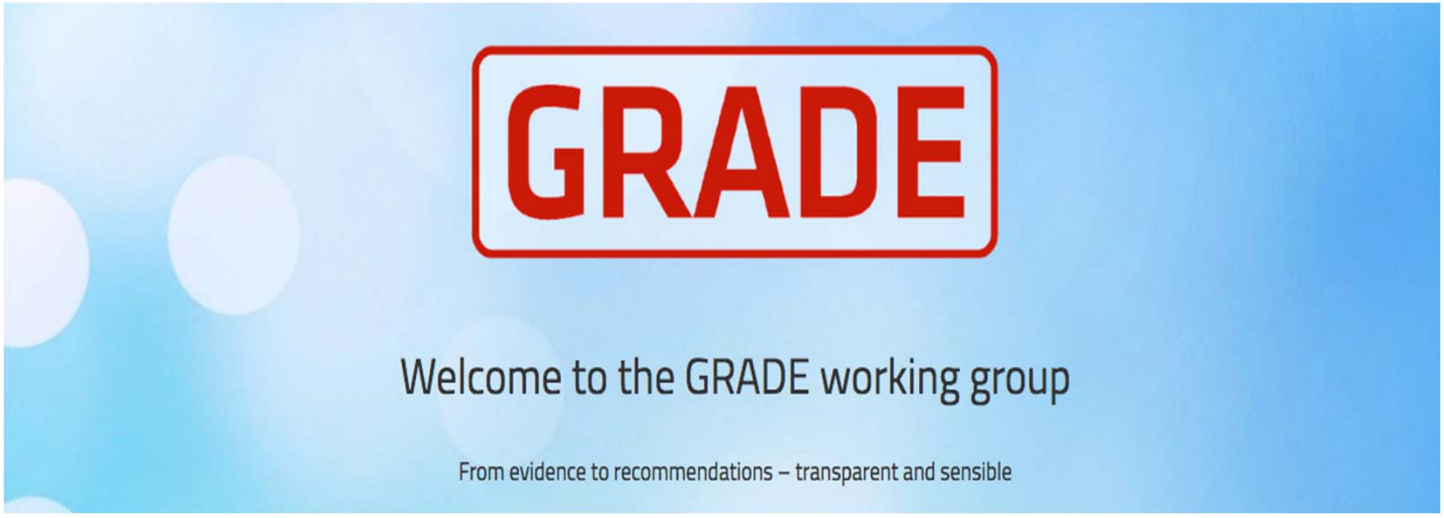
- The Guideline Development Group
- The Methodologist
- The Evidence Review Team

Public comment period (biographies posted for 14 days)

Internet search (due diligence)

Evidence retrieval, assessment and synthesis and formulation of recommendations

*To "reach agreement on a **common, sensible** approach to grading 1) quality of evidence and 2) strength of recommendations."*



Certainty of evidence

Certainty of evidence based on assessment of:

1. limitations in detailed design and execution *(risk of bias criteria)*
2. Inconsistency *(or heterogeneity)*
3. Indirectness *(PICO and applicability)*
4. Imprecision *(number of events and confidence intervals)*
5. Publication bias

3 factors can increase quality

1. Large magnitude of effect
2. All plausible residual confounding may be working to reduce the demonstrated effect or increase the effect if no effect was observed
3. Dose-response gradient

Strength of a recommendation

"The strength of a recommendation reflects the extent to which we can, across the range of patients for whom the recommendations are intended, be confident that desirable effects of a management strategy outweigh undesirable effects."

Strong recommendations: the desired consequences of adherence most likely outweigh potential undesired ones.

Conditional recommendations: the panel is less confident with regard to their judgement.

Implications

Implications of a strong recommendation

Most people in the situation would want the recommended course of action and only a small proportion would not

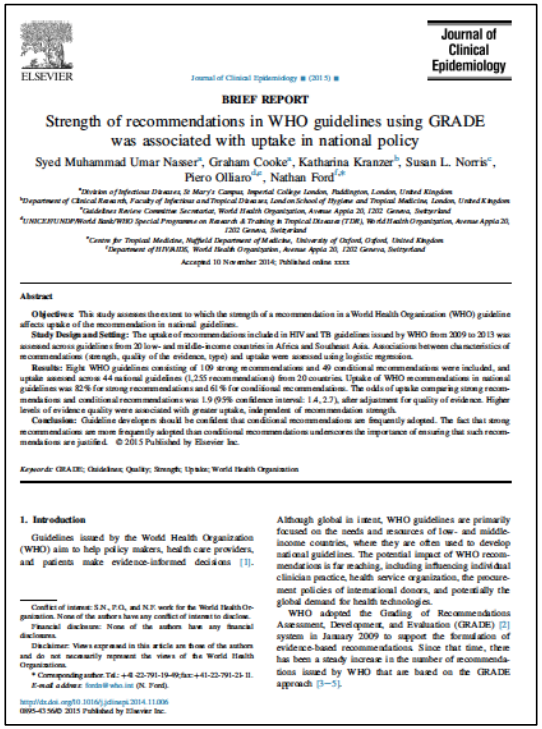
Implications of a conditional recommendation

The majority of people in your situation would want the recommended course of action, but many would not.
Requires shared decision-making and involvement of stakeholders

Factors affecting the strength of recommendations

- **Balance between benefits and harms**
  - The larger the relative benefit the more likely a strong recommendation
- **Certainty of the evidence**
  - Higher certainty (quality) evidence more likely to result in a strong recommendation
- **Values and preferences**
  - Decisions for which patient preferences or values are highly important or uncertain more likely to be graded as weak
- **Costs and resource allocation**
  - More costly/less cost-effective interventions less likely to receive a strong grade
- **Other factors**
  - Equity (how would recommendation impact equity)
  - Acceptability
  - Feasibility/ease of implementation

Uptake of recommendations



ELSEVIER

Journal of Clinical Epidemiology

Journal of Clinical Epidemiology ■ (2015) ■

BRIEF REPORT

Strength of recommendations in WHO guidelines using GRADE was associated with uptake in national policy

Syed Muhammad Umar Nasser[a], Graham Cooke[a], Katharina Kranzer[b], Susan L. Norris[c], Piero Olliaro[d,e], Nathan Ford[f,g]

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Abstract

Objectives: This study assesses the extent to which the strength of a recommendation in a World Health Organization (WHO) guideline affects uptake of the recommendation in national guidelines.

Study Design and Setting: The uptake of recommendations included in HIV and TB guidelines issued by WHO from 2009 to 2013 was assessed across guidelines from 20 low- and middle-income countries in Africa and Southeast Asia. Associations between characteristics of recommendations (strength, quality of the evidence, type) and uptake were assessed using logistic regression.

Results: Eight WHO guidelines consisting of 109 strong recommendations and 49 conditional recommendations were included, and uptake assessed across 44 national guidelines (1,255 recommendation-i) from 20 countries. Uptake of WHO recommendations in national guidelines was 82% for strong recommendations and 61% for conditional recommendations. The odds of uptake comparing strong recommendations and conditional recommendations was 1.9 (95% confidence interval: 1.4, 2.7), after adjustment for quality of evidence. Higher levels of evidence quality were associated with greater uptake, independent of recommendation strength.

Conclusion: Guideline developers should be confident that conditional recommendations are frequently adopted. The fact that strong recommendations are more frequently adopted than conditional recommendations underscores the importance of ensuring that such recommendations are justified. © 2015 Published by Elsevier Inc.

Keywords: GRADE; Guidelines; Quality; Strength; Uptake; World Health Organization

1. Introduction

Guidelines issued by the World Health Organization (WHO) aim to help policy makers, health care providers, and patients make evidence-informed decisions [1].

Although global in intent, WHO guidelines are primarily focused on the needs and resources of low- and middle-income countries, where they are often used to develop national guidelines. The potential impact of WHO recommendations is far reaching, including influencing individual clinician practice, health service organization, the procurement policies of international donors, and potentially the global demand for health technologies.

WHO adopted the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) [2] system in January 2009 to support the formulation of evidence-based recommendations. Since that time, there has been a steady increase in the number of recommendations issued by WHO that are based on the GRADE approach [3–5].

Conflict of interest: S.N., P.O., and N.F. work for the World Health Organization. None of the authors have any conflict of interest to disclose.

Financial disclosure: None of the authors have any financial disclosures.

Disclaimer: Views expressed in this article are those of the authors and do not necessarily represent the views of the World Health Organization.

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Adoption of recommendations across 44 guidelines in 20 countries

Strong: 82%
Conditional: 61%

Rules of Procedure:
Group decision making

WHO recommendations should be based on consensus

- Defined as general agreement among the decision makers
- Minor disagreements can be addressed in the Remarks Section of the guideline
- Voting can be used as a tool to achieve consensus

If consensus cannot be reached, voting can be used

- 2/3 majority, anonymous or hand-raising, Chair's discretion

Recommendation format

Recommendation
"At primary health-care facilities, health workers should provide general nutrition counselling to caregivers of overweight children aged less than 5 years (strength of recommendation: conditional; very low quality evidence)."
Justification remarks
Implementation consideration
Research priority

Supported by:
GRADE Evidence profile
Quality assessment of the body of evidence.

Evidence to decision framework
Strength assessment of the recommendation.

Summary: WHO Guidelines…

- Meet the highest quality standards for evidence-based guidelines
- Focus on UN Member States' and end-users' needs
  - Address the right questions
  - Optimize usability
  - Diverse stakeholder input into key development steps
- Are based on high-quality systematic reviews of all relevant evidence
- Use GRADE, which provides an explicit approach to:
  - Assessing the quality of the evidence across studies and outcomes
  - Translating evidence to recommendations
- Incorporate multiple processes to minimize bias
- All judgments and decision-making are transparent and explicit

Systematic review results

Dr Jason Montez

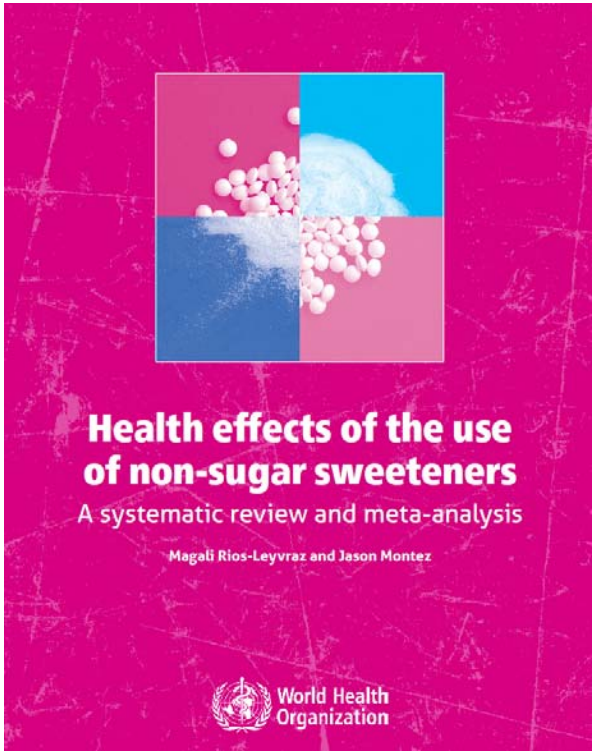
Scientist

Standards and Scientific Advice Food & Nutrition

Department of Nutrition and Food Safety

World Health Organization

Systematic review: updated and expanded

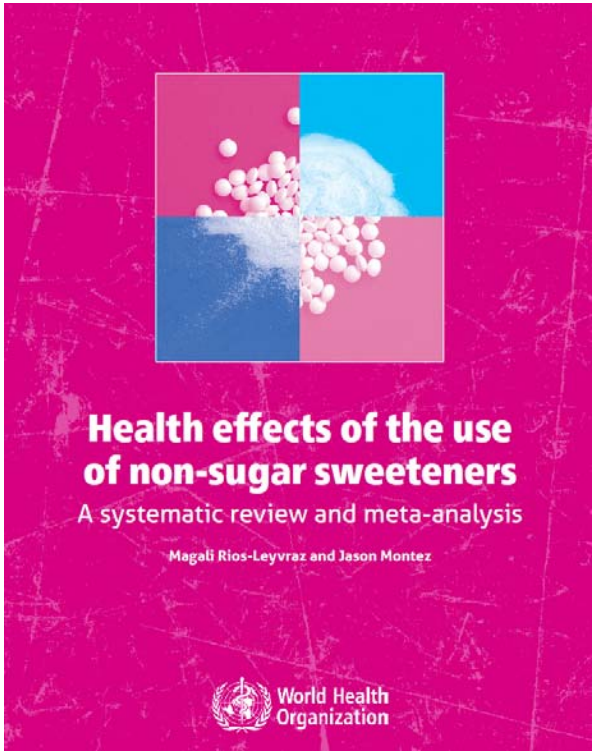


https://www.who.int/publications/i/item/9789240046429

Links on WHO NSS public consultation webpages

Google: "World Health Organization sweeteners"

Systematic review: updated and expanded



thebmj RESEARCH
2019

OPEN ACCESS

Check for updates

Association between intake of non-sugar sweeteners and health outcomes: systematic review and meta-analyses of randomised and non-randomised controlled trials and observational studies

Ingrid Toews,[1] Szimonetta Lohner,[2] Daniela Küllenberg de Gaudry,[1] Harriet Sommer,[1,3] Joerg J Meerpohl[1,4]

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[3]Institute for Medical Biometry

ABSTRACT

OBJECTIVE

To assess the association between intake of non-sugar sweeteners (NSS) and important health outcomes in generally healthy or overweight/obese adults and children.

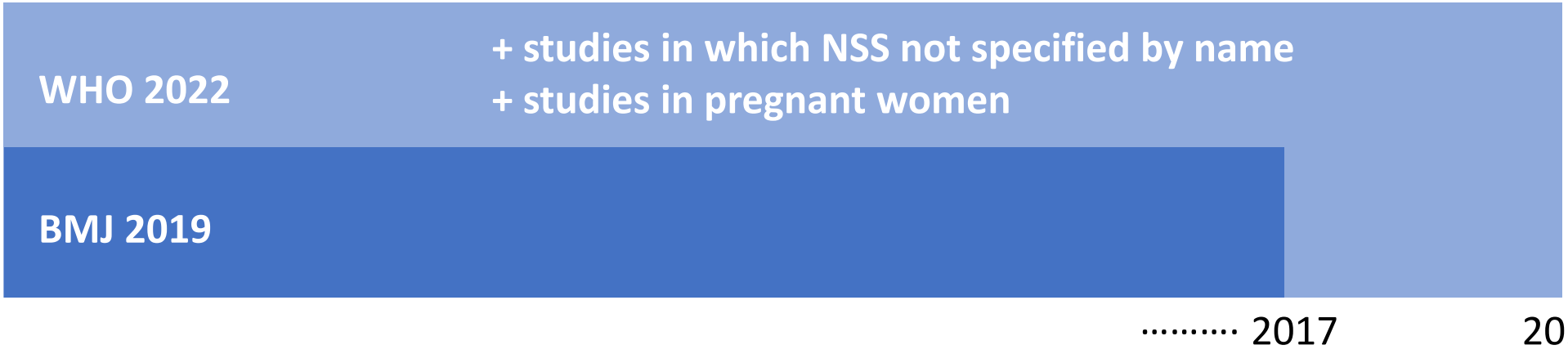
DESIGN

Systematic review following standard Cochrane review methodology.

DATA SOURCES

35 were observational studies. In adults, evidence of very low and low certainty from a limited number of small studies indicated a small beneficial effect of NSSs on body mass index (mean difference −0.6, 95% confidence interval −1.19 to −0.01; two studies, n=174) and fasting blood glucose (−0.16 mmol/L, −0.26 to −0.06; two, n=52). Lower doses of NSSs were associated with lower weight gain (−0.09 kg, −0.13 to −0.05; one, n=17 934) compared with higher doses of NSSs (very low certainty of evidence). For

What the update adds



Scope of systematic review

Key questions

- What are the health effects of NSS use?
  - What are the health effects of replacing free sugars with NSS?

Key elements of the scope of the review

- NSS = all sweeteners (– sugar alcohols, low-calorie sugars)
- Not a toxicological assessment
- Studies in individuals with pre-existing diabetes excluded

- Majority of studies assessed beverage sweetened with NSS

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  - What are the health effects of repla

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- Studies in individuals with pre-existing diabetes excluded

- Majority of studies assessed beverage sweetened with NSS

Acceptable daily intakes (ADI) as determined by the Joint FAO/WHO Expert Committee on Food Additives (JECFA)

Sweetener	ADI (mg/kg of body weight)
Acesulfame K	15
Advantame	5
Aspartame	40
Cyclamate	11
Neotame	0.3
Saccharin	15
Steviol glycosides	4
Sucralose	5

Scope of systematic review

Key questions

- What are the health effects of NSS use in general population?
  - What are the health effects of replacing free sugars with NSS?

Key elements of the scope of the review

- NSS = all sweeteners (– sugar alcohols, low-calorie sugars)
- Not a toxicological assessment
- Studies in individuals with pre-existing diabetes excluded

- Majority of studies assessed beverages sweetened with NSS

Results of systematic literature search: study types

Systematic search → 8237 references identified → 283 unique studies included

RCTs	Cohort studies	Case-control studies
50	**97**	**47**
45 adults	64 adults	41 adults
4 children	13 children	2 children
1 both	1 both	1 both
	17 pregnant women	(3 non-cancer)

+ non-RCTs (5), cross sectional studies (69), ongoing RCTs (15)

Results of systematic literature search: outcomes

Systematic search → 8237 references identified → 283 unique studies included

	RCTs	Cohort studies	Case-control studies
Body fatness	✓	✓	
Energy/sugars intake	✓		
Type 2 diabetes	✓	✓	
Cardiovascular diseases	✓	✓	
Cancer		✓	✓
Dental caries	✓		
All-cause mortality		✓	

✓ = intermediate markers of disease only (e.g. blood lipids, blood pressure, insulin, blood glucose)

Results of systematic literature search: study settings

Systematic search → 8237 references identified → 283 unique studies included

RCTs

Australia (2)
Denmark (2)
France (2)
Greece (1)
Korea (4)
India (1)
Iran (1)
Italy (1)
Latvia (1)
Mexico (6)
Netherlands (1)
New Zealand (2)
South Africa (1)
Switzerland (1)
Thailand (1)
UK (7)
US (15)
Multi-country (1)

Cohort studies

Australia (5)
Canada (1)
Denmark (7)
France (4)
Germany (1)
Iceland (1)
Japan (1)
Mexico (1)
Netherlands (1)
Norway (2)
Russia (1)
Slovenia (1)
Spain (4)
UK (3)
US (59)
Multi-country (5)

Case-control studies

Argentina (2)
Canada (4)
China (2)
Denmark (3)
Egypt (1)
France (2)
Italy (2)
Japan (2)
Lebanon (1)
Serbia (1)
Spain (1)
Sweden (2)
UK (2)
US (15)
Multi-country (1)

Results: types of RCT interventions

1. NSS or sugars given as supplement*
2. NSS or water given as supplement*
3. NSS or nothing given as supplement*
4. Existing sugars use replaced with NSS
5. Weight loss: NSS or sugars
6. NSS capsules or placebo
7. Habitual NSS users asked to stop

* In addition to the normal diet

Results: types of RCT interventions: body weight

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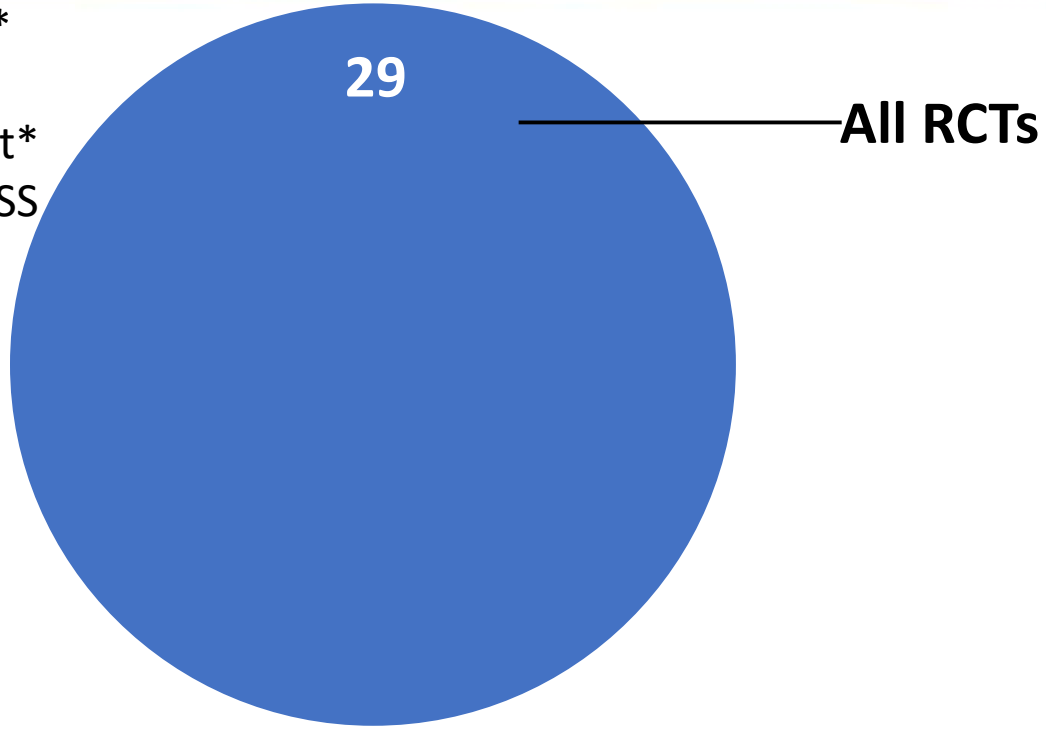

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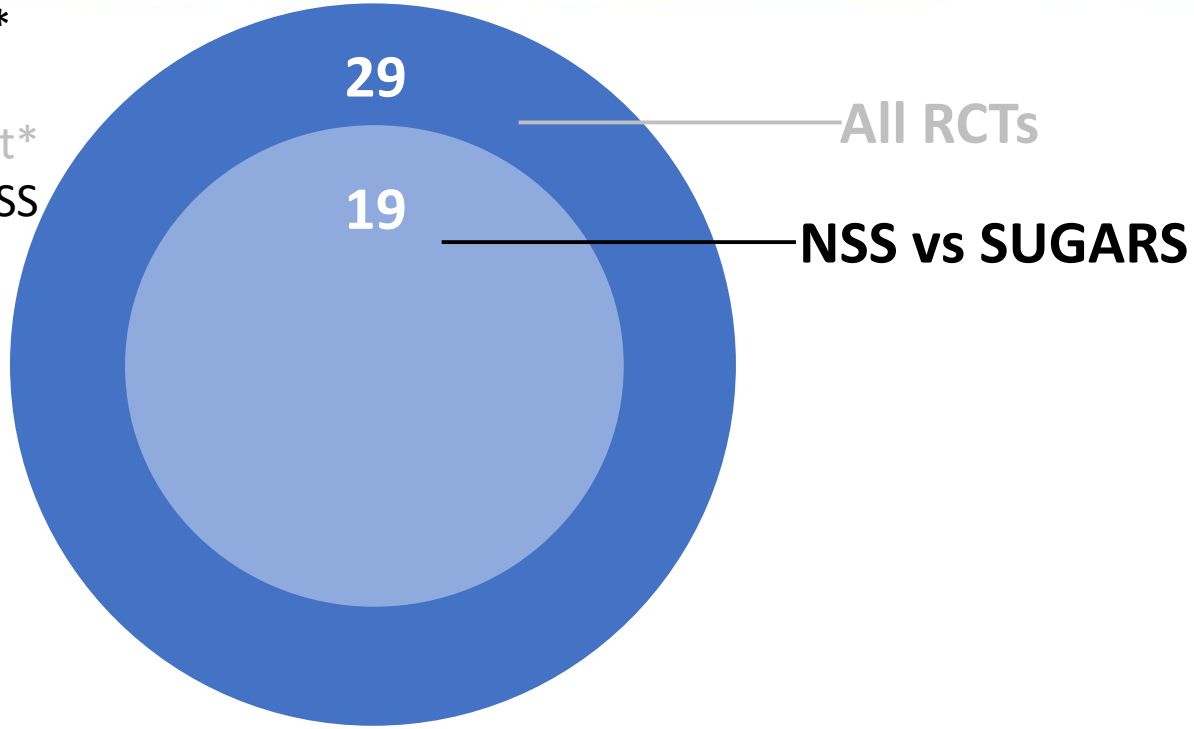

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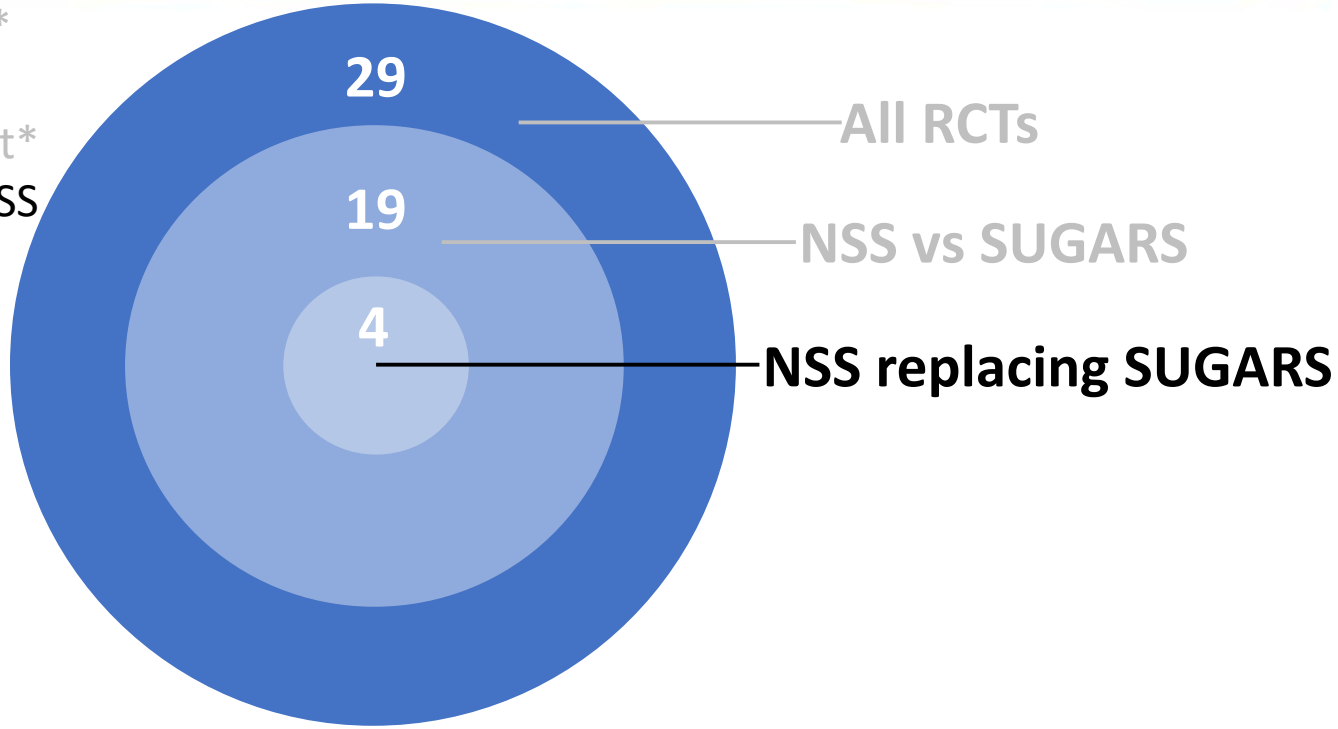
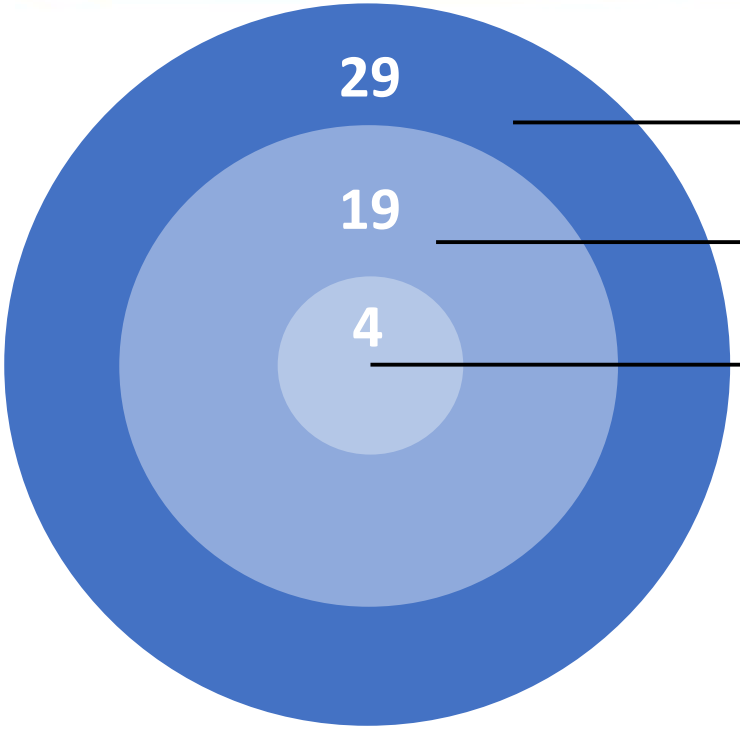
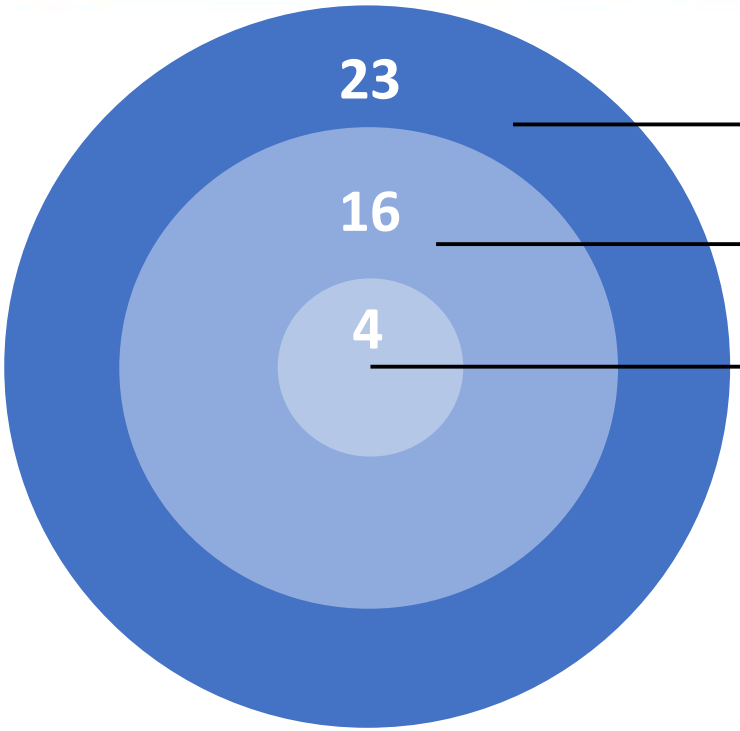


Results: types of RCT interventions: body weight



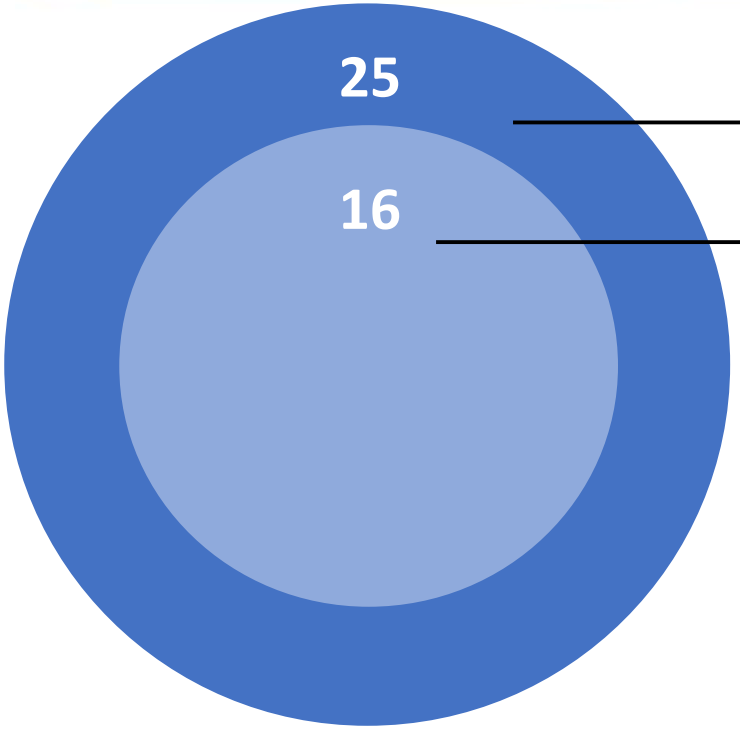
All RCTs	- 0.71 kg (-1.13, -0.28)
NSS vs SUGARS	- 0.76 kg (-1.18, -0.34)*
NSS replacing SUGARS	- 0.61 kg (-1.28, 0.06)
*NSS vs nothing	- 0.29 kg (-1.20, 0.62)
NSS vs water	- 0.51 kg (-2.40, 1.37)

Results: types of RCT interventions: BMI (kg/m^2)



All RCTs	**- 0.14 (-0.30, 0.02)**
NSS vs SUGARS	**- 0.21 (-0.36, -0.06)***
NSS replacing SUGARS	**- 0.01 (-0.38, 0.35)**
***NSS vs nothing**	**- 0.26 (-0.68, 0.16)**
NSS vs water	**0.37 (-0.02, 0.77)**

Results: types of RCT interventions: energy intake



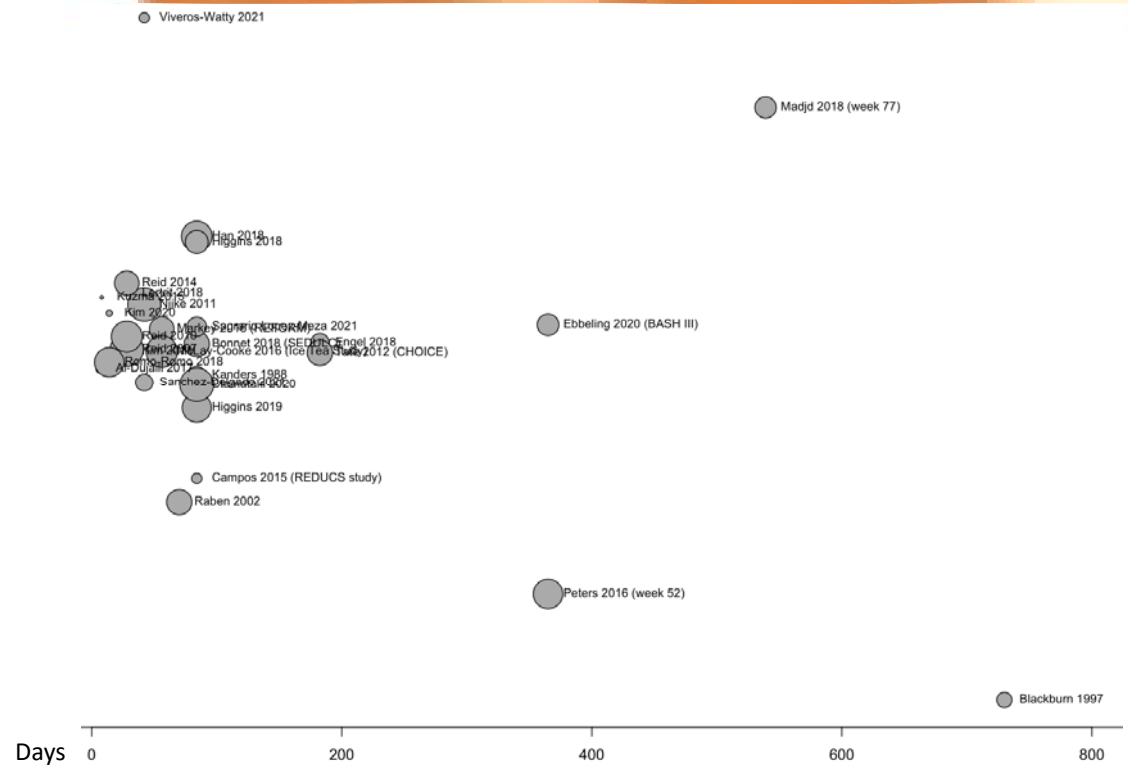
All RCTs	**- 568 kJ (-859, -278)**
NSS vs SUGARS	**- 1008 kJ (-1397, -620)***
***NSS vs nothing**	**- 478 kJ (-1426, 470)**
NSS vs water	**183 kJ (-235, 602)**

Results: assessment of RCT data

Other subgroup analyses included:

- Type of NSS
- Body weight status of participants (i.e. lean, mixed, oveweight/obese)
- Mode of delivery of NSS (e.g. food, beverage, capsule, tabletop)
- NSS consumption patterns
- Focus of trial (weight loss vs non-weight loss)

Results: RCT study duration



1 month or less	**9**
1-3 months	**14**
More than 3 months	**6**

(Cohort studies generally assessed on order of years)

Results: NSS use and measures of body fatness

Outcome	Pooled estimate (95%CI)	No. studies	No. participants	Certainty	
Body weight (kg)					
RCT	**MD –0.71 (–1.13 to –0.28)**	29	2 443	*Low*	**-0.71 kg**
Observational (cont)	MD –0.12 (–0.40 to 0.15)	4	118 457	*Very low*	
Observational (H/L)	MD –0.01 (–0.67 to 0.64)	5	11 874	*Very low*	
BMI (kg/m^2)					
RCT	MD –0.14 (–0.30 to 0.02)	23	1 857	*Low*	
Observational	**MD 0.14 (0.03 to 0.25)**	5	80 573	*Very low*	**Increase of 0.14**
Obesity					
Observational	**HR 1.76 (1.25 to 2.49)**	2	1 668	*Low*	**76% increase in risk**

No impact on other measures of body fatness (e.g. % fat, waist circumference, wait-to-hip ratio)

Results: NSS use and type 2 diabetes

Outcome	Pooled estimate (95%CI)	No. studies	No. participants	Certainty	
Type 2 diabetes					
Observational (bev)	**HR 1.23 (1.14 to 1.32)**	13	408 609	*Low*	**23% increase in risk with beverages**
Observational (TT)	**HR 1.34 (1.21 to 1.48)**	2	62 582	*Low*	**34% increase in risk with tabletop**
Fasting glucose (mmol/L)					
RCT	MD –0.01 (–0.05 to 0.04)	16	1 494	*Moderate*	
Fasting insulin (pmol/L)					
RCT	MD –0.49 (–4.99 to 4.02)	10	759	*Low*	
HbA1c (%)					
RCT	MD 0.02 (–0.03 to 0.07)	6	411	*Moderate*	
HOMA-IR					
RCT	MD 0.03 (–0.32 to 0.38)	11	786	*Low*	
High fasting glucose					
Observational	**HR 1.21 (1.01 to 1.45)**	3	11 213	*Low*	**21% increase in risk**

Results: NSS use and cardiovascular diseases

Outcome	Pooled estimate (95%CI)	No. studies	No. participants	Certainty	
CVD mortality					
Observational	**HR 1.19 (1.07 to 1.32)**	5	598 951	*Low*	**19% increase in risk**
CVD					
Observational	**HR 1.32 (1.17 to 1.50)**	3	166 938	*Low*	**32% increase in risk**
CHD					
Observational	HR 1.16 (0.97 to 1.39)	4	205 455	*Very low*	
Stroke					
Observational	**HR 1.19 (1.09 to 1.29)**	6	655 953	*Low*	**19% increase in risk**
Hypertension					
Observational	**HR 1.13 (1.09 to 1.17)**	6	234 137	*Low*	**13% increase in risk**
Systolic blood pressure (mmHg)					
RCT	MD –1.33 (–2.71 to 0.06)	14	1 440	*Moderate*	
Diastolic blood pressure (mmHg)					
RCT	MD –0.51 (–1.68 to 0.65)	13	1 137	*Moderate*	
LDL cholesterol (mmol/L)					
RCT	MD 0.03 (–0.03 to 0.09)	12	1 193	*Low*	

No impact on other measures of CVD risk (e.g. total or HDL cholesterol, triglycerides)

Results: NSS use and cancer or CKD

Outcome	Pooled estimate (95%CI)	No. studies	No. participants	Certainty
Cancer mortality				
Observational	HR 1.02 (0.92 to 1.13)	4	568 175	*Very low*
Cancer (any type)				
Observational	HR 1.02 (0.95 to 1.09)	7	942 600	*Very low*
Bladder cancer				
Observational (CC)	**OR 1.31 (1.06 to 1.62)**	26	39 660	*Very low*
Chronic kidney disease				
Observational	HR 1.41 (0.89 to 2.24)	2	18 372	*Very low*

31% increase in odds

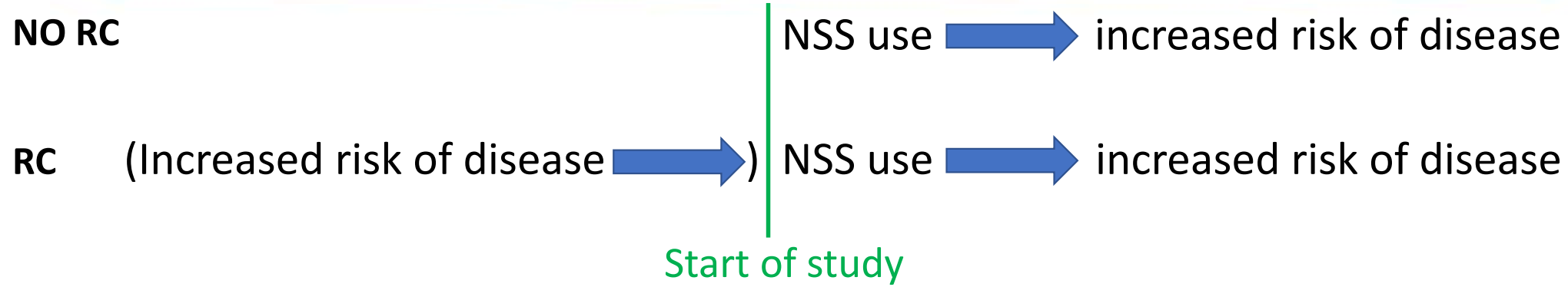
No/little impact on other types of cancers

Results: NSS use and mortality from any cause

Outcome	Pooled estimate (95%CI)	No. studies	No. participants	Certainty
All-cause mortality				
Observational	**HR 1.12 (1.05 to 1.19)**	8	860 873	*Very low*

12% increase in risk

Results: Reverse causation



Individuals assessed as higher consumers of NSS at start of study are already at high risk for disease and in response, have initiated or increased NSS intake to mitigate that risk

Efforts by study authors to statistically control for reverse causation did not significantly change the results observed

Results: NSS use by children

Outcome	Pooled estimate (95%CI)	No. studies	No. participants	Certainty	
Body weight (kg)					
RCT	**MD –1.01 (–1.54 to –0.48)**	1	641	*Moderate*	**-1.01 kg**
Observational (cont)	MD 0.03 (–0.14 to 0.21)	2	1 633	*Low*	
BMI (kg/m^2)					
Observational (cont)	MD 0.08 (–0.01 to 0.17)	5	11 907	*Very low*	
Observational (H/L)	MD 0.04 (–0.32 to 0.40)	2	2 426	*Very low*	
BMI *z* score					
RCT	MD –0.07 (–0.26 to 0.11)	2	1 264	*Moderate*	
Observational (cont)	MD –0.23 (–0.70 to 0.25)	3	610	*Very low*	
Observational (H/L)	MD 0.00 (–0.30 to 0.30)	1	98	*Very low*	
Body fat mass (%)					
RCT	**MD –1.07 (–1.99 to –0.15)**	1	641	*Moderate*	**-1.07 kg**
Observational	MD –1.53 (–5.73 to 2.66)	2	720	*Very low*	

Small decreases in waist circumference in one RCT, no difference in odds of overweight in 2 cohort studies. Limited evidence for reduction in markers of dental caries in two RCTs

Results: NSS use by pregnant women

Outcome	Pooled estimate (95%CI)	No. studies	No. participants	Certainty
Preterm birth				
Observational	**OR 1.25 (1.07 to 1.46)**	3	129 009	*Low*

25% increase in odds

Inconsistent evidence for impact on body weight of offspring

Results: summary

- Small reductions in body weight, BMI in short-term RCTs: only in NSS vs sugars, attenuated when NSS specifically replace sugars
- In the long-term (cohort studies) measures of body fatness not impacted by NSS or are increased
- Long-term use of NSS associated with increased risk of NCDs and mortality; role of reverse causation unclear
- Limited data for children and pregnant women: no clear-cut benefit, and suggestion of undesirable effects in pregnant women

Strengths and limitations of the systematic review

Strengths

- Breadth and depth of the data identified from different study types
- Rigorous assessment of the certainty in the evidence via GRADE
- Consistency with other recent systematic reviews

Limitations

- Unable to combine (meta-analyse) a portion of the data
- Unable to fully account for the effects of water compared with NSS-sweetened beverages
- Limited in our ability to assess potentially differential health effects of individual sweeteners

Acknowledgements

Dr Magali Rios-Leyvraz

Dr Ingrid Töews, Dr Szimonetta Lohner and rest of 2019 systematic review team

Dr Andrew Reynolds

Professor Lee Hooper

Dr Russell De Souza

WHO Nutrition Guidance Expert Advisory Group Subgroup on Diet and Health

Draft recommendation and supporting information

Professor Shiriki Kumanyika

Chair, WHO NUGAG Subgroup on Diet and Health
Emeritus Professor
Perelman School of Medicine
University of Pennsylvania
United States of America

Recommendation on NSS

Recommendation based on

- Review of the scientific evidence: health effects of NSS
- Review of evidence on potentially mitigating factors

- [Not assessment of safe levels of intake, ADI]

Rationale for the recommendation

Evidence and considerations:

- No evidence of long-term benefit on measures of body fatness in adults or children
- Potential undesirable effects from long-term use in the form of increased risk of type 2 diabetes, cardiovascular diseases, and mortality in adults, and from short-term use during pregnancy
- Reduction in free sugars intake can be achieved without NSS
- No identified undesirable effects or other mitigating factors that would argue against not using NSS

Rationale for the recommendation

- Because the primary role of NSS use is presumably to reduce free sugars intake, the currently available evidence on which to base a recommendation on NSS is largely indirect: i.e. most RCTs comparing NSS to free sugars did not explicitly assess the replacement of free sugars with NSS
- Because weight loss and maintenance of healthy weight must be sustained over the long-term to have a meaningful impact on health, evidence of minor, short term weight loss as observed in the RCTs without additional evidence of long-term impact, does not represent a health benefit
- The discordant results between RCTs and cohort studies suggest that weight loss resulting from NSS use in short-term experimental settings may not be relevant to the effects of long-term, real-world NSS use in the general population

Evidence to recommendation: not using NSS

Potential mitigating factor
Magnitude of the desirable effects (of using NSS)
Magnitude of the undesirable effects (of using NSS)
Overall certainty of the evidence
Balance of desirable and undesirable effects
Values and preferences
Resource implications
Cost-effectiveness
Acceptability to key stakeholders
Feasibility of implementing
Impact on health equity

Evidence to recommendation: not using NSS

Comprehensive reviews of the relevant literature were conducted for each of the potentially mitigating factors

Results were reviewed and discussed by NUGAG in order to make judgements

Evidence to recommendation: not using NSS

Potential mitigating factor	Judgement
Magnitude of the desirable effects (of using NSS)	Unknown*
Magnitude of the undesirable effects (of using NSS)	Moderate (adults, pregnant women), unknown (children)
Overall certainty of the evidence	Low
Balance of desirable and undesirable effects	Probably favours not using NSS
Values and preferences	Probably no important uncertainty or variability
Resource implications	Limited evidence, but costs of implementing likely vary
Cost-effectiveness	Unknown (insufficient evidence to assess)
Acceptability to key stakeholders	Varies
Feasibility of implementing	Probably feasible
Impact on health equity	Probably increased

* Short term weight loss not considered a desirable health effect on its own, without evidence that weight loss can be maintained in the long term

Recommendation on NSS

WHO suggests that NSS not be used as a means of achieving weight control or reducing risk of noncommunicable diseases

Strength of the recommendation

WHO suggests that NSS not be used as a means of achieving weight control or reducing risk of noncommunicable diseases (*conditional* recommendation)

Because of lack of certainty about the overall balance of desirable and undesirable effects associated with long-term effects of NSS use for reducing non communicable disease risk, including the possibility that reverse causation may have contributed to one or more of the associations observed between long-term NSS use and risk of disease in observational studies, a conservative approach was taken, and the recommendation was considered to be conditional.

Key remarks

- With the possible exception of individuals with diabetes (as noted below), this recommendation is relevant for everyone
- Assessing the health effects of NSS on individuals with pre-existing diabetes was beyond the scope of this guideline. Consequently, in the evidence reviewed, studies conducted exclusively in individuals with pre-existing diabetes were excluded, and in studies with mixed populations, diabetes was often controlled for as a potential confounding characteristic. Therefore, while individuals with diabetes can also reduce free sugars intake without the need for NSS, the recommendation may not apply to those with existing diabetes.
- “Use” of NSS means consumption of foods or beverages that contain NSS or the addition of NSS to food or beverages by the consumer.

Key remarks

- “Weight control” in this recommendation refers to weight loss in cases of existing overweight or obesity, and preventing unhealthy weight gain by maintaining a healthy weight.
- This recommendation is relevant for all NSS, which are defined in this guideline as all synthetic and naturally occurring or modified non-nutritive sweeteners that are not classified as sugars. Sugar alcohols and low-calorie sugars are not considered NSS. Common NSS include, but are not limited to, acesulfame K, aspartame, advantame, cyclamates, neotame, saccharin, sucralose, stevia and stevia derivatives.

Key remarks

- The recommendation was made based on evidence which suggests that there are health effects associated with NSS use irrespective of which NSS is being used, i.e. NSS as a class of compounds, despite individual NSS having different chemical structures, have an impact on health.
- It is recognized that NSS are not a homogenous class of compounds: each has a unique chemical structure and as a result, individual NSS have different sweetness intensities and organoleptic properties, and are processed differently by the body. Limited evidence suggests that individual NSS may also differ in their physiological effects in humans, however, evidence is currently insufficient to make recommendations for individual NSS

Key remarks

- It is noted that many medications and personal care and hygiene products contain NSS in small amounts to make them more palatable. The recommendation in this guideline does not imply that such medications or products should not be used, however, NSS-free versions of these items, when readily obtainable, can be considered

Key remarks

- Efforts to reduce free sugars intake should be implemented in the context of achieving and maintaining a healthy diet. Because free sugars are often found in highly processed foods and beverages with undesirable nutritional profiles, simply replacing free sugars with NSS results in a food or beverage in which any other unhealthy elements are mostly retained, and as a result, the overall quality of the diet remains largely unaffected.
- Replacing free sugars in the diet with sources of naturally occurring sweetness, such as fruits, as well as minimally processed unsweetened foods and beverages, will help to improve dietary quality and should be the preferred alternatives to foods and beverages containing free sugars

Public consultation process

Public consultation

- Open from: 15 July (16h CEST) – 14 August 2022 (23:59 CEST)
- The public consultation is open to all, However, a completed and signed Declaration of Interest (DOI) form **must accompany any comments**.
- All comments appreciated, in particular on:
  - overall clarity
  - considerations and implications for adaptation and implementation of the guideline
  - context and setting-specific issues that have not yet been captured, and
  - any errors of fact or missing data.

Closing remarks

Dr Francesco Branca
Director
Department of Nutrition and Food Safety
World Health Organization

World Health Organization