Commentary: Lactose and ischaemic heart disease: a weak 28-year-old hypothesis

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Ischaemic heart disease (IHD) is one of the more extensively researched diseases and most of its risk factors have been identified by consistent data from different studies. Diet and dietary patterns have been found to be correlated with the risk of IHD, for example, the dietary pattern of fruits and vegetables, whole-meal bread, low fat dairy and little alcohol has an inverse association with the risk, while high intake of red and processed meat, refined grains and sugars, French fries and high fat dairy is associated with increased IHD risk. Milk has been less consistently correlated with IHD and two recent reviews of published literature suggest there is no increased risk. Milk is a rather complex food because it is a rich source of protein, saturated fat, calcium and lactose sugar. Saturated fat from dairy products, including whole milk has been found to be related to IHD. Calcium from milk and dairy products is a major source of daily human consumption but the studies have failed to find an association with IHD. Lactose is rather specific to unfermented milk and if found related to IHD could specifically point to unfermented milk as the causative nutrient. This is the basis of the paper by Siegel titled: Hypothesis: Is lactose a dietary risk factor for IHD published 28 years ago in this journal.

The association between lactose and IHD was a reasonable and novel hypothesis to pursue three decades ago given the era of increasing awareness of IHD and the search for possible explanations from available data. This was similar to the study by Keys in 1980, which suggested that saturated fat is associated with IHD based on correlational ecological data. However, a closer look at the paper by Segall reveals some methodological problems that undermine the eloquent argument for the observed association between lactose and IHD. This might also explain why no subsequent data was published to support this hypothesis. The paper does present the arguments for a hypothesis rather than a causal association, and therefore an ecological study design for the purpose of promoting such a hypothesis is acceptable. The term ‘ecological fallacy’ was coined in the 1950s and the bias introduced by attempting to apply findings from aggregate or geographical data to the individual-level is well-known. Comparisons of countries without adjustment for important confounders between these countries, which are usually not available from aggregate data, can lead to false conclusions. The well known example of finding higher suicide rates in predominantly Protestant European countries compared with predominantly Catholic countries has been attributed to this fallacy. In his paper, Segall does present the possibility that environmental factors explain the observed association given that the group of countries with high lactose exposure [low prevalence of lactose malabsorption also known as lactose intolerance (LI)] and high IHD were the developed countries with high socioeconomic status. This explanation is then dismissed based on low IHD in Japan and high IHD in the Punjab. The data on LI from the Punjab was based only on 18 subjects, and in the cited IHD study on Punjabis, 91% of the cases were from the high and middle income Punjabi social class, while the unique diet in Japan of fish and seafood high in omega-3 fatty acids (that is mostly protective against IHD) could explain why a country with high socioeconomic status would have low IHD. In a letter to the editor on the inverse association between wine and IHD in European countries, Segall argues about the ‘possible coincidental presence of a geographical factor of unknown identity that explains this association’, an argument that can also explain the findings in the paper on milk and IHD published by Segall.

As described in the literature and by Segall, if we considered LI is an ethnically related metabolic condition that came about among populations that over centuries did not consume milk, we would then expect a continuous protection against IHD in the last three decades for certain ethnic groups based on the hypothesis of Segall. However, it is currently well known that there is rising IHD incidence across countries and in ethnic groups such as Chinese, Arabs and Mexicans in the US who were cited by Segall three decades ago as having low lactose

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exposure and low IHD. This increase is related to changing their life style and diet to that of the developed countries.

Some of the critical questions that arise from the observations of the data on ethnicity and LI are whether samples are representative of their respective ethnic groups? The paper does not provide data on that but it is highly unlikely that they were representative. The study depends on the reference ethnic groups? The paper does not provide data on observations of the data on ethnicity and LI are developed countries.

Exposure assessment based on presence or absence of LI needs to be well documented and consistent across different countries to avoid misclassification and should be further assessed in light of intake of milk as an interaction term in a multivariate model adjusting for other IHD risk factors. If individuals have no LI but do not consume milk on a regular basis, or consume fermented milk with limited lactose, they cannot be categorized similar to those with no LI and who consume milk and are exposed to high lactose levels. Such differentiation and avoidance of misclassification is not possible from poor-quality ecological data. Furthermore, having a dichotomous exposure of low vs high lactose absorption cannot be quantitatively assessed for dose–response associations to fulfil causality criteria in epidemiology. Even if it was biologically plausible that individuals are able to absorb either 100% or 0% of the lactose they ingest, we would still need to know the difference in relative risk according to the amount of lactose absorbed among those who can absorb lactose.

Another common problem, especially at the time of the study in 1980, is IHD diagnosis that requires certain criteria based on the WHO schema. This is unlikely to be consistent or to be followed by the different countries included in the study by Segell. This is especially challenging for death certification and reporting in some of the poorer countries and ethnic groups. Therefore, we have both poor exposure and outcome measures in a weak study design put forward to support an unproven hypothesis.

The biological plausibility of the hypothesis is not well established in animal models. The mechanism by which calcium intake in general is related to IHD is not well understood and the association with calcification and atherosclerosis of the coronary arteries is inconsistent. If the hypothesis of LI is related to retention of calcium, which is then deposited in the walls of arteries and leading to increased risk of IHD, we would expect a higher risk of IHD from dairy calcium because of the presence of lactose with calcium in milk. In our large prospective study of calcium and risk of IHD from the Health Professionals Follow Up Study of 39 633 men, we failed to find any association of dairy sources of calcium with IHD risk, including fatal and non-fatal IHD. As an example of the complexity of IHD risk factors, in the multivariate analyses we adjusted for possible confounders of age, energy intake, history of diabetes, history of hypercholesterolemia, family history of IHD, smoking history, aspirin intake, BMI, alcohol intake, physical activity, vitamin E intake, trans-fatty acids, ratio of polyunsaturated to saturated fatty acid, total protein intake, fibre intake, folate intake, omega-3 fatty acids and α-linolenic acid. Furthermore, calcium as the exposure of interest was measured at baseline as well as a cumulative exposure over time to adjust for change in uptake during the follow up period. For milk consumption, Segall used the FAO food database from the UN Statistics Year book that is a very crude and unreliable measure of consumption.

Looking back now after decades of extensive research on IHD aetiology it does not seem that this hypothesis is supported by any of the well designed epidemiological studies on the association between milk or more specifically lactose and IHD. The approach and the hypothesis was rather simplistic for a complex multifactorial disease such as IHD. The role of ecological correlation studies becomes less influential after the initial hypothesis testing given the inherent limitations of such studies as outlined earlier. Interestingly, Segall continued to pursue this hypothesis as recently as 2003, and in a detailed paper in 1994 using the same correlational examples between lactose and IHD for selective countries without carefully addressing the limitations of such approach and the adjustment for other risk factors. What the author refers to as epidemiological evidence, which usually implies appropriate study design and statistical analysis to address confounders and avoid spurious or chance correlations, was actually simple correlational evidence, the weakest form of evidence in the medical and epidemiological literature.

Even though since the 1950’s there was a notion that milk is associated with IHD and lactose was suggested by Segall as the nutrient explaining this association, the fact that so far no strong evidence has emerged in support of such a hypothesis does suggest that the evidence is circumstantial and other more prominent dietary and lifestyle behaviours might explain the differences observed between different countries at the time of the study. We now know that even within the same country and within developed countries there exists a significant influence of socioeconomic status on IHD. It is still possible to conduct a study on the association of lactose with IHD after adjusting for all possible IHD risk factors and then adjusting for calcium milk levels, and saturated fatty acids levels from milk according to genetic susceptibility to LI, but based on current unconvincing ecological data such a costly study is unlikely to be initiated.
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References