Discussion

Sugar tax: plausibility and value of the studies

The authors of a study [1], which extrapolated the possible effect of various tax models or a graduated manufacturer levy on sugared drinks, came to the conclusion that such a tax would have some effects (see box: 'Expected effects') in Germany in the years 2023 to 2043. Specialist organisations such as the German Diabetes Society are calling for the introduction of such a tax and claim that the benefits have been proven. This paper evaluates the plausibility and value of the observational studies used for the optimistic calculations in [1].

Non-controversial issues

>> There is no doubt :

- The availability of energy-dense foods is essential for increasing body weight in an affluent society .
- Dietary habits and the risk of disease are subject to the influence of many factors, such as depression, medication, psychological stress, shift work, poverty, education and other factors.
- When calculating the correlation between sugar consumption, weight, type 2 diabetes and associated diseases, epidemiological studies cannot differentiate between 'with' and 'because of' diabetes.
- It is undisputed that many measurable parameters (e.g. LDL cholesterol, blood glucose, weight) are altered in diseases and can be influenced by diet and exercise..

Controversial issues

It is disputed whether:

- the effects extrapolated by simulation, as in study [1], actually materialise and are clinically relevant ;
- the 'cardiometabolic effect' assumed by the authors actually exists or is merely a laboratory finding correlated with disease ;
- there is a pathophysiological basis on the basis of which a change in sugar intake can have effects on cells and blood vessels ;
- government action is justified if studies to justify the sugar tax are selectively chosen, higher-quality studies, a Cochrane review and the experience of others are not taken into account.

Why we need to comment on the statements

If the authors' statements [1] were correct, this would have the following consequences:

1. recognising disease risks and early stages of disease would fall within the remit of observational epidemiology and population-level policy-making. This would only be justifiable if the study situation suggests a health and economically relevant effect (apart from the state tax revenue).
2. it is a question of weighing up the rights of the individual against the rights of the state to intervene.s.

General background

How is type 2 diabetes mellitus defined?

A threshold value for glucose that can be measured in the laboratory, the glucose increase in the exercise test and the HbA1c value, is used for the definition. These were set so low that diabetic complications are extremely rare when the threshold value is reached [2-7]. These parameters were chosen on the assumption that their normalisation would prevent diabetes-related diseases. If this assumption were correct, it should be possible to prevent diseases associated with diabetes by normalising blood glucose levels. However, this only applies to diabetic coma, but not to all other diabetic complications. The reasons for this are the many different subgroups that can be distinguished using classical markers [7, 8] and pathophysiological criteria, e.g. DNA damage [9, Diabetology and Metabolism 2022; 17(05): 349-352], and the knowledge of the need for multifactorial therapy in type 2 diabetes [11-14].

Type 2 diabetes prevention and early detection - status of intervention studies

1. can diabetes prevention prevent secondary damage?

Calculated effects (1)

- Prevention or delay of 132,100 to 244,100 cases of type 2 diabetes.
- Gain of 106,000 to 192,300 quality-adjusted life years.
- Prevention or delay of 17,000 to 29,300 deaths.
- Savings of 10.8 to 16 billion euros, including 2.2 to 3.85 billion euros in healthcare costs, the remainder consisting of saved sick days, incapacity to work, etc.
- The long-term effect of sugar reduction on health depends on the cardiometabolic, body mass index (BMI) independent effects of sweetened drinks.

Many studies have shown that a comprehensive lifestyle intervention can reduce the incidence of diabetes by around 50% in people at risk [15-39].

1. a) Diabetes Prevention Programme and its Outcome Study (DPPOS) [16, 28, 29]

3,234 subjects with impaired glucose tolerance received either metformin 850 mg twice daily, intensive lifestyle intervention or placebo for 3 years, followed by 18 months of slightly less intensive lifestyle intervention. The effect on cardiovascular disease was analysed. The result after 21 years.

Neither metformin nor the lifestyle intervention reduced the incidence of cardiovascular events (non-fatal heart attack, stroke and death) during follow-up (up to 21 years), despite demonstrable effects on the incidence of diabetes, blood glucose levels, smoking cessation and weight loss.

1. b) Finish National Diabetes Prevention Programme (FIN-D2D) [30-37]

This study of 10,149 subjects at high risk for type 2 diabetes, produced a risk reduction in diabetes after a median follow-up of 7.4 years. Despite the diabetes prevention, which was still detectable after 13 years [33], weight

loss and improvement in cardiometabolic parameters, this intervention study showed no reduction in the occurrence of cardiovascular events or death from any cause (36-37).

1. c) Da-Quing study [35, 36, 40, 41]:

This study included only 438 adults with impaired glucose tolerance in the intervention group and 138 in the control group (n = 138) [35]. The intervention led to a 51% reduction in the incidence of type 2 diabetes, and 43% in the follow-up phase (20 years) [35]. Nevertheless, no significant effect of the intervention on the occurrence of a cardiovascular event or death was detectable after 20 years [35]. After 23 years, the result was only significant for women. After 30 years, it was reported [36, 40] that the intervention led to fewer cardiovascular events (HR 0.74, 95% CI 0.59-0.92), fewer microvascular complications (HR 0.65, 95% CI 0.45-0.95), fewer deaths (HR 0.74, 95% CI 0.61-0.89) and a mean life extension of 1.44 years (95% CI 0.2-2.68) [36].

There are several reasons to doubt the reliability of the data from the Da-Quing study:

- The small number of cases: at the 30-year evaluation [36], only 59 of 138 subjects in the control group and 220 of 438 subjects in the intervention group were still alive.
- The 95% confidence interval ranges from no effect to a good effect of prevention .
- The groups analysed were not comparable. From the second year onwards (Figure 3 C in 40), the curves for cardiovascular death diverge.
- The morbidity rate of the Da-Quing study is not comparable with the two other studies and European experience .

2. Can earlier diagnosis and treatment of type 2 diabetes prevent diabetes-associated diseases?

In an endpoint study of 16,047 patients over 10 years, no effect of early diagnosis and treatment of diabetes mellitus was found after 10 years [42].

The lack of clinical significance of cardiometabolic markers using the example of the long-term blood glucose value HbA1c

1. Can an intensified lifestyle programme reduce the incidence of cardiovascular disease in type 2 diabetics?

The UKPDS study was claimed to show that every 1% reduction in HbA1c reduces the risk of diabetes-associated disease by 21% [43]. As the UKPDS study was never designed to do this, calculations were necessary to arrive at this conclusion. A closer look at Figure 2 of this paper [43] reveals an anomaly: the difference in the incidence of myocardial infarction or microvascular complications between an HbA1c of 7% and 8.5%, i.e. the clinically relevant range, is less than 10% in each case and not - as claimed - 21%.

The difference in the incidence of disease per 1,000 patient years, i.e. between an HbA1c of 5.5% (normal) and 6.5% (slightly elevated), is relevant for the sugar tax hypothesis. It is less than 5%. The effect assumed in (1) is therefore not to be expected. This example and other examples [44-47] show that the translation of observational data into supposedly causality-proving statements such as 'this leads to ...' leads to false conclusions.

2. Does lowering HbA1c in non-diabetic patients prevent disease?

There are no good intervention studies to support this assumption. The Women Health Study, a 10-year prospective cohort study, investigated whether a slightly higher HbA1c level in non-diabetic women predicts cardiovascular disease and the onset of diabetes [48]. After multivariate analysis (smoking, origin, hypertension, BMI, etc.), the increase in risk for future diabetes remained, but there was no evidence of a prediction of cardiovascular events. One reason for this is the considerable differences between people: At a given glucose level, some make significantly more HbA1c than others [49]. This means that 21% of the differences in HbA1c levels are not explained by glucose levels ('glucose gap').

3. Can an intensified lifestyle programme reduce the incidence of cardiovascular disease in type 2 diabetics?

The Look-AHEAD study investigated whether a much more far-reaching lifestyle intervention than a control programme that only slightly reduces sugar consumption has effects on diseases (and not just laboratory values) [50-54]. Despite effects achieved on parameters predicting cardiometabolic risk, there were no effects on cardiovascular endpoints.

Effects of reducing sugar consumption in intervention studies

1. Intervention studies with a reduction in sugar consumption

In the study by C. B. Ebbeling [55, 56], 224 overweight to obese adolescents received a one-year intervention to reduce their intake of sugared drinks. There was a reduction in the intake of sugar-sweetened beverages in the intervention group, which was still around 50% even in the second year.

In the first year of the intervention, the intervention group gained 1.6 kg and the control group 3.5 kg. The difference was 1.9 kg and was reduced to 0.8 kg after the second year (although the intervention group continued to consume significantly fewer sweetened drinks). As the adolescents were still growing, the BMI difference is important: after one year it was 0.57, after two years only 0.3 in favour of the intervention group and was not statistically significant. The subgroup analysis revealed that a significant effect of -8.8 kg after 2 years and a BMI drop of -2.35 was only detectable in those with a Hispanic background. As the effect of sugar reduction diminishes over time, it must be assumed that a sugar tax has failed.

In addition, the study participants appear to look for alternative sources of calories after some time: When normal-weight children are studied over 18 months [57], the children in the sugar-free group lose weight slightly in the first 6 months. After 6 months, however, weight began to increase again, almost in line with the control group. In the end, the groups only differed by slightly more than 1 kg.

One explanation is the genetically determined relationship between obesity and the intake of sweetened beverages [58]. If sweetened drinks are omitted, the calorie requirement is compensated for in other ways. Overall, the study situation is inconclusive [57-68], with either undetectable effects or effects so small that they cannot be clinically relevant. This does not change when meta-analyses such as the one by Malik in Am J Clin Nutr 2013, 98:1084-1102 calculate that withdrawal from sweetened beverages has a stronger effect than health education at school. The small effect and a 25% dropout rate [69] in studies makes it unlikely that a tax on sugary drinks will be successful. Nevertheless, in some reviews the conclusion ('Reduction of sugar intakein sweetened be-

verages is effective') is not consistent with the previously presented results ('We found low-certainty evidence') [69].

A similar approach is taken in an expert statement (doi: 10.2903/j.efsa.2022.7074). After reviewing the literature, the working group comes to the following conclusion: 'Based on a systematic review of the literature, prospective cohort studies do not support a positive relationship between the intake of dietary sugars, in isocaloric exchange with other macronutrients, and any of the chronic metabolic diseases or pregnancy-related endpoints assessed. ... The n

cipants. Cardiovascular events occurred in 4.4% of the control group, 3.8% of the olive oil group and 3.4% of the nut group. Comparing the best with the worst group, the difference was 1% with a 95% confidence interval of 0.54-0.95 in the group with nuts and 0.53-0.91 in the group with olive oil. The absolute numbers of 109 events in the control group, 96 in the group with olive oil and 83 in the group with nuts raise doubts that the group differences (see also the size of the confidence interval) after diet could be significant or even clinically relevant without extrapolation to many patient years.

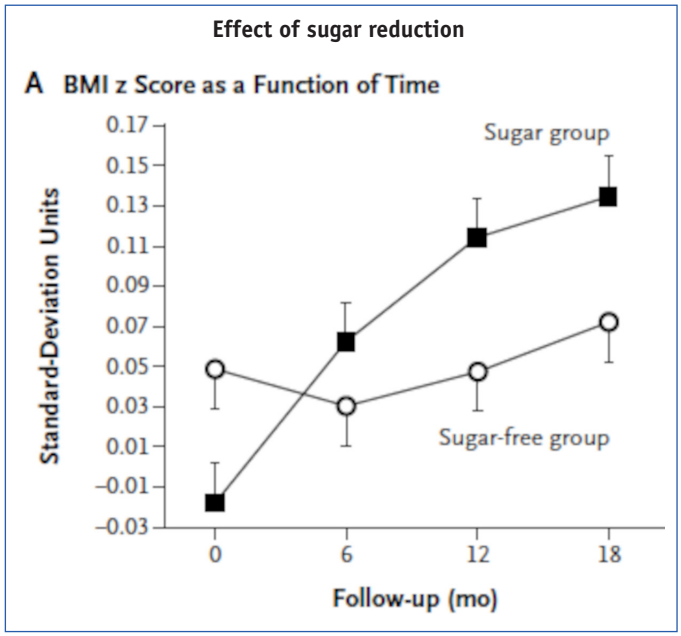


Fig. 1: *Taken from: N Engl J Med 2012;367:1397-406. DOI: 10.1056/ NEJMoa1203034.*

level of certainty is moderate for obesity and dyslipidaemia (> 50-75% probability), low for non-alcoholic fatty liver disease and type 2 diabetes (> 15-50% probability) and very low for hypertension (0- 15% probability). ... A level of sugar intake at which the risk of dental caries/chronic metabolic diseases is not increased could not be identified ... .'

The correct number would be 1397-406. DOI: 10.1056/ Conclusion: In view of the low level of evidence, nothing has been proven or disproven.

2. The success of a change to a Mediterranean diet

Sugar consumption is also reduced with a Mediterranean diet. The best-known intervention study that investigated this is the Predimed study [70, 71] with 7,447 parti-

Pathophysiological considerations

1. The rise in glucose and the importance of dietary composition

- The inter-individual differences in the rise in blood values after eating are very pronounced in healthy people [72]: The difference is 103% for triglycerides, 68% for glucose and 59% for insulin. The composition of the food components, for example, explains only 3.6% of the increase in fat after eating. In view of the large intra-individual differences in the rise in sugar after a meal and the minor importance of food composition for the fluctuations in levels [72], a sugar tax with only a small reduction in daily sugar consumption (in England only 15 grams per household per week) will have no clinically relevant effects.
- Increased glucose metabolism (glucose flux) . A short-lived and small increase in glucose after eating is not an explanation for cell damage. A look at biochemical studies shows, even if they do not differentiate between the isoforms of hexokinase [73, 74], that the glucose flux is already saturated at physiological glucose concentrations. Consequently, a brief and small increase in glucose due to the intake of sugary drinks cannot lead to increased glucose flux and cellular activation in either a healthy person or a diabetic. This also explains why in cell experiments the glucose effects only occur at glucose concentrations that are far above the 'normal' glucose increase after eating. This means that the hypothesis of positive 'cardiometabolic' effects of a tax lacks a biochemical basis.
- How can the different results of the modelling and intervention studies be explained? The decisive difference is the study methodology. The studies that calculate a health-relevant success of reducing sugar consumption [1, 75-80] are observational studies and register studies. The studies that argue against the health success of a sugar tax are intervention studies (for an understanding of the advantages and disadvantages of observational studies compared to randomised intervention studies, see also https://ww.sokrates-rationalisten-forum.de/erkenntnistheoretischegrundlagen-und-ihre-beachtung-in-derheutigen-wissenschaft). With the same quality of implementation, intervention studies are the higher quality studies, as they form the analysed groups by chance. Particularly in the case of diseases with many different causes, this makes the groups analysed more comparable. Confounding variables can be eliminated. No study can control the variety of influencing variables, which are made up of various medical, psychosocial and economic factors. No study team has the expertise and equipment to survey all risk factors from the fields of medicine, sociology, psychology and economics at the same time. Even if these many factors could be recorded, the group size would be too small to make a statistically reliable statement. Therefore, the methodology used (observational studies in study 1 ver-

sus intervention studies in this review) is decisive for the different conclusions.

If the authors of [1] had included the results of the higher-quality intervention studies in the modelling instead of the 'success reports' from observational studies, the result would have been completely different. If randomised intervention studies [81] cannot demonstrate an effect, there is much to suggest that it does not actually exist, because intervention studies are more likely to overestimate an effect than to underestimate it.

The following are some examples of results from intervention studies that contradict the observational studies:

- In men with lowered testosterone, neither diabetes nor bone fractures were prevented in the TRAVERSE study [82, 83]. Although observational studies came to the conclusion that low vitamin D3 levelscorrelate with cardiovascular diseaseand cancer, intervention studies in children and adolescents found no effect of vitamin D3 supplementation on the risk of bone fracture [84] or protection against cancer and cardiovascular disease. A study investigating the difference between low-molecular-weight and unfractionated heparin is revealing for the significance of the study design. The more rigorous the study criteria and study quality, the smaller or absent the advantage of low-molecular-weight heparin [85].
- If a confounding variable is not taken into account, the use of sophisticated mathematical models, such as microsimulation [1], creates the risk of misinterpretation of an effect. The more basic data are processed, the more input errors, for example due to a lack of comparability of the groups, become noticeable in the quality of the output due to multiplication in the calculation process [81, 86, 87]. In the case of multifactorial diseases (such as cardiovascular diseases) that are not only caused by medically accessible factors, the risk of distortion of the results due to group differences in the observational studies cannot be denied and leads to false conclusions. The microsimulation model used for Germany in (1) is based on the results of English data (UK IMPACT NCD), which are just as little based on intervention studies as the assumptions on BMI-independent effects of sugar consumption on diabetes and cardiovascular diseases [67, 75-78, 80, 88-98].

If the value of the study designs is not taken into account

The reader of the study [1] and similar studies [75-80, 88-99] is led to believe that the essential health data and risk factors were included in the calculation. This is not true because other, probably even more important factors, which also influence dietary behaviour, were not taken into account. These include many psychosocial factors, such as education, optimism, loneliness, finding meaning in one's life and much more [100-110]. It is therefore conceivable that the 'cardiometabolic' data included in the calculation by the authors [1] have no disease value, but are merely epiphenomena.

This is proven by a randomised intervention study on psychosocial intervention with the endpoints weight and HbA1c [109]. In contrast to the studies cited above on reducing sugar intake, diabetes prevention and the Mediterranean diet, the social intervention showed relevant effects on weight and HbA1c.

Experience with the introduction of a sugar tax

The aim of taxing sugar or sweetened beverages is to prevent clinically relevant diseases. The effect of this tax must therefore be measured by the following results: Reduction in the number of people with a BMI over 25 and over 30, reduction in people with high blood pressure, diabetes, heart attacks and strokes.

But in England [110], the effect of a tax on soft drink manufacturers on weight loss in children was disappointing. In girls, the decrease in obesity prevalence was only 1.6% with a confidence interval of 1.1 to 2.1 (!) and in boys it was undetectable. An important aspect of the study is the control group: as this does not exist after the introduction of the tax, the increase in obesity before the introduction of the tax was extrapolated to the period after the tax.

This results in the following:

1. nobody lost weight, but the increase in weight was only less than expected.
2. the calculated expectation is incorrectly high, as the increase in obesity in Germany was much lower in this period without the tax.

A study assuming that a reduction in sugar intake of 15 grams per week per household would have a relevant effect has been widely misinterpreted. In this study, there are no measured values for any diseases, only extrapolations that assume 15 grams per week per household (i.e. not per person) and extrapolate an expected weight loss from this.

In a systematic review and meta-analysis published in JAMA in 2022, Andreyeva and colleagues only came to the following conclusion: 'In this systematic review and meta-analysis of implemented SSB taxes worldwide, SSB taxes were associated with higher prices and lower sales of taxed beverages.' Teng and colleagues reported in Obesity Reviews 2019: 'Based on real-world evaluations, SSB taxes introduced in jurisdictions around the world appear to have been effective in reducing SSB purchases and dietary intake.' So it's only about the purchase and intake of sugar, without evidence of clinically relevant (!) effects! This also corresponds to the experiences from Mexico, South Africa and other countries.

Thow and colleagues therefore come to the right conclusion in their review in Nutrition Reviews 2014: 'Future research should use prospective study methods to determine the effect of taxes on diets and focus on the effect of taxation in conjunction with other interventions as part of a multisectoral strategy to improve diets and health.'

A Cochrane review from 2020 (doi.org/10-1002/14651858. CD012333.pub2) shows just how unclear and open the topic of a health-promoting effect of a sugar tax of any kind still is. After analysing all the studies available at the time, the following conclusion was reached: 'The evidence available on the research question of the review can be considered very limited and the certainty of the evidence is very low.'

The responsibility of the authors

Die The authors [1] did not fulfil their responsibility on several levels:

Level 1: The biased selection of 'appropriate' observational studies and lack of plausibility checks using the higher quality intervention studies.

Level 2: The readers are not told that cardiometabolic markers are only markers and that their treatment with lifestyle interventions cannot yet be proven with clinical end-

points.

Level 3: There is no long-term study that proves a long-term effect of sugar reduction on body weight and other diseases.

Level 4: In view of the weakness of theobservational studies and the lack of studies providing evidence, Emmert-Fees and coauthors wrote quite correctly in the abstract of their publication [1] under 'Conclusions': 'In this study we found, that SSB taxation in Germany could help to reduce the national burden of noncommunicable diseases ...' The subjunctive 'could' makes the difference between obvious overinterpretation and honest, albeit overoptimistic interpretation.

Level 5: The authors of the study [1] explain in PLoS: 'No tax on SSBs is currently enacted in Germany and the national government is preparing a new national strategy on food seeking evidence-based recommendations to establish policy priorities until 2050.' It remains unclear whether this is a paid expert opinion (to attract new research funding) or a truly 'free' research service.

Level 6: If a measure prolongs life, then increased care costs, medical costs and pension payments must be factored in, as well as possible side effects (increase in anorexia and orthorexia among young people who want to live particularly health-conscious lives). <<

von:
Prof. Dr. med. Dr. h.c. Peter Paul Nawroth
(ORCID 0000-0002-6134-7804)
Varun Kumar PhD
(ORCID 0000-0003-2827-1024)

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Citation

Nawroth, P.-P., Kumar, V.: „Zuckersteuer: Was spricht dagegen?“, in „Monitor Versorgungsforschung“ (05/24), S. 52–56. http://doi.org/10.24945/MVF.05.24.1866-0533.2652