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Jakobsen MU, Trolle E, Outzen M, et al. Intake of dairy products and associations with major atherosclerotic cardiovascular diseases: a systematic review and meta-analysis of cohort studies. *Scientific Reports*. 2021;11(1):1303.

What We Know, Think We Know, or Are Starting to Know

During the emergence of the "Diet-Heart Hypothesis", which proposed the relationship between dietary intake of saturated fat [SFA] and coronary heart disease, the foods which contributed most to a high levels of SFA observed in Western countries were beef, lard, butter, and whole milk [(1)]. Due to the saturated fat content of whole milk, in line with advice to lower dietary saturated fat came advice to opt for low-fat dairy produce [(1)].

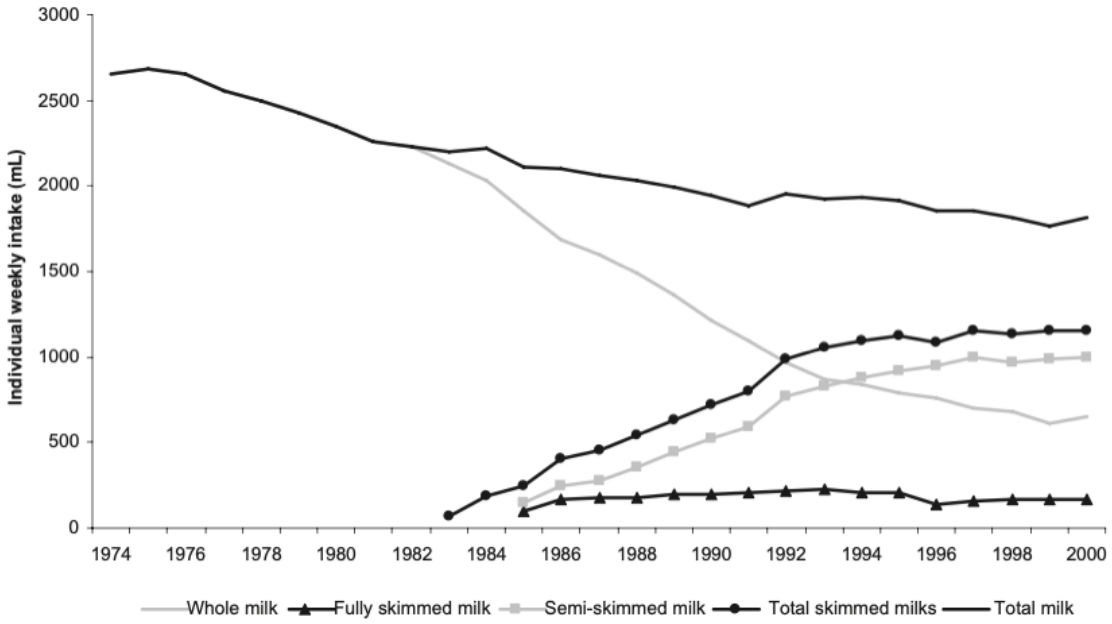


***Figure** from [(1)] indicating the changes in total milk intakes and types of milk intake, based on data in the UK. As you can see from the smooth black line at the top, right up until ~1983 [the introduction of dietary guidelines in the UK, the line graph for total milk and whole milk are identical; from ~1983, the grey line graph begins to decline, and intakes of semi-skimmed and total-skimmed milks increase to, by the early 1990's, become the main milk types consumed in the population. These UK trends are similar to those observed in other Western countries.*

However, cheese intake did not significantly change in the population [(1)]. Thus, the broad categorisation of "dairy foods"***** [see ***Geek Box**, below] remained substantial contributors to population nutrition intake, while the overall SFA intakes declined from ~20% to ~12%. And the period following the introduction of guidelines to reduce population SFA began to serve up some nuances in the dairy debate; in Finland, butter was the mainstay food contributing to the high population SFA and rates of heart disease mortality [(2–4)].

However, analysis of other dairy foods – milk, yogurts, and cheeses in particular – were serving up evidence of *lower risk*, or neutral risk, of cardio-metabolic disease [5]. At the same time, intervention trials were indicating that fermented dairy foods like cheese did not have the same effect on blood cholesterol levels as foods like butter [6,7]. All of which begs an ongoing question: for atherosclerosis specifically, what is the association between dairy foods and risk?

*Geek Box: Categorising Dairy Foods

Within the sum of the food group known overall as "dairy" is a complex diversity in individual foods, that differ relative to their form and processing. The broad use of the term "dairy" in fact only describes the common origin of the foods, and does not necessarily reflect the various levels at which dairy foods may be differentiated: fermented vs. unfermented; refined vs. unrefined; whole-milk ["full-fat"] vs. non-fat/low-fat; solid vs. liquid.

And these alterations are not academic, but relate to differential effects of the food products on intermediate risk factors, e.g., blood cholesterol levels, that in turn may provide biological plausibility to the associations between specific dairy foods and cardio-metabolic health outcome. So, let's discuss the categorisations by which we can differentiate dairy foods.

Fermented dairy produce includes fermented milks (e.g., kefir, buttermilk), yogurts, and cheeses. Fermentation has historically provided a means of preservation, and the process of fermentation yields particular nutritional characteristics, including provision of lactic acid bacteria, higher protein content (in the case of certain yogurts), and formation of bioactive peptides which may exert beneficial effects on blood lipids, pressure, gut immune and microbiota function.

Whole milk may also be subject to various refinement processes. For example, butter is produced by separating cream from whole milk, and churning the cream until the fat separates from the remaining liquid, a process which alters the nutritional composition. This distinction is thus made by categorising the food as refined [i.e., butter] or unrefined [i.e., cheese].

The refinement process alters the nutritional characteristics of the end product. Compared to cheese, butter is low in calcium, higher in fat, and the process of churning removes the milk fat globule membrane [MFGM], a tri-layered membrane rich in bioactive phospholipids and proteins which encloses the milk fat.

A final distinction can be made between whole-milk produce vs. non-fat or low-fat produce, the definitions of which related to the milk fat content: whole-milk contains 3.5% fat on average, semi-skimmed milk 2.5%, and skimmed milk 0.1% fat. The differences in fat content are achieved by mechanically separating the fat from the liquid milk.

The Study

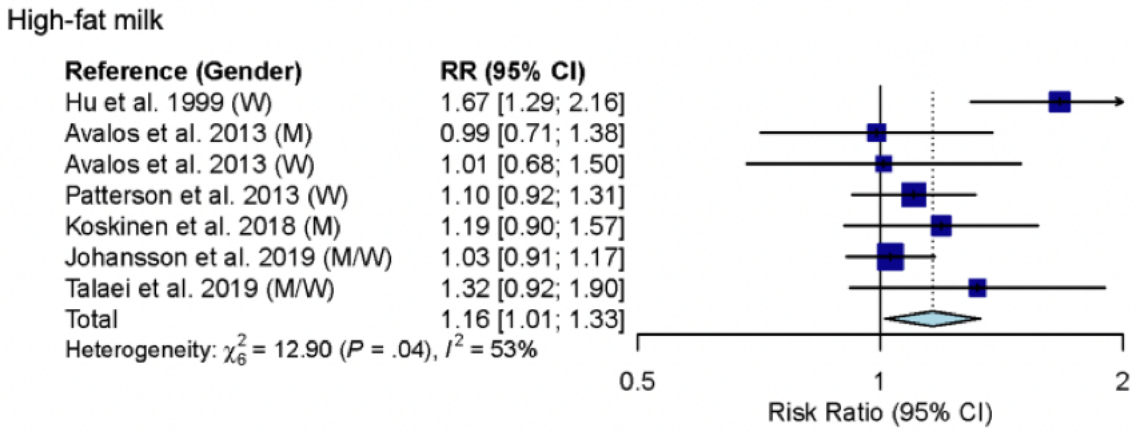
The investigators conducted a systematic review and meta-analysis of studies meeting the following criteria:

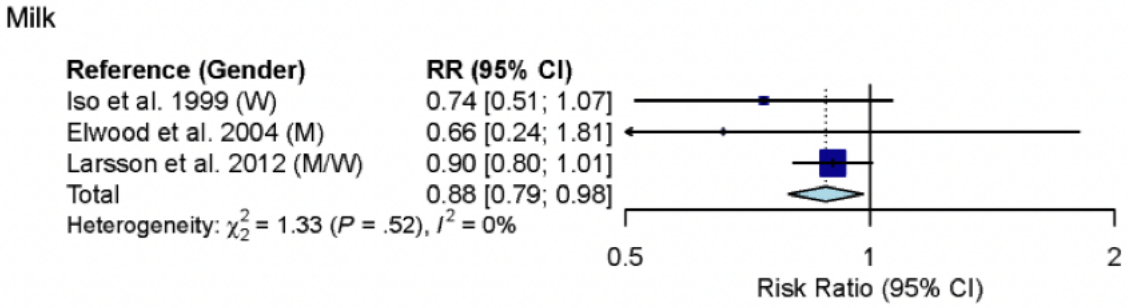
- **Design**: Prospective cohort studies
- **Population**: Adults from the general population
- **Exposure**: Milk, yogurt, cheese, and butter. High-fat and low-fat versions of foods, where available, were included. "Total dairy products" was defined as both low and high-fat milks, yogurts, and cheeses, combined. Low-fat milk, yogurt, and cheese, and high-fat milk, yogurt, and cheese, were also considered separately.
- **Comparator**: The analysis compared the highest intake of each category of the exposure to the lowest intake of that category.
- **Outcome**: Atherosclerotic cardiovascular diseases [ASCVD], including specifically coronary heart disease [CHD], total ischemic stroke, and peripheral artery disease [PAD].

The outcomes were presented as relative risks [RR] estimates with corresponding 95% confidence intervals [95% CIs].

Results: In total, 30 studies were included in the systematic review [18 reporting on CHD; 12 reporting on ischemic stroke]. No studies were identified that reported on PAD. Of these studies, 13 on CHD and 7 on ischemic stroke were included in the meta-analysis.

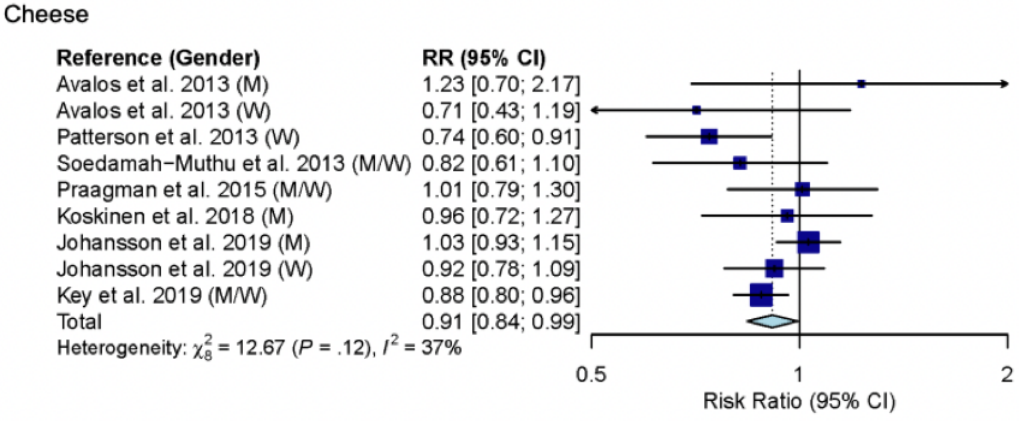
- ***Milk, CHD and Stroke*:**
  - **Total Milk**: Based on 6 studies with 619,460 participants, 16,478 incident cases of CHD, and a range of milk intake from 0 to 710g/d, there was no association [RR 0.99, 95% CI 0.91–1.08] with total high intakes of total milk and CHD. However, based on 3 studies [163,128 participants and 3,691 cases], there was an 12% [RR 0.88, 95% CI 0.79–0.98] lower risk of stroke.
  - **Low-Fat Milk**: There was no association [RR 1.05, 95% CI 0.92–1.20] between high intakes of low-fat milk compared to low intakes, and risk of CHD.
  - **High-Fat Milk**: Compared to low intakes of high-fat milk, high intakes were associated with a 16% [RR 1.16, 95% CI 1.01–1.33] higher risk of CHD.





Forest plots *from the paper illustrating [**top**] the meta-analysis of high-fat milk consumption demonstrating higher risk of CHD, and [**bottom**] the meta-analysis of total milk consumption and lower risk of ischemic stroke.*

- ***Yogurt, CHD and Stroke*:**
  - **Total Yogurt**: Based on 7 studies with 554,332 participants, 14,226 incident cases of CHD, and a range of yogurt intake from 0 to 440g/d, there was no association [RR 1.02, 95% CI 0.92–1.13] with high intakes of total yogurt and CHD. There was also no association between yogurt [RR 1.04, 95% CI 0.95–1.09] and risk of stroke.
  - **Low-Fat Yogurt**: There was no association [RR 0.97, 95% CI 0.89–1.06] between high intakes of low-fat yogurt compared to low intakes, and risk of CHD.
  - **High-Fat Yogurt**: There was no association [RR 1.01, 95% CI 0.93–1.09] between high intakes of high-fat yogurt compared to low intakes, and risk of CHD.
- ***Cheese, CHD and Stroke*:**
  - **Total Cheese**: Based on 6 studies with 554,323 participants, 14,698 incident cases of CHD, and a range of cheese intake from 0 to 120g/d, compared to the lowest intake the highest category of cheese was associated with a 9% [RR 0.91, 95% CI 0.84–0.99] lower risk of CHD. There was an 11% [RR 0.89, 95% CI 0.78–1.01] lower risk of stroke, which was not significant [CI crossed 1.0].
  - **Low-Fat Cheese**: There was no association [RR 1.17, 95% CI 0.85–1.61] between high intakes of low-fat cheese compared to low intakes, and risk of CHD.
  - **High-Fat Cheese**: There was no association [RR 0.94, 95% CI 0.77–1.14] between high intakes of high-fat cheese compared to low intakes, and risk of CHD.



Forest plot *from the paper illustrating the meta-analysis of cheese consumption that showed lower risk of CHD*

- ***Butter, CHD and Stroke*:** Based on 4 studies with 128,757 participants, 6,562 incident cases of CHD, and a range of butter intake from 0 to 163g/d, compared to the lowest intake the highest category was not associated with CHD risk [RR 0.99, 95% CI 0.92–1.07] [more under ***Interesting Finding***, below].

The Critical Breakdown

Pros: The exposure and outcomes were clearly defined [more under ***Key Characteristic***, below]. The included studies were evaluated of quality of evidence was assessed according to the NutriGrade scoring system, which adapted the biomedical GRADE system to more nutrition-specific criteria [8], and also the risk of bias assessed using the Newcastle-Ottawa Scale. Funding source for the included studies was also presented in the supplementary data [almost all were funded by national health organisations; two included funding from the dairy industry]. Many of the exposure-outcome analyses contained enormous sample sizes of ~half-a-million participants, with substantial incident cases of the outcomes of interest. The range of intakes for the exposure foods were quite broad, which enhances the strength of the "high vs. low" comparisons

Cons: Although the numbers of participants overall were high, these participants were derived from a relatively small number of studies from heterogenous populations which may have lowered the power to detect associations [more under ***Interesting Finding***, below]. It does not appear that adjustment for blood cholesterol levels were considered, which is the primary and causal mediating factor in the relationship between diet and atherosclerosis. Only two included studies considered substitution effects, i.e., of replacing one source of dairy with another [or with other food groups]. Thus, this analysis is primarily confined to the "high vs. low" comparisons, which although informative, does not tell us what effect, e.g., replacing 3% of energy from full-fat with low-fat milk might result in.

Key Characteristic

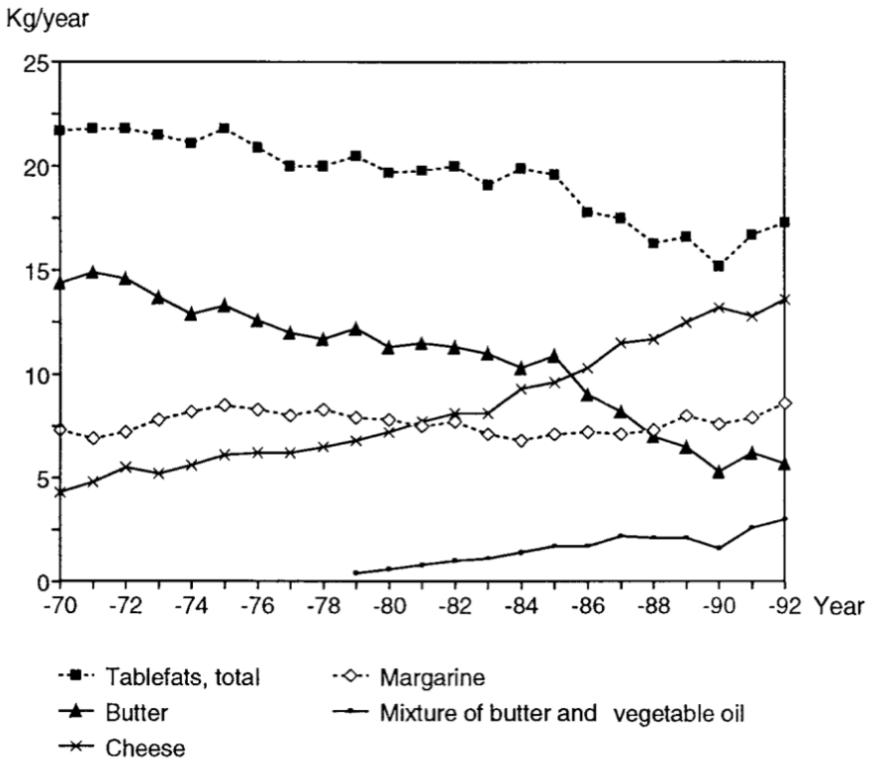
Specificity in defining the population, exposure, outcome, and study design, is crucial for developing a more refined and informed evidence-base. For cohort studies, if you have yet to watch this Research Lecture on interpreting cohort studies, then do! One aspect to this is granularity in defining the outcome. For example, we might say "cardiovascular disease", when in fact this could be a *composite outcome*, i.e., including anything from fatal heart disease to myocardial infarction to heart failure.

For dairy, these types of meta-analysis of associations with CVD have been done before, and largely found similar findings [9,10]. So, what makes the present study worth considering? The reason is because of the specificity of the outcome; the present study focused on *atherosclerotic* CVD, i.e., those that are more particularly related to atherosclerosis, for which LDL-C is the causal risk factor [11].

This itself is important because the effect of diet on CHD and stroke risk are primarily attributable to saturated fat and sodium intakes. Thus, for dairy produce it is worth considering outcomes specific to atherosclerosis, given the truism that "not all saturated fatty acids are created equal"

Interesting Finding

Interestingly, the present study found no association for butter. If we look at the studies included in this analysis, 3 out of 4 were Scandinavian cohorts; 2 were Finnish. This is where the homogeneity of population dietary intake may influence the findings. Let's consider the Finnish example; in the **figure** below taken from Pietinen *et al*. [12], you can see per capita butter consumption in kg per year decreased from ~15kg in 1970 to ~5kg in 1992.



This decreasing level of butter intake, given that this food was by orders of magnitude the largest contributor to SFA intakes in this population, correlated with an 80% reduction in blood cholesterol levels, and decline in CHD incidence and mortality [2–4]. However, if much lower levels are habitually now consumed, and blood cholesterol levels also lower through both diet and available drugs, then the effects of foods are often now more difficult to detect. It is arguable now that butter is no longer a food of concern in these populations.

Relevance

Although the present study focused on atherosclerotic CVD, the ultimately findings do not change the status quo of the evidence on dairy and CVD risk overall; that total dairy exerts either a neutral effect [i.e., CHD] or modest risk reduction [i.e., ischemic stroke]. For milk, it does appear that the type of milk matters, although high-fat milk is not consistently associated with higher risk [13].

Most of the "no association" findings in this study are also truly that; they are miniscule point estimates ranging from 0.95 to 1.05 with confidence intervals spread across the 1.0 mark, so there is very little direction of effect to discern from these findings. Thus, it is certainly unlikely that low-fat milks or yogurts [of any fat content] contribute to ASCVD risk in the population based on the totality of evidence [5,10,13].

There are two levels that we can think of the associations for different dairy foods and CHD; dairy compared to other sources of SFA in the diet, and then secondly compared to other fat subtypes and their food sources. In relation to the former, it certainly does appear – as noted under ***Key Characteristic***, above, that "not all saturated fatty acids are created equal": the Multi-Ethnic Study of Atherosclerosis showed that replacing 2% of energy from meat sources of SFA with dairy sources was associated with a significant 25% [HR 0.75, 95% CI 0.63-0.91] reduction in CVD risk [14].

However, in relation to the latter, it it also evident that the substitution of 5% energy from dairy fats with polyunsaturated fats was associated with a 26% [RR 0.74, 95% CI 0.68-0.81] lower CHD risk, and 22% [RR 0.78, 95% CI 0.7-0.88] lower stroke risk [15]. Thus, the hierarchy of benefit appears to remain in terms of the generally accepted benefit to replacing SFA with PUFA, and dairy is not an exception to that rule.

Application to Practice

Of course, people consume total diets and do not simply make dichotomised food choices that boil down to "dairy SFA vs. PUFA". That is, unless there are ethical considerations driving their food choices, which is entirely fine. From a planetary health perspective, an average of ~250g [range of 0 to 500g] is consistent with current recommendations [16].

However, these are considerations for an individual and are unrelated to the question we are concerned with here: what is the role of dairy products in atherosclerosis and CVD? This study adds to a body of evidence from both interventions and epidemiology that certain foods, in particular cheese, may modestly lower risk, while other fermented dairy like yogurts may be relatively neutral or exert modest benefits [5–7,10,13,17].

Thus, whatever an individual's own ethics and environmental considerations, there is scant reason from a health perspective to view certain dairy foods as a net negative in the diet.

References

1. Foster R, Lunn J. Food availability and our changing diet. Nutr Bull. 2007;32:187–249.
2. Vartiainen E, Laatikainen T, Peltonen M, Juolevi A, Männistö S, Sundvall J, et al. Thirty-five-year trends in cardiovascular risk factors in Finland. Int J Epidemiol. 2010;39(2):504–18.
3. Vartiainen E, Laatikainen T, Tapanainen H, Puska P. Changes in Serum Cholesterol and Diet in North Karelia and All Finland. Glob Heart. 2016;11(2):179–84.
4. Pietinen P, Vartiainen E, Seppänen R, Aro A, Puska P. Changes in diet in Finland from 1972 to 1992: Impact on coronary heart disease risk. Prev Med (Baltim). 1996;25(3):243–50.
5. Lovegrove JA, Givens DI. Dairy food products: good or bad for cardiometabolic disease? Nutr Res Rev. 2016 Dec 26;29(2):249–67.
6. Feeney EL, Barron R, Dible V, Hamilton Z, Power Y, Tanner L, et al. Dairy matrix effects : response to consumption of dairy fat differs when eaten within the cheese matrix — a randomized controlled trial. Am J Clin Nutr. 2018;(Cvd):1–8.
7. Brassard D, Tessier-Grenier M, Allaire J, Rajendiran E, She Y, Ramprasath V, et al. Comparison of the impact of SFAs from cheese and butter on cardiometabolic risk factors: A randomized controlled trial. Am J Clin Nutr. 2017;105(4):800–9.
8. Schwingshackl L, Knüppel S, Schwedhelm C, Hoffmann G, Missbach B, Stelmach-Mardas M, et al. Perspective: NutriGrade: A scoring system to assess and judge the meta-evidence of randomized controlled trials and cohort studies in nutrition research. Advances in Nutrition. 2016;7(6):994–1004.
9. Larsson SC, Virtamo J, Wolk A. Dairy Consumption and Risk of Stroke in Swedish Women and Men. Stroke. 2012 Jul;43(7):1775–80.
10. Qin LQ, Xu JY, Han SF, Zhang ZL, Zhao YY, Szeto IM. Dairy consumption and risk of cardiovascular disease: an updated meta-analysis of prospective cohort studies. Asia Pac J Clin Nutr. 2015;24(1):90–100.
11. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2017;38(32):2459–72.
12. Pietinen P, Vartiainen E, Seppänen R, Aro A, Puska P. Changes in Diet in Finland from 1972 to 1992: Impact on Coronary Heart Disease Risk. Prev Med (Baltim). 1996 May;25(3):243–50.
13. Sonestedt E, Wirfält E, Wallström P, Gullberg B, Orho-Melander M, Hedblad B. Dairy products and its association with incidence of cardiovascular disease: the Malmö diet and cancer cohort. Eur J Epidemiol. 2011 Aug 10;26(8):609–18.
14. de Oliveira Otto MC, Mozaffarian D, Kromhout D, Bertoni AG, Sibley CT, Jacobs DR, et al. Dietary intake of saturated fat by food source and incident cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis. Am J Clin Nutr. 2013;97(2):449.
15. Chen M, Li Y, Sun Q, Pan A, Manson JE, Rexrode KM, et al. Dairy fat and risk of cardiovascular disease in 3 cohorts of US adults. Am J Clin Nutr. 2016 Nov 1;104(5):1209–17.
16. Willett W, Rockström J, Loken B, Springmann M, Lang T, Vermeulen S, et al. Food in the Anthropocene: the EAT–Lancet Commission on healthy diets from sustainable food systems. Lancet. 2019;6736(18):3–49.
17. Ivey KL, Lewis JR, Hodgson JM, Zhu K, Dhaliwal SS, Thompson PL, et al. Association between yogurt, milk, and cheese consumption and common carotid artery intima-media thickness and cardiovascular disease risk factors in elderly women. Am J Clin Nutr. 2011 Jul 1;94(1):234–9.