research

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ORIGINAL RESEARCH Longitudinal study

Thyroid replacement therapy, thyroid stimulating hormone concentrations, and long term health outcomes in patients with hypothyroidism

Thayakaran R, Adderley NJ, Sainsbury C, et al

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Study question Is thyroid stimulating hormone (TSH) concentration associated with risk of cardiovascular disease and all cause mortality in patients with a diagnosis of hypothyroidism?

Methods This retrospective cohort study used data from The Health Improvement Network (THIN), including adults with incident hypothyroidism from 1 January 1995 to 31 December 2017. Primary outcome measures were ischaemic heart disease, heart failure, and stroke/transient ischaemic attack. Longitudinal TSH measurements from diagnosis to outcomes, study end, or loss to follow-up were collected. An extended Cox proportional hazards model with TSH considered as a time varying covariate was fitted for each outcome.

Study answer and limitations Compared with the reference TSH category (2-2.5 mIU/L), an increased risk of ischaemic heart disease and heart failure was seen at high TSH concentrations (>10 mIU/L; hazard ratio 1.18 (95% confidence interval 1.02 to 1.38) and 1.42 (1.21 to 1.67), respectively). A protective effect for heart failure was seen at low TSH concentrations (0.79 (0.64 to 0.99) and 0.76 (0.62 to 0.92) for TSH <0.1 mIU/L and 0.1-0.4 mIU/L, respectively). Increased mortality was observed in both the lowest and the highest TSH categories. The dataset was routinely collected, so the diagnosis of hypothyroidism could not be confirmed or the causes of hypothyroidism differentiated. Median follow-up was six years, which may not be sufficient to observe all long term outcomes.

What this study adds In patients with hypothyroidism, no evidence was found to suggest a clinically meaningful difference in the pattern of long term health outcomes when TSH concentrations were within current recommended treatment targets (0.4-4.0 mIU/L). Adverse health outcomes were seen when TSH was outside this range, particularly above the upper reference value.

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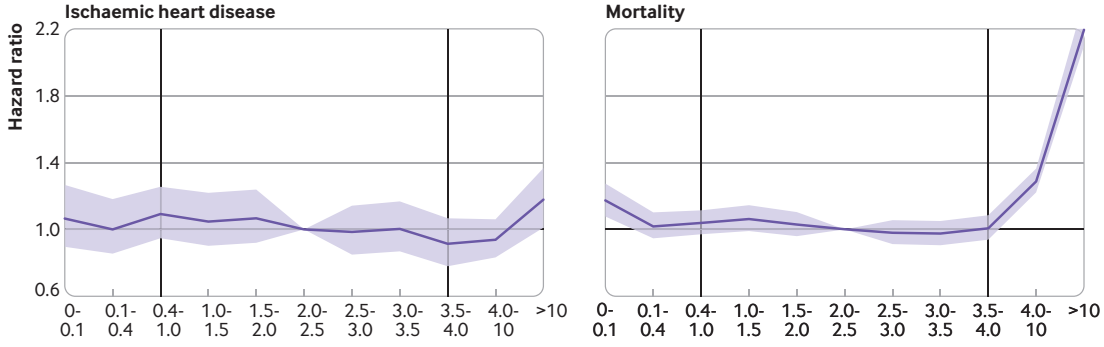

Hazard ratios with confidence intervals for cardiovascular and mortality outcomes for different TSH categories relative to 2-2.5 mIU/L reference category

Vegetarian diets and health

ORIGINAL RESEARCH Results from the prospective EPIC-Oxford study

Risks of ischaemic heart disease and stroke in meat eaters, fish eaters, and vegetarians over 18 years of follow-up

Tong TYN, Appleby PN, Bradbury KE, et al
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Study question What are the associations between vegetarianism and the risks of ischaemic heart disease and stroke?

Methods In the prospective EPIC-Oxford study, participants were recruited in 1993-2001 and classified into three diet groups: meat eaters (reference; n=24 428), fish eaters (n=7506), and vegetarians (including vegans; n=16 254). Multivariable adjusted Cox regression was used to estimate the risk of ischaemic heart disease and stroke (including ischaemic and haemorrhagic types) identified through record linkage until 2016. Analyses included age as the underlying time variable; were stratified by sex, method of recruitment, and region; and were adjusted for sociodemographic and lifestyle confounders.

Study answer and limitations Over 18.1 years of follow-up, 2820 cases of ischaemic heart disease and 1072 cases of total stroke were recorded. Fish eaters and vegetarians had 13% (hazard ratio 0.87, 95% confidence interval 0.77 to 0.99) and 22% (0.78, 0.70 to 0.87) lower rates of ischaemic heart disease than meat eaters, respectively (P<0.001 for heterogeneity). This difference was equivalent to 10 fewer cases of ischaemic heart disease (95% confidence interval 6.7 to 13.1 fewer) in vegetarians than in meat eaters per 1000 population over 10 years. The associations for ischaemic heart disease were partly attenuated after adjustment for self reported high blood cholesterol, high blood pressure, diabetes, and body mass index (hazard ratio 0.90, 95% confidence interval 0.81 to 1.00 in vegetarians with all adjustments). Vegetarians had 20% higher rates of total stroke (hazard ratio 1.20, 95% confidence interval 1.02 to 1.40) than meat eaters, equivalent to three more cases of total stroke (95% confidence interval 0.8 to 5.4 more) per 1000 population over 10 years, mostly due to a higher rate of haemorrhagic stroke. The associations for stroke did not attenuate after further adjustment of disease risk factors. As the study was observational, causality cannot be determined, and residual confounding is possible.

What this study adds This study shows that vegetarians had a higher risk of haemorrhagic and total stroke than meat eaters, and that alongside vegetarians, fish eaters had lower risks of ischaemic heart disease than meat eaters.

Funding, competing interests, and data sharing
Supported by the Medical Research Council and Wellcome Trust. KEB is supported by the Girdlers' New Zealand Health Research Council Fellowship. The authors declare no competing interests. The data access policy for EPIC-Oxford is available at www.epic-oxford.org/data-access-sharing-and-collaboration/

COMMENTARY Stroke risk should be explored further, but kept in perspective

A substantial proportion of the world's population is vegetarian and most studies to date have reported protective associations between vegetarian diets and chronic disease risk factors. One meta-analysis reported a significant protective effect against ischaemic heart disease but not total cardiovascular and cerebrovascular diseases.[2] However, there have been calls for more evidence on possible associations between dietary patterns and stroke.[1]

In this issue, Tong and colleagues report latest findings from the EPIC-Oxford study,[3] showing that compared with meat eaters, fish eaters and vegetarians had 13% and 22% lower rates of ischaemic heart disease, respectively; a finding that is broadly consistent with previous findings.

Conversely, the study also showed that vegetarians had a 20% higher risk of total stroke than meat eaters, mostly due to a higher rate of haemorrhagic stroke. This is a new contribution to the body of evidence on the health effects of a vegetarian diet.

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Tong and colleagues' study has many strengths that diminish the likelihood that this association is an artefact. It focused on dietary patterns that nutrition science now recognises as the key dietary exposure of interest in chronic disease epidemiology.[4] The study was based on a large longitudinal cohort, the ideal study design for examining long term effects of dietary patterns on health. The authors paid particular attention to adjusting for sociodemographic and lifestyle confounders and to applying rigorous statistical methods.

Vegetarians and others should keep the reported stroke risk in perspective, however. It is based on results from just one study, and the increase is modest relative to meat eaters: "equivalent to three more cases of total stroke [...] per 1000 population over 10 years."[3] Relevance to vegetarians worldwide must also be considered. Participants were all from the United Kingdom where dietary patterns and other lifestyle behaviours are likely to differ from those prevalent in low and middle income countries, where most of the world's vegetarians live.

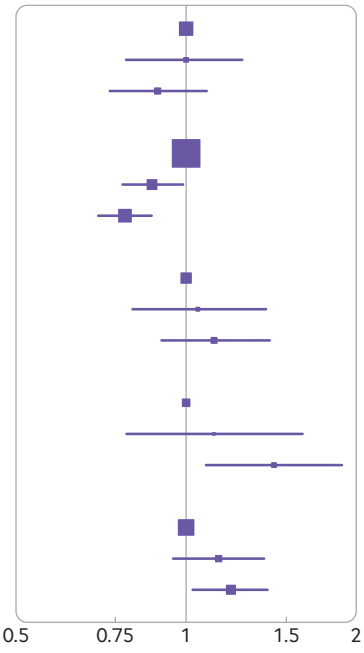
When interpreting these results, any plausible dietary mediators of the association between vegetarian diets and stroke should be considered. In addition to differences in intakes of total protein and protein sources, vegetarians had higher intakes of fruit, vegetables, legumes, and nuts than meat eaters, and lower intakes of sodium. Previous analyses suggest no cause for concern for many of these individual dietary components,[6 7] although further work is needed to understand the impact of substitution within the overall diet.

Vitamin B12 is considered a nutrient at risk in some vegetarian diets, unless fortified foods and supplements are used.[8] The role of suboptimal intake of B12 in stroke risk is unclear,[1] and further exploration should include re-evaluation of existing vitamin B trials[9] and mechanistic studies to support observational evidence.

Ultra processed foods

Dietary guidelines contain the most evidence informed advice available for vegetarians, as well as for fish and meat eaters.[10] They consider dietary associations with multiple health outcomes—not

Outcome and diet groups	Cases	Person years	Hazard ratio (95% CI)	P heterogeneity
Acute myocardial infarction				
Meat eaters	559	438 001	Reference	
Fish eaters	84	132 168	1.00 (0.78 to 1.26)	
Vegetarians	145	278 800	0.89 (0.73 to 1.09)	0.51
Ischaemic heart disease				
Meat eaters	2026	429 125	Reference	
Fish eaters	298	130 816	0.87 (0.77 to 0.99)	
Vegetarians	496	276 938	0.78 (0.70 to 0.87)	<0.001
Ischaemic stroke				
Meat eaters	340	438 418	Reference	
Fish eaters	62	132 040	1.05 (0.80 to 1.39)	
Vegetarians	117	278 383	1.12 (0.90 to 1.41)	0.59
Haemorrhagic stroke				
Meat eaters	173	438 418	Reference	
Fish eaters	38	132 040	1.12 (0.78 to 1.61)	
Vegetarians	89	278 383	1.43 (1.08 to 1.90)	0.04
Total stroke				
Meat eaters	678	438 418	Reference	
Fish eaters	136	132 040	1.14 (0.94 to 1.38)	
Vegetarians	258	278 383	1.20 (1.02 to 1.40)	0.06



Rates of ischaemic heart disease and stroke in fish eaters and vegetarians (including vegans) compared with meat eaters in the EPIC-Oxford study (n=48 188). P heterogeneity=significance of heterogeneity in risk between diet groups based on Wald tests. Box sizes are proportional to the number of cases in each group

just ischaemic heart disease and stroke—alongside nutritional adequacy; a dietary outcome of particular importance to vegetarians. Dietary guidelines increasingly recognise the need to reduce intake of ultra-processed foods,[11] a dietary component that is substantially more widespread than it was when Tong and colleagues' data were collected. This recommendation is particularly relevant to vegetarians who might be unaware that many foods marketed to vegetarians are ultra-processed.

Finally, dietary guidelines[12] and other recent authoritative reports[13 14] also recognise plant based diets for their environmental sustainability as well as health benefits. Shifting towards a plant based diet for reasons of personal or planetary health does not necessarily mean becoming a vegetarian. Indeed, populations in some low and middle income countries who consume very low amounts of animal source foods may benefit from being able to eat a little more of these foods to gain additional nutrients necessary to help combat all forms of malnutrition.

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Dietary guidelines contain the most evidence informed advice available for vegetarians, as well as for fish and meat eaters

Potential impact on prevalence of obesity in the UK of a 20% price increase on high sugar snacks

Scheelbeek PFD, Cornelsen L, Marteau TM, et al

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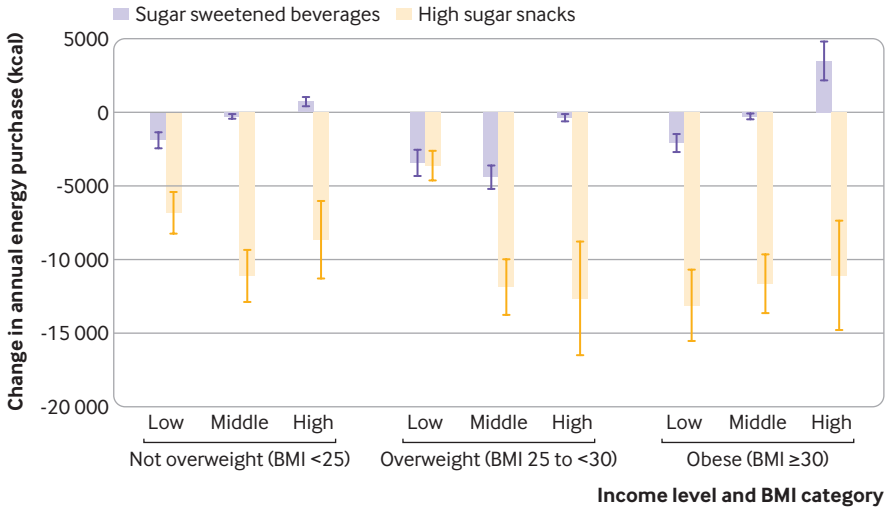
Study question What are the likely effects of a 20% price increase in high sugar snacks on energy purchase, body mass index (BMI), and prevalence of obesity in the UK adult population?

Methods The authors modelled the potential effect of a 20% price increase in three categories of high sugar snacks—confectionery (including chocolate), biscuits, and cakes—on energy purchased, and used this to estimate changes in weight, BMI, and the prevalence of obesity in the UK. Data from the Kantar FMCG (fast moving consumer goods) panel were used to estimate changes in energy purchase associated with the price increase in high sugar snacks. The National Diet and Nutrition Survey was used to estimate resulting changes in BMI and prevalence of obesity.

Study answer and limitations A 20% price increase in high sugar snacks was associated with an average reduction in energy purchase of -8.9×10^3 kcal (95% confidence interval -13.1×10^3 to -4.2×10^3 kcal ; 1 kcal=4.18 kJ). BMI was estimated to decrease by −0.53 kg m^2 (95% confidence interval −1.01 to −0.06 kg/m^2) on average. The model suggests that this change could reduce the UK prevalence of obesity by 2.7 percentage points (95% confidence interval −3.7 to −1.7 percentage points) after one year. This finding was in a UK context and was double that modelled for a similar price increase in sugar sweetened beverages. The study does not reflect on the possible health impacts of nutrient substitution alongside changes in energy—that is, after a price increase people might purchase and consume less sugar but consume more saturated fats or salt.



Impact of 20% price increase in sugar sweetened beverages and high sugar snacks on change in annual energy purchase by body mass index (BMI) and household income group. Stratification by income group (low <£20 000, middle £20 000-49 999, high ≥£50 000) and BMI group. £1.00=$1.2; €1.1. Whiskers represent 95% confidence intervals

What this study adds Increasing the price of high sugar snacks by 20% could reduce energy intake, BMI, and prevalence of obesity in the UK.

Funding, competing interests, and data sharing
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Editorial: Taxing confectionery, biscuits, and cakes to control obesity (*BMJ* 2019;366:l5298)