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Consumption of sugar-sweetened and artificially-sweetened soft drinks and risk of cancers not related to obesity

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Key words: Sugar-sweetened soft drinks; artificially-sweetened soft drinks; cancer; prospective study

Abbreviations

MCCS	Melbourne Collaborative Cohort Study
CRP	C-reactive protein
HR	Hazard ratio
CI	Confidence interval
BMI	Body mass index
IARC	International Agency for Research on Cancer

Article category: Short Report

Novelty and Impact

Previously we reported a positive association between consumption of sugar-sweetened soft drinks and risk of obesity-related cancers, but this association was not completely explained by obesity. In this prospective study, we investigated sugar-sweetened soft drink consumption and non-obesity-related cancers and found no association. An unexpected positive association was observed with artificially-sweetened soft drinks. These findings leave unresolved the question of whether consumption of sugar-sweetened soft drinks influence cancer risk independently of their association with body size.

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Abstract

Consumption of sugary drinks increases the risk of obesity. Previously we reported a positive association between sugar-sweetened soft drink consumption and obesity-related cancer but this association was not fully explained by obesity; in contrast, we found no association for consumption of artificially-sweetened soft drinks. Our aim was to determine whether the consumption of sugar-sweetened or artificially-sweetened soft drinks was associated with cancers other than those currently identified as being related to obesity. We used data from the Melbourne Collaborative Cohort Study. Participants completed a 121-item food-frequency questionnaire (FFQ) at baseline including separate questions about the number of times in the past year they had consumed sugar-sweetened and artificially-sweetened soft drinks. Cox regression models were fitted to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the risk of cancers not related to obesity. During 19 years of follow-up, there were 35,109 eligible participants who developed 4,789 cancers not related to obesity. There was no association between frequency of consuming sugar-sweetened soft drinks and the risk of these cancers, but an unexpected positive association was observed for consumption of artificially-sweetened soft drinks. Although, we did not find an association with sugar-sweetened soft drinks, we previously reported a positive association with obesity-related cancers, not fully explained by obesity. These findings leave unresolved the question of whether consumption of sugar-sweetened soft drinks influences cancer risk independently of their influence on body size.

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Introduction

Consumption of sugary drinks is associated with weight gain and an increased risk of obesity.[1] We previously examined whether the consumption of sugar-sweetened soft drinks was associated with the development of 11 obesity-related cancers in the Melbourne Collaborative Cohort Study (MCCS) and found a small positive association that was not completely explained by obesity and was not evident for artificially-sweetened soft drinks[2]. This suggested that the association was not due to other components of soft drinks such as flavours and colours, specifically 4-methylimidazole which is used in cola drinks and has been classified as possibly carcinogenic by the International Agency for Research on Cancer (IARC)[3]. We also found that most of the difference in total sugar consumption between the highest and lowest consumers of sugar-sweetened soft drinks could be explained by their soft drink consumption[2].

There are plausible pathways through which sugar-sweetened soft drinks, but not artificially sweetened soft drinks could be associated with cancer risk, including sugar promoting inflammation, activating the insulin signalling pathway and through oxidative stress.[4, 5] A recent study found sugar-sweetened soft drink consumption was associated with a higher circulating C-reactive protein (CRP) concentration, a biomarker of inflammation[6]. A recent study from the NutriNet-Santé cohort also reports that sugary drinks (more broadly than just soft-drinks), but not artificially sweetened soft drinks, were associated with total cancer, and adjusting for sugar intake attenuated this association, suggesting that the association was at least to some extent mediated by sugar intake [7].

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We, therefore, hypothesised that sugar-sweetened soft-drinks would be associated with risk of cancers other than those related to obesity, and artificially-sweetened soft drinks would not show this association.

The aim of our study was to use the MCCS to investigate prospectively whether sugar-sweetened soft drink consumption is associated with risk of non-obesity-related cancers. Artificially-sweetened soft drink consumption was included in the study for comparison and, thereby, control for possible associations with other components of soft drinks.

Materials and Methods

The MCCS is a prospective cohort study which recruited 41,513 men and women aged 27 to 76 years (99% were aged between 40 and 70) between 1990 and 1994[8]. The Cancer Council Victoria Human Research Ethics Committee approved the study protocol. Participants gave written consent to participate.

We excluded 6,404 participants because they had a pre-baseline diagnosis of cancer (N=1568), were in the top or bottom 1% of the energy intake distribution (N=849), had reported a history of a heart attack, angina or diabetes at baseline (N=3212), were diagnosed with prostate cancer during follow-up but we were unable to determine aggressiveness of the tumour (N=47), or had missing data for any of the confounders (N=728), leaving 35,109 participants in the analysis sample.

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At baseline, participants completed a 121-item food frequency questionnaire including separate questions about the number of times in the past year they had consumed regular (sugar-sweetened) or diet (artificially-sweetened) soft drinks (never or less than once per month; 1-3 per month; 1 per week; 2-4 per week; 5-6 per week; 1 per day; 2-3 per day; 4-5 per day; 6+ per day). Other data from the food frequency questionnaire were used to calculate a Mediterranean diet score, as described previously[9]. The FFQ has been validated in comparison with biomarkers of fatty acids[10] and carotenoids[11]. Anthropometric measurements, including waist circumference, were taken, and questions about smoking, leisure time physical activity and intake of alcoholic beverages were completed [12].

Incident cancer cases were ascertained from the Victorian Cancer Registry or the Australian Cancer Database (for cases diagnosed outside of Victoria) as the earliest diagnosis of an invasive or metastatic primary cancer (excluding *in situ* or benign tumours). Obesity-related cancers were defined by 13 cancer types (oesophagus [adenocarcinoma]; pancreas; colorectum; breast [postmenopausal women]; endometrium; kidney; ovary; gallbladder; liver; gastric cardia; meningioma; thyroid; multiple myeloma) identified in 2016 by IARC for which there was sufficient evidence to be linked to overweight or obesity[13]. All other confirmed cancers were defined as not related to obesity. Mortality data, including cause of death, were obtained via linkage to Victorian death records, the National Death Index or the Australian Bureau of Statistics.

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We fitted Cox regression models to estimate hazard ratios (HR) and 95% confidence intervals (CI) for risk of cancer not related to obesity associated with soft drink consumption using age as the timescale. Participants were followed-up from baseline to the earliest of diagnosis of any cancer, death, last known to be in Australia or 30 June 2015 (when ascertainment of cancer diagnoses by the cancer registry was complete). Models for frequency of artificially-sweetened soft drink consumption were also fitted as a control, to rule out an association due to other components of soft drinks such as potential carcinogenic colours and flavourings. Cox regression models were also fitted (i) to confirm that body mass index was not associated with the development of non-obesity related cancers and (ii) to estimate the overall risk of developing one of the 13 cancer types related to obesity in relation to sugar-sweetened and artificially-sweetened soft drink consumption (to confirm our previous findings for 11 previously identified obesity-related cancers).

In order to have reasonable numbers of people in soft drink consumption categories, we collapsed the original nine categories into five categories as follows: never or <1 time/month; 1-3 times per month; 1-6 times per week; once per day; more than once per day. To test linear trends on a log hazard scale we assigned the median daily equivalent frequency to each of the five categories of soft drink consumption and used this as a continuous variable. To investigate departures from linearity in the relationship between soft drink consumption and risk of cancers not related to obesity, the likelihood ratio test was used to compare the linear and categorical models. Potential confounders were identified from directed acyclic graphs [14, 15] (Supplementary Figure 1 and Supplementary Figure 2). All models included alcohol intake

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(abstainers; ex-drinkers; >0 to <20 grams/day; 20 to <40 grams/day; ≥40 grams/day), country of birth (Australia/New Zealand/other; United Kingdom; Italy; Greece), Mediterranean diet score (continuous), physical activity (score based on intensity and frequency, classified into 4 ordered categories), socio-economic position (quintiles of area-based relative socio-economic disadvantage), sex and smoking status (never; former, quit<10 years; former, quit≥10 years; current, <15 cigarettes/day; current, ≥ 15 cigarettes/day). In our models for artificially-sweetened soft drink consumption we also adjusted for sugar-sweetened soft drink consumption. Where cancers not related to obesity was our outcome we did not consider body size as a confounder in either model. For the analysis of obesity-related cancers we used the same models as in our previous study (which included the same confounders as above (Supplementary Figure 3) with the inclusion of waist circumference in the artificially-sweetened soft drink model (Supplementary Figure 4)).

Sensitivity analyses were conducted by further excluding from the definition of non-obesity related cancers (i) fatal prostate cancer (which IARC determined had limited evidence of association with obesity[13]) as this had previously been reported to be an obesity-related cancer[16] and (ii) fatal prostate cancer, male breast cancer and diffuse large B-cell lymphoma (which IARC determined had limited evidence of association with obesity[13]). We also repeated analyses after excluding the first 2 years of follow-up to account for the possibility that the observed associations were due to pre-existing disease. To rule out confounding by sugar intake, we also fitted a model to estimate the risk of non-obesity related cancer

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associated with sugar-sweetened soft drink consumption, adjusting for sugar intake from sources other than sugary soft drinks.

Tests based on Schoenfeld residuals and graphical comparisons showed no evidence of violation of the proportional hazards assumption, except for socio-economic position, sex and smoking status in the models for the risk of cancer not related to obesity (and for sex in the models of obesity-related cancer), so we stratified for these variables in our main analyses. All statistical tests were two sided, with $P < 0.05$ considered statistically significant. Statistical analyses were performed using the statistical software package Stata/MP version 14.2.

Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Results

There were 4,789 participants who developed a cancer not related to obesity (Table 1). Table 2 shows the baseline characteristics by frequency of soft drink consumption. Frequent consumers of sugar-sweetened soft drinks had larger body size, higher sugar intake and were more likely to be male, socio-economically disadvantaged, physically inactive, current smokers and were frequent (>1/day) consumers of artificially-sweetened soft drinks. Frequent consumers of artificially sweetened soft-drinks had similar characteristics as those who

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consumed fewer such drinks, except they had larger body size. For both types of soft drinks, BMI and waist circumference increased with frequency of consumption.

There was no evidence of an association with risk of developing cancers not related to obesity for consumption of sugar-sweetened soft drinks; this was the case for the categories of frequency of consumption and for a linear trend (Table 3). For artificially-sweetened soft drinks, there was a positive association with frequency of consumption (HR = 1.23; 95% CI 1.02, 1.48, for those consuming artificially-sweetened soft drinks more than once per day relative to non-consumers; P-trend =0.006). There was no departure from linearity in the models for sugar-sweetened (P=0.72) or artificially-sweetened (P=0.14) soft drinks. Body mass index was not associated with the cancers we defined as non-obesity related (HR = 1.02; 95% CI 0.98, 1.06 per 5 kg/m^2 increment).

Our results were similar when we excluded additional cancer sites with limited evidence of relationships with obesity from our non-obesity related cancers; when we excluded the first 2 years of follow-up and after adjusting for sugar intake from sources other than sugary soft drinks.

Consistent with our previous findings based on 11 obesity-related cancer types, we found a positive association between the frequency of sugar-sweetened soft drink consumption and the development of 13 obesity-related cancer types and no association with artificially sweetened soft drinks (Supplementary Table 1).

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Discussion

We found no association between consumption of sugar-sweetened soft drinks and cancers not established to be obesity-related. However, we found a positive association with artificially-sweetened soft drinks. Our findings are not consistent with our hypothesis.

A strength of our study is the large number of cases of cancers not established to be associated with obesity. We collected data on many confounders and were able to control for these in our analyses, however, consumption of sugar-sweetened soft drinks was associated with more unhealthy behaviours, and it is possible we have not adequately controlled for all aspects of these. Limitations of our analysis include that we did not investigate site-specific cancer risk as we had small numbers of site-specific cases, particularly in our highest consumption category (>1/day). Further, the aetiology of the cancers considered may be varied, and combining them inappropriate. When combining a large number of heterogenous cancer types it is difficult to adequately adjust for confounders as some of the types included have specific risk factors which we were unable to control for, such as UV exposure for melanoma and Helicobacter pylori infection status for non-cardia gastric cancer.

Another limitation of our study is that we only had self-reported frequency of soft drink consumption and do not know the actual amount consumed on each occasion, and these measures have not been specifically validated. MCCS participants did not consume soft drinks very often, with only 8% consuming sugary soft drinks, and 6% consuming diet soft

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drinks, at least once per day. A recent study has suggested that, at least in relation to weight change, different artificial sweeteners may work differently [17], which may extend to potential differences in association with cancer risk. We did not have data on which types of artificial sweeteners were included in soft drinks in this study.

Our findings do not support our hypothesis that sugar-sweetened soft drinks could increase the risk of cancers not related to obesity. Possibly our hypothesis was based on an incorrect premise and the association we observed previously in the MCCS between sugar-sweetened soft drinks and obesity-related cancers, independent of obesity, was an artefact of residual confounding or measurement error. The positive association we observed in the present study between frequency of consumption of artificially-sweetened soft drinks and cancer unrelated to obesity was not expected and could be due to unmeasured confounding or to chance. We included this analysis to act as a control, to rule out that any association we might have observed between sugar-sweetened soft drinks and cancer could be attributed to other components in soft drinks such as potentially carcinogenic colours or flavourings. We have seen in the MCCS, and it has been reported from the National Nutrition and Physical Activity Survey 2011-12[18], that artificially-sweetened soft drinks are consumed by people who have a higher BMI.

A recent report from the French NutriNet-Santé study [7] found that consumption of sugary drinks, including soft drinks, fruit juice and sugar sweetened tea and coffee, were associated with cancer overall (not just obesity-related), and breast cancer, but there were not sufficient

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cases of cancer at other sites to analyse separately. Adjusting for sugar attenuated the associations, consistent with a mediating role for sugar, however, our results were unchanged after adjusting for sugar intake from sources other than sugary soft drinks. In this cohort, artificially sweetened soft drinks showed no association with cancer. Differences between our current analysis and the NutriNet-Santé study could be due to the different demographic makeup of the cohorts and the relative numbers of different type of cancer, for example in the MCCS, prostate cancer was the single most common cancer, contributing 31% of the total number of cases, while in the French cohort there were 291 cases within 101,257 (0.3%) total cancer cases, more than half (n=56,901) of which were pre-menopausal breast cancer cases.

In a recent review[19] of non-sugar sweeteners (which included artificial sweeteners and natural non-caloric sweeteners) a meta-analysis based on 8 case-control studies found no evidence of association with bladder or lower urinary tract cancer and little evidence for other cancers not related to obesity. Another recent review [20] suggested that non-nutritive sweeteners could affect tissues in the endocrine system. It has also been proposed that these sweeteners could affect bacteria in the human gut, which are known to play an important role in metabolism, inflammation, immune function and chronic disease[21]. A recent review of experimental studies and clinical trials on the effect of sweeteners on gut microbiota suggested that different types of artificial sweeteners might have different effects on the composition of the gut microbiome, but most of these were animal studies; the authors recommended that further research on the effect of sweeteners on human gut microbiota was needed[22]. In a pooled analysis of the Nurses' Health and Health Professionals' Follow-up studies, sugar-sweetened

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beverage consumption was positively associated with cancer mortality (from all sites) but there was no association for artificially-sweetened beverages [23]. They also investigated cancer-specific mortality for lung, colon, breast and prostate cancer and showed the positive association with sugar-sweetened beverages was restricted to the two obesity-related cancers, breast cancer in women and colon cancer, with no association for any of the four sites for artificially-sweetened beverages.

Our hypotheses that sugar-sweetened, but not artificially-sweetened, soft drinks would be associated with non-obesity related cancers were not supported by the data. While the positive association observed for artificially sweetened soft drinks may be due to chance, more research is needed to confirm the long-term safety of these products in view of their increasing consumption. Although our study did not find an association between consumption of sugar-sweetened soft drinks and non-obesity-related cancer, there is still evidence for a positive association with the risk of obesity-related cancer, supporting recommendations to limit soft drink consumption and to drink water instead.

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ascertained through the Victorian Cancer Registry and the Australian Institute of Health and Welfare, including the National Death Index and the Australian Cancer Database.

Conflict of Interest

None of the authors report a conflict of interest.

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References

1. Pereira MA. Sugar-sweetened and artificially-sweetened beverages in relation to obesity risk. *Adv Nutr* 2014;**5**: 797-808.

2. Hodge AM, Bassett JK, Milne RL, English DR, Giles GG. Consumption of sugar-sweetened and artificially sweetened soft drinks and risk of obesity-related cancers. *Public Health Nutr* 2018;**21**: 1618-26.

3. Smith TJ, Wolfson JA, Jiao D, Crupain MJ, Rangan U, Sapkota A, Bleich SN, Nachman KE. Caramel color in soft drinks and exposure to 4-methylimidazole: a quantitative risk assessment. *PLoS One* 2015;**10**: e0118138.

4. Klement RJ, Kammerer U. Is there a role for carbohydrate restriction in the treatment and prevention of cancer? *Nutr Metab (Lond)* 2011;**8**: 75.

5. Makarem N, Bandera EV, Nicholson JM, Parekh N. Consumption of Sugars, Sugary Foods, and Sugary Beverages in Relation to Cancer Risk: A Systematic Review of Longitudinal Studies. *Annu Rev Nutr* 2018;**38**: 17-39.

6. Tamez M, Monge A, Lopez-Ridaura R, Fagherazzi G, Rinaldi S, Ortiz-Panozo E, Yunes E, Romieu I, Lajous M. Soda Intake Is Directly Associated with Serum C-Reactive Protein Concentration in Mexican Women. *J Nutr* 2018;**148**: 117-24.

7. Chazelas E, Srour B, Desmetz E, Kesse-Guyot E, Julia C, Deschamps V, Druesne-Pecollo N, Galan P, Hercberg S, Latino-Martel P, Deschasaux M, Touvier M. Sugary drink consumption and risk of cancer: results from NutriNet-Sante prospective cohort. *BMJ* 2019;**366**: l2408.

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8. Milne RL, Fletcher AS, MacInnis RJ, Hodge AM, Hopkins AH, Bassett JK, Bruinsma FJ, Lynch BM, Dugue PA, Jayasekara H, Brinkman MT, Popowski LV, Baglietto L, Severi G, O'Dea K, Hopper JL, Southey MC, English DR, Giles GG. Cohort Profile: The Melbourne Collaborative Cohort Study (Health 2020). *Int J Epidemiol* 2017;**46**: 1757-i.

9. Hodge AM, Bassett JK, Shivappa N, Hebert JR, English DR, Giles GG, Severi G. Dietary inflammatory index, Mediterranean diet score, and lung cancer: a prospective study. *Cancer Causes Control* 2016;**27**: 907-17.

10. Hodge AM, Simpson JA, Gibson RA, Sinclair AJ, Makrides M, O'Dea K, English DR, Giles GG. Plasma phospholipid fatty acid composition as a biomarker of habitual dietary fat intake in an ethnically diverse cohort. *Nutr Metab Cardiovasc Dis* 2007;**17**: 415-26.

11. Hodge AM, Simpson JA, Fridman M, Rowley K, English DR, Giles GG, Su Q, O'Dea K. Evaluation of an FFQ for assessment of antioxidant intake using plasma biomarkers in an ethnically diverse population. *Public Health Nutr* 2009;**12**: 2438-47.

12. MacInnis RJ, English DR, Hopper JL, Haydon AM, Gertig DM, Giles GG. Body size and composition and colon cancer risk in men. *Cancer Epidemiol Biomarkers Prev* 2004;**13**: 553-9.

13. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K. Body Fatness and Cancer--Viewpoint of the IARC Working Group. *N Engl J Med* 2016;**375**: 794-8.

14. Textor J, van der Zander B, Gilthorpe MS, Liśkiewicz M, Ellison GT. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. *Int J Epidemiol* 2017;**45**: 1887-94.

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15. Rothman K, Greenland S, Lash T. *Modern Epidemiology*, 3rd ed. Philadelphia: Lippincott Williams and Wilkins, 2008.

16. World Cancer Research Fund International. Obesity, physical activity and cancer, 2016: https://www.wcrf.org/sites/default/files/Obesity-physical-activity-and-cancer-infographic.pdf [accessed September 2017].

17. Higgins KA, Mattes RD. A randomized controlled trial contrasting the effects of 4 low-calorie sweeteners and sucrose on body weight in adults with overweight or obesity. *Am J Clin Nutr* 2019;**109**: 1288-301.

18. Grech A, Kam CO, Gemming L, Rangan A. Diet-Quality and Socio-Demographic Factors Associated with Non-Nutritive Sweetener Use in the Australian Population. *Nutrients* 2018;**10**: 833.

19. Toews I, Lohner S, Kullenberg de Gaudry D, Sommer H, Meerpohl JJ. 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. *BMJ* 2019;**364**: k4718.

20. Rother KI, Conway EM, Sylvetsky AC. How Non-nutritive Sweeteners Influence Hormones and Health. *Trends Endocrinol Metab* 2018;**29**: 455-67.

21. Backhed F. Programming of host metabolism by the gut microbiota. *Ann Nutr Metab* 2011;**58 Suppl 2**: 44-52.

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22. Ruiz-Ojeda FJ, Plaza-Diaz J, Saez-Lara MJ, Gil A. Effects of Sweeteners on the Gut Microbiota: A Review of Experimental Studies and Clinical Trials. *Adv Nutr* 2019;**10**: S31-S48.

23. Malik VS, Li Y, Pan A, De Koning L, Schernhammer E, Willett WC, Hu FB. Long-Term Consumption of Sugar-Sweetened and Artificially Sweetened Beverages and Risk of Mortality in US Adults. *Circulation* 2019;**139**: 2113-25.

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Table 1. Distribution of incident cancer types unrelated to obesity

Cancer type	N	(%)
Prostate	1,473	(31)
Diffuse large B-cell lymphoma	111	(2.3)
Non-cardia gastric	125	(2.6)
Lung	464	(9.7)
Melanoma	723	(15)
Premenopausal breast	181	(3.8)
Bladder	157	(3.3)
Brain	106	(2.2)
Unknown Primary	117	(2.4)
Lymphoid leukemia	105	(2.2)
Other	1,227	(26)
All non-obesity-related cancers	4,789	(100)

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Table 2. Baseline characteristics by soft drink type and frequency of intake

	Frequency of sugar-sweetened soft drink consumption									
	Never or <1 time/ month N=18,355		**1-3 times/month N=6,135**		**1-6 times /week N=7,723**		**1 time/day N=1,909**		**>1 times /day N=987**	
Age years, mean (SD)	55.6	(8.5)	53.6	(8.5)	53.4	(8.6)	54.6	(8.7)	55	(8.5)
BMI kg/m^2, mean (SD)	26.5	(4.4)	26.6	(4.1)	27.1	(4.3)	27.5	(4.4)	28.5	(4.4)
Waist cm, mean (SD)	83.4	(12.7)	84.4	(12.4)	86.7	(12.5)	88.2	(12.6)	91.1	(12.9)
Alcohol intake g/d, median (IQR)	2	(0, 15.0)	2.6	(0, 15.0)	3.1	(0, 15.6)	2.7	(0, 16.3)	2.3	(0, 17.3)
Mediterranean diet score, median (IQR)	4	(3, 6)	4	(3, 6)	4	(3, 6)	4	(3, 6)	4	(3, 6)
Sugar intake g/d, mean (SD)	115.8	(61.6)	123	(60.8)	132.7	(63.3)	151.6	(66.6)	190.9	(74.4)
Country of birth, n (%)										
Australia/New Zealand/other	12,620	(69)	4,468	(73)	5,669	(73)	1,160	(61)	488	(49)
United Kingdom	1,472	(8)	424	(7)	509	(7)	142	(7)	47	(5)
Italy	2,054	(11)	667	(11)	920	(12)	447	(23)	350	(36)
Greece	2,209	(12)	576	(9)	625	(8)	160	(8)	102	(10)
Male, n (%)	5,934	(32)	2,506	(41)	3,836	(50)	980	(51)	547	(55)
SEIFA Q5[1] [least disadvantaged], n (%)	5,025	(27)	1,830	(30)	2,170	(28)	425	(22)	169	(17)
Physical activity score[2] ≥6 [most active], n (%)	4,313	(24)	1,430	(23)	1,810	(23)	336	(18)	171	(17)
Current smoker, n (%)	2,017	(11)	560	(9)	866	(11)	268	(14)	166	(17)
Diet soft drink >1/day, n (%)	392	(2.1)	68	(1.1)	111	(1.4)	57	(3.0)	116	(11.8)
	Frequency of artificially-sweetened soft drink consumption									
	Never or <1 time/ month N=26,284		**1-3 times/month N=2915**		**1-6 times /week N=3,887**		**1 time/day N=1,279**		**>1 times /day N=744**	
Age years, mean (SD)	55.1	(8.6)	53.4	(8.3)	53.2	(8.4)	53.7	(8.5)	53.9	(8.5)
BMI kg/m^2, mean (SD)	26.4	(4.2)	27.4	(4.3)	27.9	(4.5)	28.4	(4.7)	29.1	(5.1)
Waist cm, mean (SD)	84.1	(12.6)	85.9	(12.6)	86.7	(12.8)	87.6	(13.1)	89.3	(13.9)
Alcohol intake g/d, median (IQR)	2.2	(0, 15.3)	2	(0, 14.5)	2.8	(0, 15.0)	2.8	(0, 15.0)	1.7	(0, 15.0)
Mediterranean diet score, median (IQR)	4	(3, 6)	4	(3, 6)	4	(3, 6)	4	(3, 6)	4	(3, 6)
Sugar intake g/d, mean (SD)	125	(64.3)	121.3	(63.2)	123.5	(62.1)	129.8	(66.2)	131.7	(69.7)
Country of birth, n (%)										
Australia/ New Zealand/other	18,228	(69)	1,952	(67)	2,780	(72)	902	(71)	543	(73)
United Kingdom	1,997	(8)	171	(6)	284	(7)	92	(7)	50	(7)

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Italy	3,352	(13)	355	(12)	422	(11)	192	(15)	117	(16)
Greece	2,707	(10)	437	(15)	401	(10)	93	(7)	34	(5)
Male, n (%)	10,404	(40)	1,191	(41)	1,499	(39)	441	(35)	268	(36)
SEIFA Q5[1] [least disadvantaged], n (%)	7,242	(28)	788	(27)	1,106	(29)	314	(25)	169	(23)
Physical activity[2] ≥6 score [most active], n (%)	5,968	(23)	669	(23)	980	(25)	294	(23)	149	(20)
Current smoker, n (%)	2,962	(11)	298	(10)	388	(10)	140	(11)	89	(12)
Sugar-sweetened soft drink >1/day, n (%)	732	(2.8)	49	(1.7)	58	(1.5)	32	(2.5)	116	(15.6)

IQR, interquartile range (25th, 75th percentile)

[1] quintiles of Socio-Economic Indexes for Areas - Disadvantage: Q1 (first quartile), most disadvantaged and Q5 (5^{th} quartile), least disadvantaged

[2] Physical activity score (derived from activity type/intensity and frequency) ≥ 6 represents the most active participants

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Table 3. Hazard ratios (HR) and 95% CIs for risk of cancers not related to obesity, by type and frequency of soft drink consumption

	Sugar-sweetened soft drink			Artificially-sweetened soft drink		
	Cases/ Person-years	**HR[1]**	**(95% CI)**	**Cases/ Person-years**	**HR[2]**	**(95% CI)**
Frequency of consumption						
Never/<1/month	2,389/351,002	1.00		3,625/501,849	1.00	
1-3/month	831/118,195	1.03	(0.95, 1.12)	371/57,119	0.96	(0.86, 1.07)
1-6/week	1,128/149,179	1.03	(0.96, 1.11)	490/75,675	0.96	(0.87, 1.06)
1/day	293/36,269	1.06	(0.94, 1.20)	189/24,684	1.23	(1.06, 1.43)
>1/day	148/18,763	1.02	(0.86, 1.21)	114/14,082	1.23	(1.02, 1.48)
Linear model (per 1 serving/day increment)	4,789/673,409	1.02	(0.96, 1.08)	4,789/673,409	1.10	(1.03, 1.17)
P-trend		0.56			0.006	

[1] adjusted for alcohol intake, country of birth, Mediterranean diet score, physical activity, socio-economic position, sex and smoking status

[2] adjusted for the same confounders as the sugar-sweetened soft drink model and frequency of sugar-sweetened soft drink consumption

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Previously, the authors reported a positive association between consumption of sugar-sweetened soft drinks and risk of obesity-related cancers, but this association was not completely explained by obesity. In this prospective study, they investigated sugar-sweetened soft drink consumption and non-obesity-related cancers and found no association. An unexpected positive association was observed with artificially-sweetened soft drinks. Even though these findings leave unresolved whether consumption of sugar- sweetened soft drinks influences cancer risk independently of their association with body size, the work still supports recommendations to limit soft drink consumption. More research is needed to confirm the long-term safety of artificially-sweetened soft drinks.

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