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Letters

Sugary Drinks, Artificially-Sweetened Beverages, and Cardiovascular Disease in the NutriNet-Santé Cohort

Sugary drinks consumption has increased worldwide in recent years, while evidence demonstrating their detrimental impact on cardio-metabolic health is accumulating (1,2). Artificially sweetened beverages (ASB) are marketed as a healthier alternative, but their cardiometabolic impact is debated (2). We investigated the relationships between the consumption of sugary drinks, ASB, and the risk of cardiovascular disease (CVD) in a large prospective cohort.

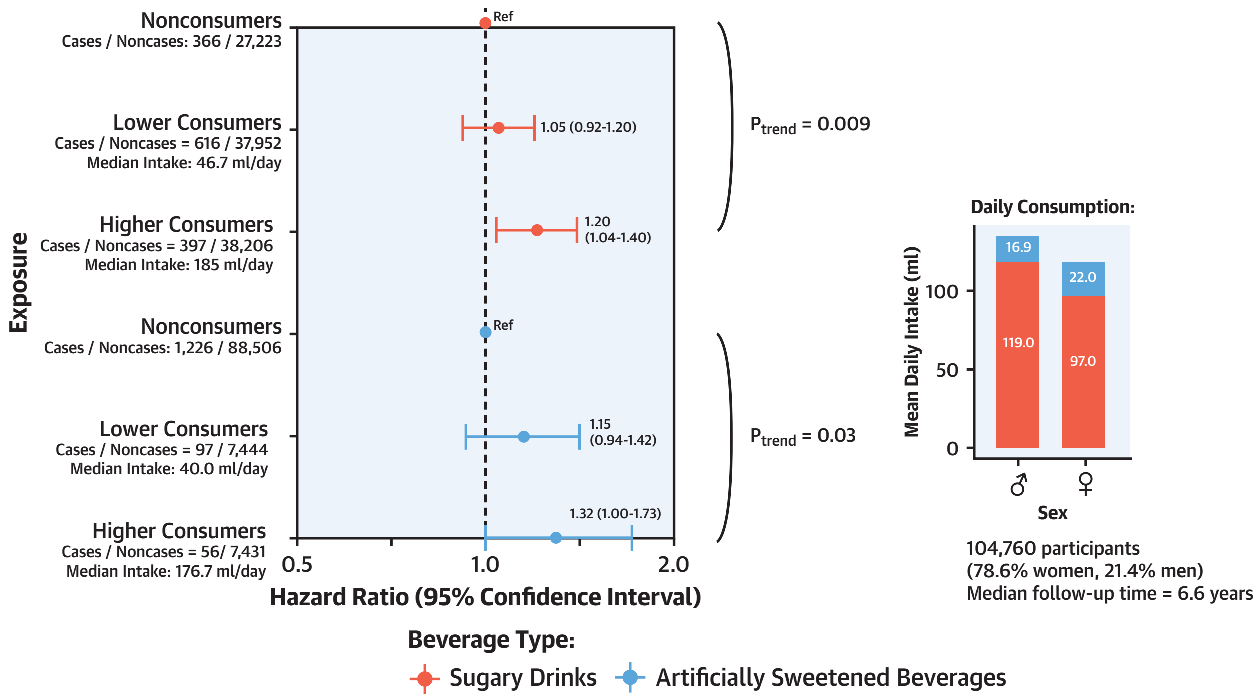
The French NutriNet-Santé cohort (NCT03335644) was launched in 2009 (3). Regulation and ethics approvals by the Inserm Institutional Review Board and Commission Nationale Informatique et Libertés are available online. Online questionnaires (examining physical activity, socioeconomic status, anthropometry) are regularly administered to participants. Every 6 months, participants are asked to fill out 3 validated web-based 24-h dietary records (2 minimum were mandatory). ASB were defined as beverages containing non-nutritive sweeteners (NNS). Sugary drinks consisted of all beverages containing ≥5% sugar (i.e., soft drinks, syrups, 100% juice, fruit drinks). All major health events reported by participants were validated based on their medical records. Data were also linked to the national health insurance system (SNIIRAM) and to the French national mortality registry (CépiDC). We classified CVD cases using International Classification of Diseases-Clinical Modification codes. The present study focused on first incident cases of stroke, transient ischemic attack, myocardial infarction, acute coronary syndrome, and angioplasty. For each type of beverage, 3 categories of intake were defined: nonconsumers, low consumers, and high consumers (separated by sex-specific median among consumers). Multiadjusted Cox proportional hazard models (age as timescale) were performed. To account for potential reverse causality bias (especially important for ASB), cases occurring during the first 3 years of follow-up were excluded. Participants contributed person-time until the date of diagnosis of CVD, last completed questionnaire, death, or October, 23, 2019, whichever occurred first. R version 3.5.2 (R Foundation, Vienna, Austria) was used for the analyses.

A total of 104,760 participants were included (mean baseline age 42.9 ± 14.6 years). Mean number of dietary records was 5.7 ± 3.1. Mean BMI was 23.7 ± 4.5 kg/m^2, 17.2% were current smokers, and 31.7% had a family history of CVD. Baseline prevalence of type 2 diabetes was 1.4%, hypercholesterolemia 8.0%, hypertension 8.2%, and hypertriglyceridemia 1.4%. During follow-up (2009 to 2019), 1,379 first incident cases of CVD occurred. Compared with non-consumers, higher consumers of sugary drinks and ASB had higher risks of first incident CVD (hazard ratio: 1.20; 95% confidence interval: 1.04 to 1.40; p for trend = 0.009) (**Figure 1**) and (hazard ratio: 1.32; 95% confidence interval: 1.00 to 1.73; p for trend = 0.03), respectively.

The health effects of NNS are currently debated based on conflicting epidemiological results (2,4). Mechanistic data suggest various metabolic impacts of NNS, notably through gut microbiota perturbation (5). The main strengths of this study are its large sample size, prospective design, and detailed and up-to-date assessment of beverage consumption. Limitations lie in potential residual confounding and reverse causality. However, we adjusted for a large range of confounders and limited reverse causality by excluding early CVD cases. In addition, both sugary drinks and ASB were associated with CVD risk. Sugary drinks were also associated with risk of cancer in a previous analysis (3).

In this cohort, higher intakes of sugary drinks and ASB were associated with a higher risk of CVD, suggesting that ASB might not be a healthy substitute for sugary drinks. These data provide additional arguments to fuel the current debate on taxes, labeling, and regulation of sugary drinks and ASB. To establish a causal link, replication in other large-scale prospective cohorts and mechanistic investigations are needed.

FIGURE 1 **Associations Between the Consumption of Artificially Sweetened Beverages, Sugary Drinks, and Cardiovascular Disease Risk From Multiadjusted Cox Proportional Hazard Models, NutriNet-Santé Cohort, 2009 to 2019**



Adjustments: age (time scale); sex; body mass index; sugar intake from other dietary sources; number of 24-h records; smoking status; educational level; physical activity; family cardiovascular disease history; intakes of: alcohol, energy, fruit and vegetables, red and processed meat, nuts, whole grains, legumes, saturated fatty acids, and sodium; proportion of ultraprocessed food in the diet (NOVA classification); and presence of type 2 diabetes, dyslipidemia, hypertension, hypertriglyceridemia, and treatments for these conditions. Artificially sweetened beverages (ASB) and sugary drink models were mutually adjusted. All diet beverages containing non-nutritive sweeteners such as aspartame, sucralose, and natural sweeteners (stevia, and so on) were considered as ASB. Missing data in covariates was handled using the multiple imputation by chained equations method. Associations among sugary drinks, ASB, and cardiovascular disease were not modified by body mass index, smoking status, or physical activity (p interaction for sugary drinks = 0.7, 0.3, 0.4; and for ASB = 0.1, 0.3, 0.5, respectively).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC* author instructions page.

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Beyond the Valve, Left Ventricle Remodeling May Be the Pivotal Factor for Survival in AR

We have read with great interest the paper by Yang et al. (1). Hemodynamically significant aortic regurgitation (AR) is commonly coexistent with greater than or equal to moderate mitral regurgitation (MR), and AR + functional MR is associated with high morbidity and mortality. The authors should be congratulated for their efforts. After reading their paper, we would like to highlight a few points that demand due consideration.

In patients with AR, the type of dysfunction is important for sequence change of mitral valve and left ventricle (LV). For type I pathology, the cause of AR is dilation of aortic annulus with normal leaflet motion. The regurgitation could cause LV dilation. However, for type II pathology, especially for the right cusp prolapse, the regurgitated jet washes the anterior leaflet directly. This may cause organic MR (endocarditis, prolapse). Yang et al. (1) reported 140 patients with AR with cusp prolapse and 732 with annular dilation. Could the author provide the proportion of functional MR and organic MR in different types of patients with AR? This would help clinicians better understand the cause of MR in patients with AR.

Both AR and MR can increase LV preload, and AR can also increase the afterload as increased total stroke volume ejected on systemic vascular resistance and systolic hypertension. The volume and pressure load increase the LV dilation and wall thickness. The regression of LV eccentric hypertrophy is a direct parameter that quantifies the reduced work of the LV and judges the hemodynamic efficiency of the valve surgery. It is logical to assume that clinical outcome parallels the benefits on LV remodeling. It would be helpful for the authors to describe the pre-operative and post-operative LV wall thickness. Magnetic resonance imaging has an established role in the assessment of LV size and function and MR severity. Did the author consider the predictive effect of magnetic resonance imaging in AR+MR?

Lastly, MR may decrease with relief of LV pressure overload from AV surgery. However, the degree of improvement in MR after pure AR surgery is still unknown (2). It would be helpful to provide the detailed changes of MR and LV in pure AR group during the follow-up period.

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REPLY: Beyond the Valve, Left Ventricle Remodeling May Be the Pivotal Factor for Survival in AR

We greatly appreciate the comments from Dr. Jiang and colleagues regarding our work (1). We believe it is important first to recognize that our study demonstrated that coexistence of significant aortic regurgitation (AR) and significant mitral regurgitation (MR) is actually not considerably frequent (i.e., 14%) (1), yet it is enough to warrant clinical attention, especially given its association with death, particularly for AR plus functional (FMR), but also for AR plus organic MR (OMR). Whether the mechanism of AR determines the mechanism of MR is a fascinating question, because aortic cusp prolapse/ annular dilation in association with mitral prolapse