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Feeney EL, Barron R, Dible V, 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;108(4):667–674.

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

As nutrition science has moved away from the purely reductionist focus, the importance of the food matrix as a crucial factor influencing the physiological responses to a food, and the nutrients within in, has come into sharp focus. The role of dairy foods in the context of their saturated fat content is perhaps the best example of this fundamental difference between 'foods vs. nutrients'.

It is understandable how the distinction may have been missed during the evolution of the Diet-Heart Hypothesis; many Western diets consumed over 18% of total energy from saturated fats in the 1950's and 1960's. For example, in the Seven Countries Study, the cohorts with the highest levels of intake included [(1)]:

- East Finish cohort: 22%
- West Finish cohort: 19%
- Dutch cohort: 20%
- Croatian cohort: 17%
- US cohort: 21%

The UK were not included in the Seven Countries Study, but at the time consumed 20% of energy from saturated fat [(2)]. In the UK, the food sources which contributed the most to total daily energy intake were meat, bacon, lard, butter, cheese, milk, and eggs [(2)]. In East Finland, it was common to spread butter on cheese [(3)]. If ever a distinct effect of dairy fatty acids was going to be confounded by the relationship between dairy and other saturated fat-rich foods, this was the period. Consequently, included in public health advice to reduce total saturated fat intake was the sum of all 'full-fat' dairy: milk, cheese, butter*, in particular.

Fast forward to more recent times, and observational evidence began to highlight the differential effects of food sources of saturated fatty acids. In the Multi Ethnic Study of Atherosclerosis [(4)], opposed effects of dairy and meat fats were found over a 10-year follow-up period: dairy SFA was associated with a significant 38% reduction in risk of CVD [HR 0.62, 95% CI 0.48-0.82], but increased risk from meat SFA [HR 1.48, 95% CI 0.98-2.23]. Substitution analysis found that replacing 2% of energy from meat sources of SFA with dairy sources was associated with a significant 25% reduction in CVD risk [HR 0.75, 95% CI 0.63-0.91].

*Geek Box: Dairy - A Broad Food Group

Within the sum of the food group known overall as 'dairy' is a complex diversity in individual foods, relative to their form and processing. Broad definition of 'dairy' fails to capture 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. 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. Milk may also be subject to various refinement processes, which alter the nutritional characteristics of the end product. 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. For example, 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. These alterations, as will be discussed further below specifically in relation to cardiovascular disease, are not academic, but relate to differential effects of the food products on intermediate risk factors, in particular blood cholesterol levels. 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 study was a randomised, unblinded, parallel arm intervention with 4 diet groups:

- Group A: 120g full-fat white cheddar cheese [FFCC];
- Group B: 120g reduced-fat white cheddar cheese + 21g butter;
- Group C: 49g butter + 30g calcium-casein powder + calcium supplement;
- Group D: 120g full-fat white cheddar cheese [following 6-weeks of cheese-free diet]

Each intervention provided 40g dairy fat in total, but in different food matrices. The foods for each intervention were matched for energy [489kcal/d], total fat, casein protein content, and calcium.

Group D was the exact same intervention as Group A, however, they consumed their intervention after a 6-week run-in period where they excluded all cheese from their diet.

Participants were instructed to consume no more than 50ml/d milk as their only other dairy intake, but continued with their habitual diet for the rest of their intake, i.e., no other restrictions were placed on diet. The study was conducted in free-living conditions.

Consuming 80% of the provided study food was the minimum threshold to be considered compliant, and included in analysis. 3-day diet diaries were completed at baseline, and again mid-intervention at 3-4 weeks.

The primary outcome measure was change in blood cholesterol from baseline to completion, comparing the diet groups. Secondary outcomes included triglycerides, free fatty acids, glucose, insulin, blood pressure, and high-sensitivity C-reactive protein.

Results: 164 participants completed the study, of which **127 achieved the minimum 80% compliance target**. The main paper presented the results from compliant participants. Mean age was 60yo, although mean age in Group A was 63yo. Baseline total cholesterol and HDL-C were higher in Group B at baseline; analysis was adjusted for baseline values. Baseline saturated fat was higher in Group C.

In relation to total cholesterol there were statistically significant differences between:

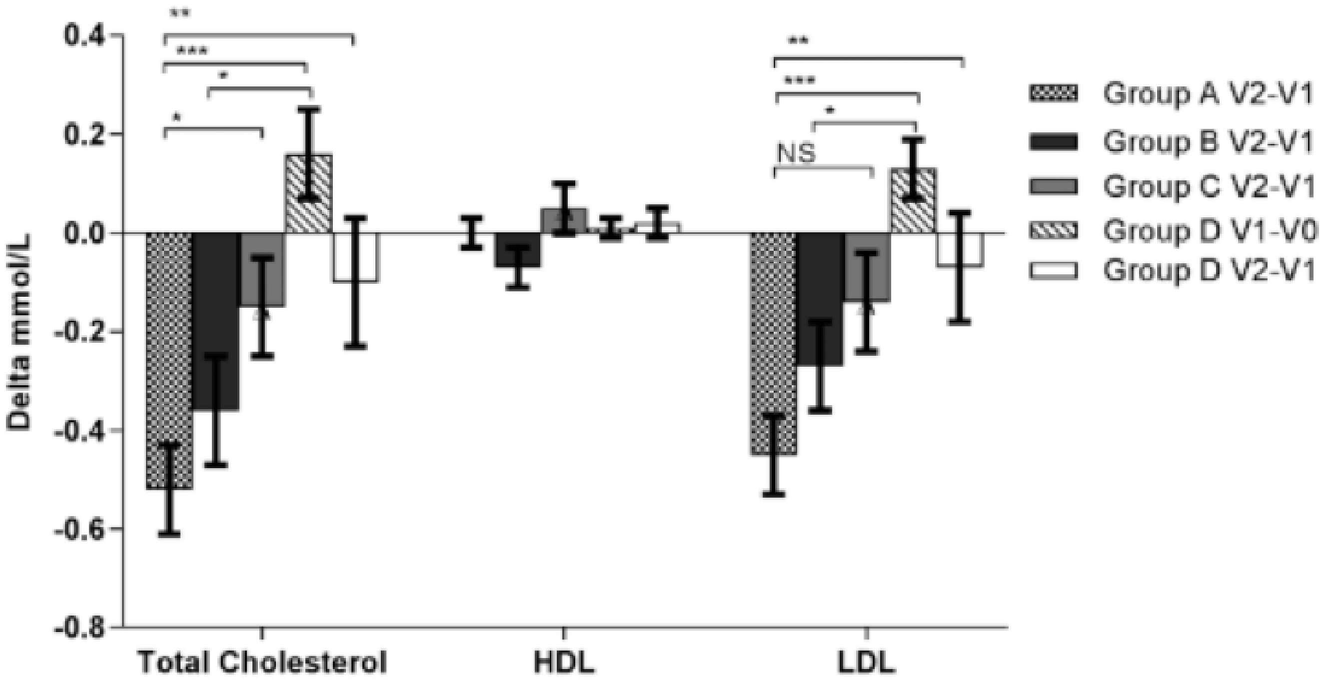
- Group A [**0.51mmol/L decrease**] vs. Group B [**0.37mmol/L decrease**]
- Group A [**0.51mmol/L decrease**] vs. Group C [**0.15mmol/L decrease**]

In relation to LDL-C there were statistically significant differences between:

- Group A [**0.45mmol/L decrease**] vs. Group B [**0.27mmol/L decrease**]
- Group A [**0.45mmol/L decrease**] vs. Group C [**0.14mmol/L decrease**]
- Group A [**0.45mmol/L decrease**] vs. Group D [**0.07mmol/L decrease**]

Group D were also compared to their value at the start of the 6-week cheese exclusion run-in: TC increased by 0.16mmol/L while LDL increased by 0.13mmol/L. **Following inclusion of cheese, total and LDL-cholesterol decreased by 0.10mmol/L and 0.07mmol/L, respectively.**

There were no significant difference in HDL, or any of the secondary outcomes measured.



***Graph** from Feeney et al. illustrating the effects on total, LDL, and HDL-cholesterol following 6-weeks of consuming dairy fat in various food matrices: the effect of lowering total and LDL-cholesterol increased linearly in response to the extent to which dairy fat was consumed in the cheese matrix vs. when butterfat was included in various amounts. The greatest effect was observed when all fat was consumed in the cheese matrix [which by implication means all fat, casein protein, and calcium was consumed from the food matrix].*

The Critical Breakdown

Pros: The study was a food-based intervention, and included different dairy food matrices. There was an even mix of sexes [46% male], important given potential sex differences in blood lipids. The intervention diets were matched for important variables, including calcium.

Cons: No intention-to-treat analysis was conducted, and the analysis used was a 'per protocol' analysis, which confines analysis to those who completed the study, resulting in imbalances between groups (and potential bias). The investigators at least acknowledge these issues: many do not. There were differences in baseline characteristics between the groups, and a stratified randomisation* to balance these differences could have been used, and wasn't. The usual caveats of a free-living intervention apply; diet outside of the study foods may have influenced outcomes, in particular Groups B and C could have consumed the different foods at different times, rather than all together. There was a high dropout rate for a short intervention, which imbalanced groups for the final analysis: Group C and D may have been underpowered to detect differences.

*Geek Box: Randomisation Methods

Randomisation provides a means of minimizing the risk of bias, and is most effective particularly where there are unknown factors which could influence the results: randomisation then balances the distribution of these unknown factors between groups. There are a number of type of randomisation: simple, block, and stratified, being common randomisation methods. Simple randomisation involves dividing subjects at random to allocation of either treatment group or control, either using computer generated or numbered tables. The essential characteristic of simple randomisation is that all subjects have an equal chance of allocation to either group. A potential disadvantage may be observed in trials with small sample sizes, where simple randomisation may result in unequal numbers between groups. To address this, block randomisation divides subjects into multiple, smaller groups of equal subjects based on a predetermined group size, allowing for control of balance across similar-sized groups. A potential disadvantage to block randomisation is that the process of randomisation may lead to different covariates between block groups. To address this potential, stratified randomisation is used to achieve balance of characteristics between block groups. Stratification allows for covariate baseline characteristics, for example age, cholesterol, hypertension, and/or sex, to be balanced by grouping together particular characteristics which could influence the outcome. Subjects would then be randomised to blocks, within that particular stratum identified by the covariate characteristic, i.e., similar numbers of subjects with the same level of blood cholesterol. Disadvantages to stratified randomisation arise where there are multiple covariates in small sample sizes, or where subjects are enrolled on an ongoing basis, and baseline characteristics of all subjects are not available prior to randomisation.

Key Characteristic

In the full-fat cheese Group A, the entirety of the dairy fat was consumed as part of the whole-food matrix, compared to the mixed sources of the Group B [reduced fat cheese + butter] and Group C [butter + casein protein powder + supplement].

The order of effect directly reflected the amount of fat consumed directly from the cheese matrix: Group A>Group B>Group C. What may explain the difference is also the fact that casein protein and calcium were matched across diets: the effect of butter in Group B and Group C may have been attenuated by the calcium and protein content of these intervention diets, as casein and calcium are hypothesised to have a role in the the lipid-lowering effect of dairy fats [8].

Therefore, the fact that the greatest magnitude of effect was observed in Group A consuming the full-fat cheese suggests that the effect may go beyond the fat content, to an overall synergistic effect of the mix of dairy fat, casein, and calcium, within the whole-food matrix.

Interesting Finding

The investigators mentioned in their Results section that there was a significant difference between groups in energy from saturated fat. With LDL-C and TC as primary outcomes in this study, this is not an insubstantial factor. In the supplementary data, the dietary information presented indicates the following changes in saturated fat from baseline to end of intervention in each diet group:

- Group A: 13.9% to 10.1% [3.8% difference]
- Group B: 14.8% to 9.4% [5.4% difference]
- Group C: 15.1% to 9.6% [5.5% difference]
- Group D: 12.0% to 10.4% [1.6% difference]

Per 1% decrease in SFA we could expect a 0.02-0.04mmol/L decrease in LDL-C. If we take the middle value here [0.03mmol/L], this could amount to around 0.11mmol/L difference in Group A, and 0.16mmol/L difference in Group B and C. Thus, the change in saturated fat alone could account for 25% of the difference in Group A, 50% of the difference in Group B, and 100% of the difference in Group C.

Of course, this still leaves the fact that in Group A, the majority of the difference may be attributable to the effects of the whole-food itself.

P.s., always read the supplementary data 🙂

Relevance

Although there are some methodological issues with the present study, it remains consistent with other research. Multiple studies have now shown that, compared to cheese, butter will negatively influence TC and LDL-C (5-7). This has been evident where studies have compared the same amount of fat from butter or cheese: one study compared 40g fat from cheese vs. 40g fat from butter, finding higher TC and LDL-C from butter (5). Another intervention similar to the present study compared dairy fat from cheese vs. butter + calcium-casein powder vs. butter + egg white protein; both TC and LDL-C were reduced in the cheese only group, compared to the other groups (6).

Mechanistically, it is not currently thought that the casein protein influences blood lipids: studies comparing high vs. low protein in the context of high vs. low calcium have found effects of calcium, but not protein (8). Calcium may lead to the formation of "soaps" in the intestine, reducing fat absorption and increasing exertion of fat; this may reduce the impact of diary foods that are rich in calcium, such as cheese [but not butter, the calcium is depleted during churning]. The relevance of the casein matrix may be that fat globules are trapped within it, in a protective encapsulation known as the 'milk-fat globule membrane' [MFGM], which research has shown dairy fat within the MFGM does not impair blood lipids (9). There are also other important potential mechanisms, in particular the effects of fermentation of cheese on the gut microbiota, and the fatty acid composition of dairy fat (10).

Thus, "dairy" as a food group is likely too broad to encapsulate the nuances of biological responses to different food matrices. The findings in intervention studies in relation to blood lipids may explain why consistent observations in epidemiology associate cheese with reduced risk of stroke and cardiovascular disease (11).

Application to Practice

That there are benefits to dairy as a food group is unquestionable on the totality of evidence; the moral/ethical and environmental considerations for whether one does include dairy, are a matter for the individual. If someone does decide to include dairy, it appears that cheese can be excepted from its saturated fat content, and included in the context of a diet lower in overall saturated fat content. Indeed, the current recommendations to reduce total saturated fat remain evidence-based, but it is arguably not evidence-based to achieve that aim through reducing cheese, in addition to whole-milk and yogurt.

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