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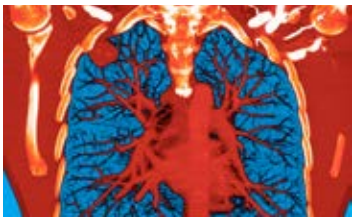

CRP concentration associated with the risk of lung cancer in smokers p 17

Non-sugar sweeteners have limited effects on important health benefits p 18

CT radiation doses vary substantially by country and institution p 20

ORIGINAL RESEARCH Nested case-control study within Lung Cancer Cohort Consortium

Circulating high sensitivity C reactive protein concentrations and risk of lung cancer

Muller DC, Larose TL, Hodge A, et al

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Find the full version with references at http://dx.doi.org/10.1136/bmj.k4981

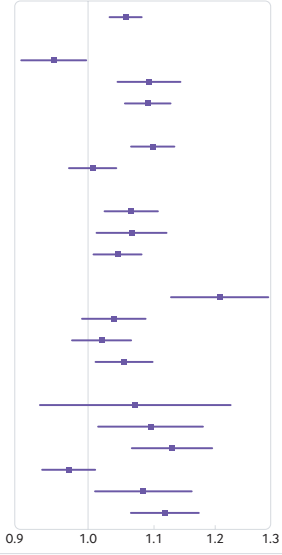
Study question Is there an association between prospectively measured circulating high sensitivity C reactive protein (hsCRP) concentration and risk of lung cancer overall, by smoking status and histological subtype?

Methods A pooled analysis of prospective case-control studies nested within 20 population based cohort studies in Asia, Europe, Australia, and the US was conducted. 5299 incident lung cancer cases, with individually incidence density matched controls had hsCRP concentrations measured in prediagnostic serum or plasma samples.

Study answer and limitations

A positive association between circulating hsCRP concentration and the risk of lung cancer for current (odds ratio associated with a doubling in hsCRP concentration 1.09, 95% confidence interval 1.05 to 1.13) and former smokers (1.09, 1.04 to 1.14) was observed, but not for never smokers (P<0.01 for interaction). This association was strong and consistent across all histological subtypes, except for adenocarcinoma, which was not strongly associated with hsCRP concentration regardless of smoking status (odds ratio for adenocarcinoma overall 0.97, 95% confidence interval 0.94 to 1.01). The association between circulating hsCRP concentration and the risk of lung cancer was strongest in the first two years of follow-up for former and current smokers. The study was limited by the use of hsCRP measurements from a single time point for each patient. Individual repeated samples would have been particularly useful for better evaluation of circulating hsCRP concentrations in the years leading up to lung cancer diagnosis.

Covariate	No of cases	Odds ratio (95% CI)	Odds ratio (95% CI)	P value
Overall	5299		1.05 (1.03 to 1.08)	
Smoking status				<0.01
Never	1305		0.95 (0.91 to 1.00)	
Former	1498		1.09 (1.04 to 1.14)	
Current	2496		1.09 (1.05 to 1.13)	
Sex				<0.01
Men	2873		1.10 (1.06 to 1.13)	
Women	2426		1.01 (0.97 to 1.04)	
Region				0.71
Asia	1757		1.06 (1.02 to 1.11)	
Europe and Australia	1159		1.06 (1.01 to 1.12)	
US	2383		1.04 (1.01 to 1.08)	
Time from blood draw to diagnosis (years)				<0.01
0.0-1.9	583		1.21 (1.13 to 1.29)	
2.0-4.9	1325		1.04 (0.99 to 1.09)	
5.0-9.9	1631		1.02 (0.98 to 1.06)	
10.0-35.6	1577		1.05 (1.01 to 1.10)	
Histology				<0.01
Large cell	173		1.07 (0.93 to 1.23)	
Small cell	484		1.09 (1.01 to 1.18)	
Squamous cell	831		1.13 (1.07 to 1.19)	
Adenocarcinoma	2030		0.97 (0.94 to 1.01)	
Other	595		1.08 (1.01 to 1.16)	
Unknown or missing	1186		1.12 (1.06 to 1.17)	



Odds ratios for doubling in high sensitivity C reactive protein (hsCRP) concentration, overall and by participant characteristics. P values are from likelihood ratio tests of the interaction between hsCRP and each covariate

What this study adds Circulating hsCRP concentration is associated with the risk of lung cancer in former and current smokers, but not in never smokers. The association is strongest in the first two years from blood draw to diagnosis. hsCRP concentration is not associated with the risk of lung adenocarcinoma.

Funding, competing interests, and data sharing See bmj.com for funding. The authors have no competing interests. No additional data are available.

Non-sugar sweeteners and health

ORIGINAL RESEARCH Systematic review and meta-analyses

Association between intake of non-sugar sweeteners and health outcomes

Toews I, Lohner S, Küllenberg de Gaudry D, Sommer H, Meerpohl JJ

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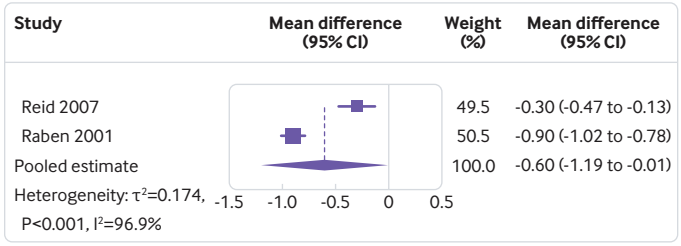
Study question What is the association between the intake of non-sugar sweeteners and important health outcomes?

Methods In a systematic review following standard Cochrane review methodology, randomised and non-randomised controlled trials and observational studies were searched in relevant literature databases, trials registries, and reference lists of relevant publications. Studies including generally healthy adults or children with or without overweight or obesity in any setting were eligible. The non-sugar sweeteners used had to be clearly named, the dose had to be within the acceptable daily intake, and the intervention had to be of at least seven days' duration. Relevant outcomes were: body weight/body mass index, glycaemic control, oral health, eating behaviour, preference for sweet taste, cancer, cardiovascular disease, kidney disease, mood, behaviour, neurocognition, and adverse effects.



Effect of non-sugar sweeteners versus caloric sweeteners on body mass index in adults

Study answer and limitations Of 56 studies that provided data in this review, 35 were observational studies. In adults, evidence for a beneficial effect of non-sugar sweeteners on body mass index was seen (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 non-sugar

COMMENTARY The weight of evidence hints at benefits, but the full picture has yet to emerge

There is much public and scientific interest in whether foods and beverages containing non-sugar sweeteners (NSS)—which contain few or no calories—should be recommended as a strategy to reduce consumption of free sugars, particularly sugar sweetened beverages. However, inconsistent research findings and potential safety concerns have hampered official guidance.[1]

To clarify the benefits and harms of NSS consumption and to inform WHO guidance, Toews and colleagues conducted a systematic review and meta-analysis evaluating the effect of NSS intake on a broad range of health outcomes in adults and children.[2] They included 56 interventional and observational studies, making this review the most comprehensive on this topic so far.

Among adults, findings from the few trials comparing NSS intake with sugar intake suggested small improvements in body mass index and fasting concentrations of blood glucose favouring NSS. Among children, NSS intake led to a smaller increase in body mass index z score than sugar intake, but NSS made no difference to body weight. For most other outcomes, no statistically or clinically relevant differences were observed.

The included studies had important limitations, however, including small sample sizes and short duration. Few studies were identified for each outcome. The inconsistent results might also stem from methodological approaches to the design and conduct of the meta-analysis. By excluding studies that did not specify the type of NSS, for example, many prospective cohort studies were not considered, including those examining clinical outcomes such as diabetes and cardiovascular disease. Many cohort studies evaluate diet using food frequency questionnaires that would reflect the predominant type of NSS used in the food supply at that time, so type of NSS could be inferred.[3]

Favourable associations

To reduce the possibility of reverse causation, some cohort studies use repeated measurements to examine the association between changes in intake and changes in body weight.[4] Overall, these studies suggest a favourable association between consuming diet beverages and long term weight change.[5,6] In the same studies, substituting one serving per day of diet beverage with the same amount of sugar sweetened beverage was associated with 0.47 kg less weight gain over four-year intervals.[6] Consumption of diet beverages has been positively associated with risk of diabetes in multiple cohorts.[7] However, associations were attenuated after the researchers adjusted for adiposity, implying that the association might be due to reverse causation.

In experimental trials, the intended effects of NSS are expected to differ depending on the energy content of the comparator.[11,12] Toews and colleagues' review did not differentiate trials according to the nature of the comparator. Among included studies, benefits on blood pressure and body weight were observed when NSS were compared with sugars rather than non-caloric placebos.

While meta-analyses are important for guiding recommendations and policies, individual high quality studies should also be emphasised. For example, trials by de Ruyter and colleagues[13] and Ebbeling and colleagues,[14] the largest and most rigorously conducted so far, provide strong evidence that the replacement of sugar sweetened beverages with diet alternatives reduces weight gain in children and adolescents after one year of follow-up.

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sweeteners were associated with lower weight gain (−0.09 kg, −0.13 to −0.05; one, n=17 934). In children, a smaller increase in body mass index z score was observed with non-sugar sweetener intake compared with sugar intake (−0.15, −0.17 to −0.12; two, n=528). For other outcomes, no differences between study groups were detected. Similarly, no evidence of any effect of non-sugar sweeteners was seen in overweight or obese adults or children actively trying to lose weight. Few studies were identified for each outcome, of which most studies had few participants and were of short duration; therefore, their methodological and reporting quality is limited.

What this study adds There was no compelling evidence for important health benefits from the use of non-sugar sweeteners on the health outcomes in this systematic review. Potential harms from non-sugar sweetener consumption could not be excluded.

Competing interests, funding, and data sharing The research was funded by the World Health Organization. The authors declare no conflicts of interest. Datasets can be requested from the corresponding author at Meerpohl@cochrane.de.

Overall, these studies suggest a favourable association between consuming diet beverages and long term weight change

Toews and colleagues' findings highlight the need for larger and longer term studies of NSS to guide policy development and elucidate underlying biological mechanisms. Understanding the potential health effects of NSS is especially important for sugar reduction policies such as taxation and labelling, which could lead to product reformulation and more NSS in the food supply.

Based on existing evidence including long term cohort studies with repeated measurements and high quality trials with caloric comparators, use of NSS as a replacement for free sugars (particularly in sugar sweetened beverages) could be a helpful strategy to reduce cardiometabolic risk among heavy consumers, with the ultimate goal of switching to water or other healthy drinks. Policies and recommendations will need updating regularly as more evidence emerges to ensure that the best available data are used to inform the important public health debate on sugar and its alternatives.

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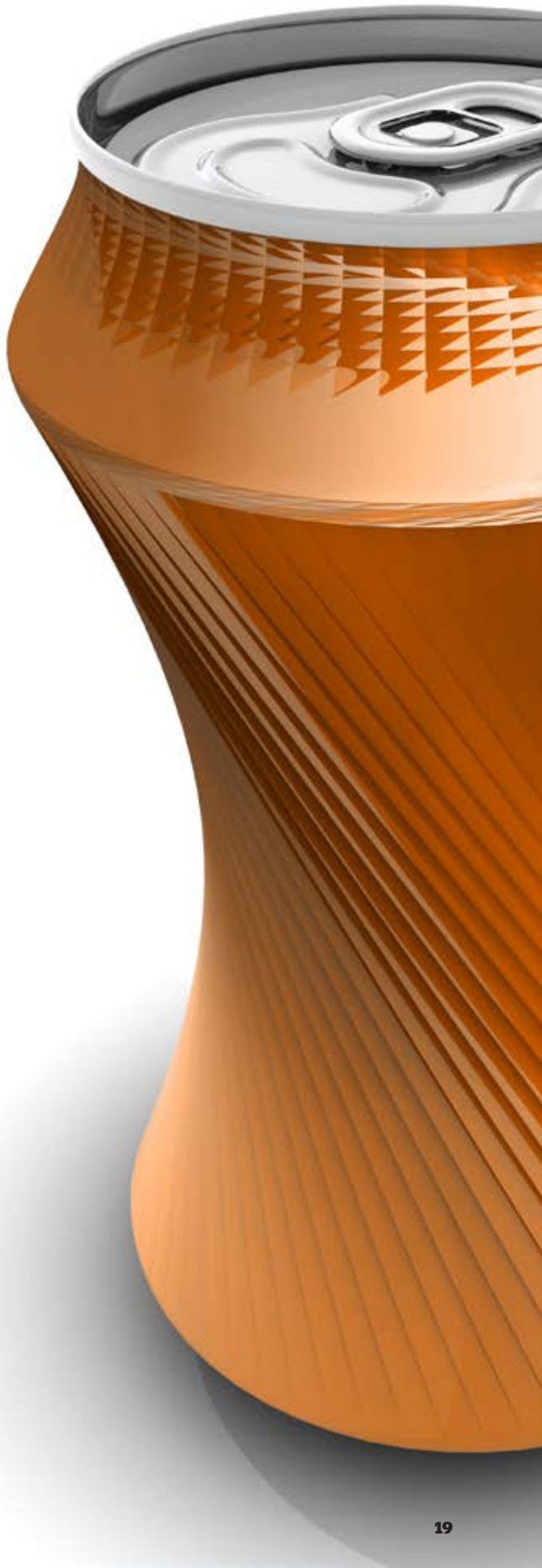

International variation in radiation dose for computed tomography examinations

Smith-Bindman R, Wang Y, Chu P, et al

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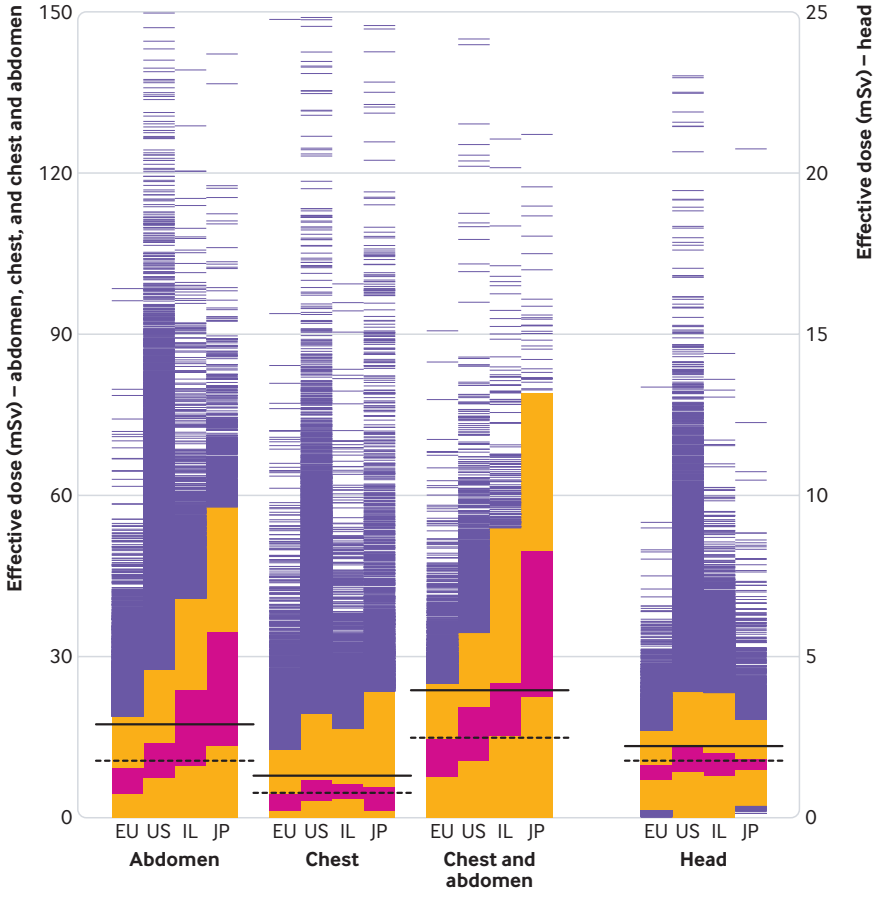
Study question Do patient, institution, and machine characteristics contribute to the wide variation in radiation doses used for computed tomography (CT) examinations?

Methods Data were assembled and analysed from the University of California San Francisco CT International Dose Registry. This study included standardised data from over 2.0 million CT examinations of adults who underwent CT between November 2015 and August 2017 from 151 institutions, across seven countries (Switzerland, Netherlands, Germany, UK, US, Israel, and Japan). Main outcome measures were mean effective dose and proportions of high dose examinations (defined as CT scans with doses above the 75th percentile) by anatomical area, according to patient characteristics, type of institution, machine factors, country, and how scanners were used, before and after adjustment for patient characteristics, using hierarchical linear and logistic regression.

Study answer and limitations The mean effective dose and proportion of high dose examinations varied substantially across institutions, and across countries. Even after adjusting for patient characteristics, wide variations in doses across countries persisted, with a fourfold range in mean effective dose for abdomen CT examinations (7.0-25.7 millisievert (mSv)) and a 17-fold range in proportion of high dose examinations (4-69%). Similar variation across countries was observed for chest (mean effective dose 1.7-6.4 mSv, proportion of high dose examinations 1-26%) and combined chest and abdomen CT (10.0-37.9 mSv, 2-78%). Doses for head CT varied less (1.4-1.9 mSv, 8-27%). In multivariable models, the dose variation across countries was primarily attributable to institutional decisions regarding technical parameters (that is, how the scanners were used).

What this study adds The variation in doses used for CT scanning of patients is primarily driven by how CT scanners are used, and not by patient factors, institutional characteristics, or machine factors. These findings suggest that optimising doses to a consistent standard should be possible.



Distribution in effective radiation dose by country or the European Union and scan region, adjusting for patient characteristics. Each column signifies one country or the European Union, with one horizontal line denoting each observation within the country. Pink lines=within the 25th and 75th percentiles; orange lines=within the 5th-25th percentiles and the 75th-95th percentiles or between the 5th and 95th percentiles; purple lines=outliers; horizontal solid line and dashed line=benchmark and target doses for each anatomical area, defined as the 75th and 50th percentiles of dose for all scans of that type performed before 30 April 2016. mSv=millisievert; EU=European Union; US=United States; IL=Israel; JP=Japan

Competing interests, funding, and data sharing
Competing interests are listed in full on bmj.com. Funding provided by the US National Institutes of Health and the Patient Centered Outcomes Research Institute. No additional data are available.

Study registration ClinicalTrials.gov NCT03000751.