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How Much Can Water Intake Protect Against Sugary Drink Consumption?

Children and young adults with any water intake had about half as much sugar-sweetened beverage calorie consumption as those with no water intake.

Sugar-sweetened beverages (SSBs) have become an important focus in efforts to reduce children's empty calorie intake, but their relationship to water intake has not been described well at the national level.

Researchers analyzed cross-sectional 24-hour dietary recall data from 8400 children and young adults included in a large U.S. national nutrition survey (2011–2016) to compare SSB caloric intake between children who had any water intake and those who had none. SSBs were classified as soda, fruit drinks, sports and energy drinks, sweetened coffees and teas, and other. Children were grouped by age (2–5, 6–11, and 12–19 years) and stratified by race/ethnicity (non-Hispanic white, non-Hispanic black, non-Hispanic Asian, and Hispanic). Analyses were adjusted for sex and federal income-to-poverty ratio.

No water intake was associated with higher total SSB calories and percent of total calories from SSBs. Approximately twice the SSB calories were consumed among those with no water intake (vs. those with any water intake) among all participants and in each age subgroup, and SSB consumption rose with age. Among racial/ethnic subgroups, the patterns were similar except for in 2- to 5-year-old non-Hispanic Asians, who showed a smaller increase of SSB calories with no water intake.

COMMENT: In what can feel like an impossible battle against sugary drink consumption, it is encouraging to see that water intake of any amount might protect against excessive SSB calories. This study lends further support to the American Academy of Pediatrics' recent call to reduce sweetened drinks and champion water consumption (NEJM JW Pediatr Adolesc Med Apr 17 2019; [e-pub] and *Pediatrics* 2019; 143:e20190282) Clinicians should use simple, clear messaging on the role of water as the primary drink for all children, adolescents, and young adults when discussing healthy habits with families.

CITATION(S): Rosinger AY et al. Association of caloric intake from sugar-sweetened beverages with water intake among US children and young adults in the 2011–2016 national health and nutrition examination survey. *JAMA Pediatr* 2019 Apr 22; [e-pub]. (<https://doi.org/10.1001/jamapediatrics.2019.0693>)

Circulation 2019 Mar 18

Artificially Sweetened Beverages May Be Associated with Some Health Risks

And women might be at greater risk than men.

Sugar-sweetened beverages (SSBs) have consistently been associated with deleterious health outcomes, but the data on artificially sweetened beverages (ASBs) are still accumulating. These authors examined associations between consumption of SSBs or ASBs and risk for total and cause-specific mortality among 37,716 men from the Health Professionals Follow-up Study and 80,647 women from the Nurses' Health Study.

During 3.4 million person-years of follow-up, 36,436 deaths occurred (deaths related to cardiovascular disease [CVD], 7896). Analyses adjusted for diet and lifestyle factors. Consumption of SSBs at least twice weekly, compared with less than monthly use, was associated with higher risks for all-cause mortality (hazard ratios: 2–6 portions/week, 1.06; once-daily use, 1.14; ≥ 2 /day, 1.21) and CVD mortality (HRs, 1.10, 1.19, 1.31, respectively); risks increased with greater use (P -trends, <0.0001).

For ASBs, only the highest intake category (≥ 2 /day) was associated with significantly higher total mortality (HR, 1.07) and CVD mortality (HR, 1.13); risks increased with greater use (P -trends: total mortality, 0.01; CVD mortality, 0.02). In stratified analyses, the heightened risk with ASBs occurred only in people who were overweight or had high levels of physical activity. In further analyses, ASBs were associated with mortality only in the female-predominate Nurses' Health Study, and the association was restricted to very high use (≥ 4 /day). ASBs were not associated with cancer mortality (12,380 deaths).

COMMENT: Consumption of SSBs is associated with elevated risks for death, driven by an increase in CVD mortality. Only very high consumption of ASBs was associated with total and CVD mortality. Stratified analyses showed that the positive association between ASBs and mortality was found only among those who were overweight or had high levels of physical activity, possibly indicating reverse causation. But as we counsel our patients, we should be mindful that ASBs appear to carry some risk.

CITATION(S): Malik VS et al. Long-term consumption of sugar-sweetened and artificially sweetened beverages and risk of mortality in US adults. *Circulation* 2019 Mar 18; [e-pub]. (<https://doi.org/10.1161/CIRCULATIONAHA.118.037401>)

Prenatal Vitamin Use Lowers Risk for Autism Spectrum Disorder in Vulnerable Families

In families with a child who has ASD, taking vitamins in the first month of a later pregnancy halves the risk for ASD in the younger sibling.

In population-based studies, maternal prenatal vitamin intake, particularly folic acid, appears to reduce the risk for autism spectrum disorder (ASD). But the recurrence rate of ASD in families who have a child with ASD is upwards of 1 in 5 siblings, and whether the benefit of prenatal supplementation extends to these families is less clear. To examine this question, investigators prospectively enrolled mothers who had a child with confirmed ASD and who either were pregnant or were planning a pregnancy.

The sample included 241 younger siblings (58% boys), with a mean age of 36.5 months at final follow-up. Although 96% of mothers reported taking prenatal vitamins during pregnancy, only 36% took vitamins in the 6 months preceding pregnancy. ASD prevalence was 14.1% in children whose mothers took prenatal vitamins in the first month of pregnancy and 32.7% in children whose mothers did not (adjusted relative risk, 0.50). Among children with ASD, those in the prenatal-vitamin group also had significantly lower ASD symptom severity and higher cognitive scores than children whose mothers did not take vitamins in the first month. Folic acid intake of ≥ 600 μg and higher total mean daily iron intake during the first month of pregnancy were each associated with lower estimated ASD risks.

COMMENT: Prenatal vitamin intake during the first month of pregnancy appears to reduce ASD recurrence and severity in siblings of children with ASD. The size of the effect is dramatic — and very encouraging, given that at least some children likely were genetically predisposed to ASD. Indeed, this study will be extraordinarily helpful in encouraging prospective mothers to start prenatal vitamin supplementation. The results might also lead to a better understanding of genetic predictors of response and a better appreciation of optimal dosing and biologic mechanisms.

CITATION(S): Schmidt RJ et al. Association of maternal prenatal vitamin use with risk for autism spectrum disorder recurrence in young siblings. *JAMA Psychiatry* 2019 Feb 27; 76:391. (<https://doi.org/10.1001/jamapsychiatry.2018.3901>)

Exposure to Ambient Pesticides and Autism Risk

Exposure to some pesticides is not good for the growing brain, according to a population-based study.

Increases in prevalence of autism spectrum disorder have directed attention to environmental factors that could contribute to risk. Studies using animal models have documented neurobehavioral abnormalities after pesticide exposure, and organophosphates and organochlorines have been suggested to increase autism risk. In a population-based study, investigators ascertained prenatal and infant exposure to 11 high-use pesticides that have evidence of their potential neurodevelopmental toxicity.

The investigators used detailed California records on pesticide use and registries for births and developmental services to geographically link pesticide use in agricultural counties to nearby autism diagnoses (2961 cases; 35,370 sex- and birth-year-matched controls). Children with pervasive developmental disorder or Asperger disorder were not included; children with comorbid intellectual disability were analyzed separately.

Analyses adjusted for sociodemographics and traffic-related air pollution. Six of the eleven pesticides were each associated with about a 10% increase in autism risk compared with no exposure. These associations were weaker in

analyses adjusting for all 11 compounds. Regarding children with autism plus intellectual disability, exposure to any of six pesticides during pregnancy or infancy increased the risk to an even greater extent (by 30%–40%).

COMMENT: It is surprising that the risk for autism with exposure to potential neurotoxins is so low. Although some pesticides appear to carry risk, no compelling class effect is likely to emerge; researchers will need to focus on specific compounds, to cast a broader net for adverse neurodevelopmental outcomes, and to assess risk in the context of potential genetic liability. The value of such studies will come not from reaffirmations that pesticide exposure is bad but from improved understanding of the pathophysiological pathways leading to autism, intellectual disability, and perhaps other, more subtle conditions.

CITATION(S): von Ehrenstein OS et al. Prenatal and infant exposure to ambient pesticides and autism spectrum disorder in children: Population based case-control study. *BMJ* 2019 Mar 20; 364:1962. (<https://doi.org/10.1136/bmj.1962>)

Bakian AV and VanDerslice JA. Pesticides and autism. *BMJ* 2019 Mar 20; 364:11149. (<https://doi.org/10.1136/bmj.11149>)

U.S. Officials Stress Vaccination as Measles Cases Top 700

By Kelly Young Edited by David G. Fairchild, MD, MPH, and Jaye Elizabeth Hefner, MD

The CDC has recorded 704 confirmed cases of measles in the U.S. so far in 2019, up 78 from the week prior. This is the highest since 1994, when there were 963 measles cases.

Roughly 9% of cases have been hospitalized, and 3% have developed pneumonia. Most cases have been in unvaccinated children.

This week, new outbreaks of three or more cases were reported in Maryland, Georgia, and California's Los Angeles and Sacramento counties. In a media briefing, CDC officials said that outbreaks in New York and Washington State have accounted for most cases overall.

Some 1.3% of children under age 2 in the U.S. haven't been vaccinated against measles, CDC Director Dr. Robert Redfield noted in a statement. He said: "I call upon healthcare providers to encourage parents, and expectant parents, to vaccinate their children for their own protection and to avoid the spread of vaccine-preventable diseases within their families and communities."

For the CDC's measles, mumps, and rubella vaccine recommendations, see the fourth link below.

LINK(S): MMWR article (Free); CDC measles surveillance site (Free); CDC director's statement (Free);

CDC's MMR vaccine recommendations (Free)

Who Is at Highest Risk for Miscarriage?

A large Norwegian cohort study confirms that miscarriage risk is markedly affected by maternal age.

Risk for miscarriage (spontaneous pregnancy loss before 20 weeks' gestation) can be difficult to quantify. Prevalence of miscarriage was studied in a Norwegian cohort of >420,000 pregnancies from 2009 through 2013 that resulted in live birth (71.0%), induced abortion (18.3%), miscarriage (10.4%), and stillbirth (0.3%).

Excluding induced abortions, risk for miscarriage varied with maternal age (17% [<20 years], 11% [20–24], 10% [25–29], 11% [30–34], 17% [35–39], 33% [40–44], and 57% [\geq 45]). Analysis adjusted for maternal age showed that miscarriage risk rose among women with previous miscarriages (1 prior miscarriage: adjusted odds ratio [aOR], 1.54; 2 prior miscarriages: aOR, 2.21; 3 prior miscarriages: aOR, 3.97). Miscarriage risk was modestly increased for women with a history of prior preterm birth (aOR, 1.22) or non-elective cesarean delivery (aOR, 1.29).

COMMENT: These findings confirm prior reports that risk for miscarriage is higher among both younger (age <20) and older (age \geq 35) women; in this Norwegian cohort, the lowest rate of miscarriage (10%) occurred in women aged 25 to 29. Many biological factors can cause a miscarriage, prominently genetic abnormalities in the pregnancy tissue (including aneuploidy). For women planning to become pregnant, these data should help provide an accurate estimate of their risk for miscarriage.

CITATION(S): Magnus MC et al. Role of maternal age and pregnancy history in risk of miscarriage: Prospective register based study. *BMJ* 2019 Mar 20; 364:l869. (<https://doi.org/10.1136/bmj.l869>)

Live Birth Rates in Euthyroid Women with Thyroid Peroxidase Antibodies

Randomized trial showed no benefit of exogenous levothyroxine in women with histories of infertility or miscarriage.

Euthyroid women with thyroid peroxidase antibodies are at excess risk for miscarriage and preterm birth, but whether exogenous levothyroxine is beneficial to such women remains unknown. Investigators in the U.K. conducted a multicenter trial in which 952 euthyroid women (age range, 16–40) with a history of miscarriage or infertility and seeking to conceive were randomized to 50- μ g oral levothyroxine or placebo daily from before conception through the end of pregnancy. Euthyroid status was defined as serum thyrotropin 0.44–3.63 mIU/L and free thyroxine 10.0–21.0 pmol/L (0.78–1.63 ng/dL). Group assignments were balanced by age (<35 or \geq 35), number of previous miscarriages, infertility treatment, and baseline thyrotropin concentration (\leq 2.5 or >2.5 mIU/L). Adherence to levothyroxine was confirmed by measuring serum thyrotropin and free thyroxine.

Live-birth rates after \geq 34 weeks' gestation were 37.4% (levothyroxine) and 37.9% (placebo; relative risk, 0.97). Subgroup analysis by factors such as maternal age, number of previous miscarriages, and baseline thyrotropin also showed no significant between-group differences in live birth, pregnancy loss, preterm birth, or neonatal outcomes. Serious adverse events did not differ between groups.

COMMENT: Although this trial is limited because the entire intervention group received the same dose of levothyroxine, the results should put to rest the possibility of using exogenous levothyroxine to treat euthyroid women positive for thyroid peroxidase antibodies. Perhaps the findings are to be expected, as the principal association with infertility and miscarriage involves thyroid peroxidase antibodies, not circulating thyroxine — and these antibody levels were not directly lowered by treatment. The study also suggests that thyroid peroxidase antibody testing in euthyroid women with

histories of miscarriage or infertility may be unnecessary, given the failure of exogenous levothyroxine to lower risks for miscarriage or infertility.

CITATION(S): Dhillon-Smith RK et al. Levothyroxine in women with thyroid peroxidase antibodies before conception. *N Engl J Med* 2019 Mar 23; [e-pub]. (<https://doi.org/10.1056/NEJMoa1812537>)

Ann Intern Med 2019 Apr 9

Dietary Supplements Aren't Associated with Lower Mortality

But adequate intake of nutrients from food confers health benefits.

Many U.S. adults report taking dietary supplements, despite no evidence of benefit. In a prospective cohort study, investigators evaluated the effects of dietary supplements and nutrient intake from foods and supplements on mortality in $\geq 30,000$ adults who participated in the U.S. National Health and Nutrition Examination Survey and were followed for ≥ 6 years.

Fifty percent of participants used dietary supplements. In analyses adjusted for demographics, habits, and comorbid conditions, use of dietary supplements was not associated with lower mortality. However, people who did not maintain at least adequate intake of vitamins A and K, magnesium, and zinc from foods (according to Institute of Medicine standards) had excess risk for death. Excessive calcium intake (≥ 1000 mg daily) *from supplements* was associated with significantly higher relative risk for cancer-related death (1.5 additional deaths per 1000 person-years). Excessive vitamin D intake (≥ 10 μg [400 IU] daily) *from supplements* in people without vitamin D deficiency was associated with significantly higher relative risk for death.

COMMENT: In this study, researchers went to great lengths to accurately calculate participants' vitamin and mineral intake (distinguishing nutrient sources) and to assess mortality outcomes. Findings mirror those of other large cohorts and a systematic review, supporting findings that adequate vitamin and mineral intake *from foods* leads to positive outcomes, with little or no additional benefit from supplements. Whether the excess mortality associated with calcium and vitamin D supplementation reflects residual confounding in this observational study is unclear, but clinicians might want to share these findings with patients who routinely take these supplements.

CITATION(S): Chen F et al. Association among dietary supplement use, nutrient intake, and mortality among U.S. adults: A cohort study. *Ann Intern Med* 2019 Apr 9; [e-pub]. (<https://doi.org/10.7326/M18-2478>)

Lancet 2019 Apr 25

Safety and Efficacy of Peanut Oral Immunotherapy

Although OIT provides desensitization in most patients, it can lead to side effects and anaphylaxis in some.

Peanut allergy affects 2% of children and is the most common cause of fatal food-induced anaphylaxis. Several studies have shown that patients can be desensitized with peanut oral immunotherapy (OIT; e.g., *NEJM JW Pediatr Adolesc Med Jan 2019* and *N Engl J Med* 2018; 379:1991). Now, researchers have performed a systematic review of 12 randomized, controlled trials (with >1000 mostly pediatric patients) to examine how OIT affects quality of life and anaphylaxis incidence.

Median starting dose of peanut protein was 0.5 mg (1/600th of a peanut), with a median target dose of 2000 mg (6–7 peanuts) escalated during a median 31 weeks. Patients in the OIT groups experienced significantly more anaphylactic reactions than did an untreated historical cohort (22% vs. 7%), and a third of OIT-treated patients experienced substantial gastrointestinal side effects. Anaphylaxis frequently was triggered by exercise, menstruation, concomitant illness, heat, uncontrolled asthma, or dosing on an empty stomach. No improvement was seen in quality of life in the active-treatment groups.

COMMENT: As many as 75% of peanut-allergic children can be desensitized successfully using OIT, but it does not provide a “cure” or long-term tolerance. As editorialists point out, the trade-off for potential protection in accidental exposures is the possibility of markedly more side effects and anaphylaxis associated with daily in-home dosing. Although peanut powder for OIT still is investigational, the FDA might approve it within the year, and its risks and benefits will have to be reviewed carefully with families.

CITATION(S): Chu DK et al. Oral immunotherapy for peanut allergy (PACE): A systematic review and meta-analysis of efficacy and safety. *Lancet* 2019 Apr 25; [e-pub]. ([https://doi.org/10.1016/S0140-6736\(19\)30420-9](https://doi.org/10.1016/S0140-6736(19)30420-9))

Roberts G and Angier E. Peanut oral immunotherapy: Balancing benefits and risks for individuals. *Lancet* 2019 Apr 25; [e-pub]. ([https://doi.org/10.1016/S0140-6736\(19\)30767-6](https://doi.org/10.1016/S0140-6736(19)30767-6))

Brain 2019 Apr 14

Is Botulinum Toxin A Useful in Treating Medication Overuse Headache?

Despite a lack of difference in outcomes from placebo during acute-medication withdrawal for medication overuse headache, BTA may have some efficacy in these patients.

To investigate the add-on efficacy of botulinum toxin A (BTA) in the treatment of medication-overuse headache (MOH), researchers randomized 179 adults with chronic migraine and MOH to receive either BTA injections (155 U) or placebo (saline, with 17.5 U of BTA in the forehead to maintain blinding), followed by ambulant withdrawal therapy for 12 weeks.

In weeks 9 through 12 after injection, the number of headache days was reduced by 26.9% in the BTA group (n=90) and by 20.5% (n=89) in the placebo group, a nonsignificant difference. All other secondary endpoints and the 1-year evaluation of MOH (still present or not) were not significantly different between groups. The authors conclude that BTA is not effective as an additional treatment for MOH and that withdrawal therapy should first be tried alone.

COMMENT: This study was long awaited because of controversy over whether BTA should be given to enhance withdrawal therapy in MOH. However, the data must be interpreted with caution. First, compared with the PREEMPT trial (n=1384), this study was small. If this trial had been as large as PREEMPT, the outcome differences in this trial probably would have been significant. Second, placebo patients received some BTA. Since there is no scientific evidence that 17.5 U in the forehead is not efficacious, the placebo group may also have experienced efficacy by verum. Third, the authors examined their primary outcome measure at weeks 9 to 12, whereas the PREEMPT trial examined outcomes at weeks 21 to 24. It is well known that the efficacy of BTA increases with time. In summary, *yes*, the study supports the view that withdrawal therapy alone should be tried first in MOH before adding BTA, but *no*, the study does not prove that adding BTA is of no efficacy at all in these patients.

Dr. Evers is Professor of Neurology, University of Münster and Director, Department of Neurology, Krankenhaus Lindenbrunn, Germany.

CITATION(S): Pijpers JA et al. Acute withdrawal and botulinum toxin A in chronic migraine with medication overuse: A double-blind randomized controlled trial. *Brain* 2019 Apr 14; [e-pub]. (<https://doi.org/10.1093/brain/awz052>)

Gastroenterology 2019 Apr 11;

Underwater Endoscopic Mucosal Resection for Nonpedunculated Colorectal Polyps 10 to 20 mm

Underwater EMR is associated with a higher rate of complete resection compared with conventional EMR.

Underwater endoscopic mucosal resection (UEMR) is a polypectomy technique where the colon lumen is filled with water and resection performed without submucosal fluid injection. Although UEMR has been shown to be effective and safe, it is not widely performed and is used mostly for large (≥ 20 mm) polyps.

In a multicenter, randomized, controlled trial in Japan, researchers investigated whether UEMR is superior to conventional EMR for sessile and superficial elevated polyps 10 to 20 mm in size. The procedures were performed by 28 endoscopists with varying degrees of experience, and 210 patients with 210 lesions were included. The primary endpoint was R0 resection, defined as en bloc resection with a histologically negative resection margin. Compared with conventional EMR, UEMR was associated with:

- Significantly higher R0 resection rate (69% vs. 50%)
- Significantly higher en bloc resection rate (89% vs. 75%)
- Similar median procedure time (about 3 minutes)
- Similar and low incidence of adverse events, which were limited to bleeding within 48 hours in 2%. No perforations occurred.

COMMENT: Underwater polypectomy techniques are gaining traction as effective and safe alternatives to conventional resection, and this is the first randomized, controlled trial comparing UEMR with conventional EMR for nonpedunculated polyps 10 to 20 mm in size. The lower rate of piecemeal resection is notable, but it is not known whether this translates into a lower recurrence rate on longer-term follow-up. The impact on clinical practice remains to be seen: EMR techniques are not consistently used in the West for polyps in this size range, and I suspect many endoscopists still rely on standard hot snare polypectomy without submucosal injection. However, EMR in this setting facilitates en bloc resection and is associated with lower rates of deep thermal injury, particularly for larger polyps within the 10 to 20 mm category.

Note to readers: At the time we reviewed this paper, its publisher noted that it was not in final form and that subsequent changes might be made.

CITATION(S): Yamashina T et al. Comparison of underwater vs conventional endoscopic mucosal resection of intermediate-size colorectal polyps. *Gastroenterology* 2019 Apr 11; [e-pub]. (<https://doi.org/10.1053/j.gastro.2019.04.005>)
