research

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ORIGINAL RESEARCH Results from the prospective NutriNet-Santé cohort

Artificial sweeteners and risk of cardiovascular diseases

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Study question Are artificial sweeteners from all dietary sources (beverages, table top sweeteners, dairy products, etc), overall and by molecule (aspartame, acesulfame potassium, and sucralose), associated with risk of cardiovascular diseases (overall, coronary heart disease, and cerebrovascular disease)?

Methods This population based prospective study (2009-21) consisted of 103 388 French participants from the web based NutriNet-Santé cohort (mean age 42.2±14.4, 79.8% female, 904 205 person years). Dietary intakes and consumption of artificial sweeteners were assessed using 24 hour dietary records that included brand names of industrial products. Associations between sweeteners (coded as continuous variables, log10 transformed) and cardiovascular disease risk were assessed by multivariable adjusted Cox hazard models.

Study answer and limitations Total artificial sweetener intake was associated with increased risk of cardiovascular diseases (1502 events; hazard ratio 1.09, 95% confidence interval 1.01 to 1.18, P=0.03); absolute incidence rate in higher consumers (above the sex specific median) and non-consumers was 346 and 314 per 100 000 person years, respectively. Artificial sweeteners were more particularly associated with cerebrovascular disease risk (777 events; 1.18, 1.06 to 1.31, P=0.002; incidence rates 195 and 150). Aspartame intake was associated with increased risk of cerebrovascular events (1.17, 1.03 to 1.33, P=0.02; incidence rates 186 and 151), and acesulfame potassium and sucralose were associated with increased coronary heart disease risk (730 events; acesulfame potassium: 1.40, 1.06 to 1.84, P=0.02; incidence rates 167 and 164; sucralose: 1.31, 1.00 to 1.71, P=0.05; incidence rates 271 and 161). Limitations of this study include potential selection, residual confounding, and reverse causality biases, although sensitivity analyses were performed to address these concerns and showed consistent results.

What this study adds Artificial sweeteners (especially aspartame, acesulfame potassium, and sucralose) were associated with increased risks of cardiovascular, cerebrovascular, and coronary heart diseases.

Funding, competing interests, and data sharing
Funded by the European Research Council, the French National Cancer Institute, the French Ministry of Health, and the Université Paris Cité.

No competing interests declared. Researchers from public institutions can submit a collaboration request to collaboration@etude-nutrinet-sante.fr

Trial registration
ClinicalTrials.gov NCT03335644.

Can vitamin D protect against covid-19?

ORIGINAL RESEARCH
Phase 3 randomised controlled trial

Effect of a test-and-treat approach to vitamin D supplementation on risk of all cause acute respiratory tract infection and covid-19 (CORONAVIT)

Jolliffe DA, Holt H, Greenig M, et al
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Study question Does population level implementation of a test-and-treat approach to correct suboptimal vitamin D status reduce the risk of all cause acute respiratory tract infection and covid-19?

Methods This phase 3 open label randomised controlled trial (CORONAVIT) used trial-within-cohort methodology. The study sample comprised 6200 people living in the UK who were aged 16 years and older and who were not taking vitamin D supplements at baseline. The intervention was an offer of a postal finger prick test of blood 25-hydroxyvitamin D concentration, with a six month supply of lower dose (800 IU/day, n=1550) or higher dose (3200 IU/day, n=1550) vitamin D for those found to have concentrations ‹75 nmol/L. The comparator was no offer of testing or supplementation (n=3100). The primary outcome was the proportion of participants who experienced at least one swab test or doctor confirmed acute respiratory tract infection of any cause. Secondary outcomes included the proportion of participants who developed swab test confirmed covid-19.

Study answer and limitations Of 3100 participants offered a vitamin D test, 2958 (95.4%) accepted and 2674 (86.3%) had 25-hydroxyvitamin D levels ‹75 nmol/L and received vitamin D supplements (n=1328 lower dose, n=1346 higher dose). Compared with 136/2949 (4.6%) participants in the no offer group, at least one acute respiratory tract infection of any cause occurred in 87/1515 (5.7%) participants in the lower dose group (odds ratio 1.26, 95% confidence interval 0.96 to 1.66) and 76/1515 (5.0%) in the higher dose group (1.09, 0.82 to 1.46). Compared with 78/2949 (2.6%) participants in the no offer group, 55/1515 (3.6%) developed covid-19 in the lower dose group (1.39, 0.98 to 1.97) and 45/1515 (3.0%) in the higher dose group (1.13, 0.78 to 1.63). A limitation of the study was that some participants randomised to no offer of a test or supplementation took off-trial vitamin D supplements. However, sensitivity analyses excluding these participants also yielded null findings for primary and secondary outcomes.

What this study adds Among people aged 16 years and older with a high baseline prevalence of suboptimal vitamin D status, implementation of a population level test-and-treat approach to vitamin D supplementation was not associated with a reduction in risk of all cause acute respiratory tract infection or covid-19.

Funding, competing interests, and data sharing This study was mainly supported by Barts Charity, Pharma Nord, and the Fischer Family Foundation. The trial was supported by grants from companies that manufacture and sell vitamin D supplements. Data will be made available on reasonable request to a.martineau@qmul.ac.uk.

Trial registration ClinicalTrials.gov NCT04579640.

Trial outcomes by allocation: intention-to-treat analysis. Values are percentages (number with at least one event) unless specified otherwise

	No offer (n=2949)	800 IU/day offer (n=1515)	800 IU/day *v* no offer		3200 IU/day offer (n=1515)	3200 IU/day *v* no offer	
			Odds ratio (95% CI)	P value		Odds ratio (95% CI)	P value
Swab test or doctor confirmed ARI of any cause	4.6 (136)	5.7 (87)	1.26 (0.96 to 1.66)	0.10	5.0 (76)	1.09 (0.82 to 1.46)	0.55
Swab test confirmed covid-19	2.6 (78)	3.6 (55)	1.39 (0.98 to 1.97)	0.07	3.0 (45)	1.13 (0.78 to 1.63)	0.53

ARI=acute respiratory tract infection.

ORIGINAL RESEARCH
Quadruple blinded, randomised placebo controlled trial

Prevention of covid-19 and other acute respiratory infections with cod liver oil supplementation, a low dose vitamin D supplement

Brunvoll SH, Nygaard AB, Ellingjord-Dale M, et al
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Study question Does daily supplementation with cod liver oil, a low dose vitamin D supplement, prevent SARS-CoV-2 infection, serious covid-19, or other acute respiratory infections when given to adults in Norway in winter?

Methods This quadruple blinded, randomised placebo controlled trial was carried out between 10 November 2020 and 2 June 2021 in Norway. 34 741 adults (aged 18-75 years) were randomised to receive 5 mL/day of cod liver oil (10 µg vitamin D) or placebo (corn oil) for six months. Predefined co-primary endpoints were positive SARS-CoV-2 test result, serious covid-19 (defined as self-reported dyspnoea, admission to hospital, or death) and other acute respiratory infections indicated by a negative SARS-CoV-2 test result and self-reported symptoms.

Study answer and limitations Supplementation with cod liver oil was not associated with a reduced risk for any of the co-primary endpoints. Participants took the supplement (cod liver oil or placebo) for a median of 164 days, and 227 (1.31%) participants in the cod liver oil group and 228 (1.32%) in the placebo group had a positive SARS-CoV-2 test result (relative risk 1.00, multiple comparison adjusted confidence interval 0.82 to 1.22). Serious covid-19 was identified in 121 (0.70%) participants in the cod liver oil group and 101 (0.58%) in the placebo group (1.20, 0.87 to 1.65). 8546 (49.46%) and 8565 (49.44%) participants in the cod liver oil and placebo groups, respectively, had ≥1 negative SARS-CoV-2 test results (1.00, 0.97 to 1.04). 3964 (22.94%) and 3834 (22.13%) participants in the cod liver oil and placebo groups, respectively, reported ≥1 acute respiratory infections (1.04, 0.97 to 1.11). Study limitations included self-reported data, a relatively short intervention time, and not distinguishing between the potential effect of vitamin D and eicosapentaenoic acid or docosahexaenoic acid present in the cod liver oil. How blood levels of vitamin D at the start of the trial were related to the risk of SARS-CoV-2 infection, serious covid-19, or other acute respiratory infections was not studied. Only 34 601 participants were included in the trial from the initial aim of 80 000 participants.

What this study adds The results of the trial suggested no difference in the incidence of SARS-CoV-2 infection, serious covid-19, or other acute respiratory infections for participants randomised to receive supplementation with cod liver oil or placebo.

Funding, competing interests, and data sharing
Funded by Orkla Health, Oslo University Hospital, and the University of Oslo. No competing interests declared. Data will be made available to researchers on approval.

Trial registration ClinicalTrials.gov NCT04609423.

Absolute and relative risk, and confidence intervals, for first, second, third, and fourth co-primary endpoints, according to randomisation to cod liver oil or placebo group, in intention-to-treat analyses

Co-primary endpoint	Overall (n=34 601) (No (%))	Cod liver oil group (n=17 278)		Placebo group (n=17 323)		Relative risk (CI*)	P value†
		No	Absolute risk (% (CI*))	No	Absolute risk (% (CI*))		
Covid-19							
First: SARS-CoV-2 positive test result	455 (1.32)	227	1.31 (1.13 to 1.50)	228	1.32 (1.13 to 1.50)	1.00 (0.82 to 1.22)	0.98
Second: serious covid-19‡	222 (0.64)	121	0.70 (0.55 to 0.85)	101	0.58 (0.45 to 0.72)	1.20 (0.87 to 1.65)	0.17
Acute respiratory infections							
Third: ≥1 SARS-CoV-2 negative test results	17 111 (49.45)	8546	49.46 (48.21 to 50.71)	8565	49.44 (48.19 to 50.69)	1.00 (0.97 to 1.04)	0.97
Fourth: ≥1 self-reported acute respiratory infections	7798 (22.54)	3964	22.94 (21.89 to 24.00)	3834	22.13 (21.09 to 23.17)	1.04 (0.97 to 1.11)	0.07

*First and second co-primary endpoints (covid-19), 97.0% and 98.2% confidence interval, respectively; third and fourth co-primary endpoints (acute respiratory infections), 99.9% confidence interval.
†Logistic procedure P value for difference between cod liver oil and placebo groups determined with the Wald test.
‡SARS-CoV-2 positive test result and self-reported dyspnoea (n=222), admission to hospital (n=17, eight in the cod liver oil group and nine in the placebo group), or death (n=0). Data were missing for n=17 (13 in the cod liver oil group and four in the placebo group) for the variable serious covid-19; these were included in the non-serious covid-19 outcome.

COMMENTARY

Two new trials find no effect, but aren't the final word

Vitamin D is an important regulator of calcium balance. In addition, it has important effects on the immune system, directly inducing antimicrobial peptides at mucosal surfaces and modulating the function of T cells.[1 2] Observational studies from the pre-pandemic era found an association between low levels of vitamin D and an increased risk of respiratory tract infections.[3] Results from randomised controlled trials were mixed, but two large meta-analyses found some evidence of a protective effect of vitamin D supplementation against respiratory tract infections, particularly in vitamin D deficient individuals.[4 5] Could vitamin D help protect against covid-19?

At a mechanistic level, vitamin D boosts antiviral defences against other respiratory viruses, such as influenza A virus and rhinovirus.[6 7] Data from observational studies suggest that low levels of 25-hydroxyvitamin D (25(OH)D) may be a risk factor for severe covid-19.[8] However, this association could be due to reverse causality or confounding[9 10]: both covid-19 and vitamin D deficiency are independently associated with obesity, old age (>65 years), and male sex, for example. Two new randomised studies in this issue add much needed evidence to this important question.

The first study was conducted in the United Kingdom between May and October 2021.[11] Jolliffe and colleagues randomised 3100 participants to a vitamin D test and either 3200 IU/day or 800 IU/day of vitamin D_3 for six months if their blood 25-hydroxyvitamin D concentrations were <75 nmol/L. A further 3100 controls received no test and no supplementation. The authors found that neither of the vitamin D doses had any effect on incidence of covid-19. This trial had several strengths: a high prevalence (64.6%) of participants with inadequate 25-hydroxyvitamin D levels (<50 nmol/L), good adherence to the protocol, and a rigorous endpoint with polymerase chain reaction confirmed covid-19.

However, several important caveats need to be acknowledged. Firstly, vaccination against covid-19 was being rolled out during the study. At baseline, only 1.2% of participants had been vaccinated, although by the end of the study 89.1% had received at least one dose. It is possible that vaccination masked any effect of vitamin D. Notably, in the unvaccinated group, covid-19 was less frequent among participants taking 3200 IU/day compared with the control group with no supplementation (0/68 (0.0%) *v* 9/191 (4.7%)), but the difference was not statistically significant. Secondly, the study drug was provided open label, so participants' awareness of taking an active drug could have influenced health seeking behaviour and thereby the results. Finally, almost 50% of control participants took vitamin D supplements during the study period, which could have diluted any effects of vitamin D.

The other trial was conducted in Norway between November 2020 and June 2021, using cod liver oil as a surrogate for low dose (400 IU/day) vitamin D supplementation.[12] Brunvoll and colleagues randomised 34 741 participants to either 5 mL cod liver oil or 5 mL placebo oil daily for six months. Again, the authors found no effect of cod liver oil on any outcome, including polymerase chain reaction confirmed covid-19.

A large sample size and masked placebo controlled design were this trial's key strengths. One limitation was that only 35% of participants were vaccinated during the study, although a stratified analysis found no effect in the unvaccinated group. In addition, participants were relatively young and healthy, and 86.3% had adequate vitamin D levels (>50 nmol/L) at baseline. Most participants were women (65%), most had normal body mass index (mean 26.1), and the mean age was 44.9 years. Finally, cod liver oil also contains a substantial amount of vitamin A, which is a potent immunomodulator.[13] Excessive intake of vitamin A can cause adverse effects and may also interfere with vitamin D mediated effects on the immune system.[14-16]

> Vaccination is still the most effective way to protect people from covid-19

Unforeseen challenges

Both research teams should be commended for having completed large and well designed clinical trials during the covid-19 pandemic with its unforeseen logistical challenges. However, the null findings of the studies should be interpreted in the context of a highly effective vaccine rolled out during both studies.

Vaccination is still the most effective way to protect people from covid-19, and vitamin D and cod liver oil supplementation should not be offered to healthy people with normal vitamin D levels. Importantly, these new trials remain compatible with the two large meta-analyses suggesting that vitamin D supplementation may be beneficial for vitamin D deficient individuals.[4 5] A pragmatic approach for the clinician could be to focus on risk groups; those who could be tested before supplementation, including people with dark skin, or skin that is rarely exposed to the sun; pregnant women; and elderly people with chronic diseases. For those with inadequate vitamin D levels (<50 nmol/L), supplementation with 1000-2000 IU/day could be a safe, simple, and affordable way to restore vitamin D levels, improve bone health, and take advantage of any possible protective effect against respiratory tract infections.

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