Commentary: Ecologic studies in identifying dietary risk factors for coronary heart disease and cancer

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The hypothesis study by Jeffrey Segall, suggesting that milk consumption was an important risk factor for ischaemic heart disease (IHD, or coronary heart disease (CHD)), was based on considerations of lactose intolerance and IHD rates for 23 populations. However, a recent meta-analysis of cohort studies found that milk consumption was actually correlated with a small but significant reduced risk, suggesting that the work by Segall was somehow in error.

In the well-known Seven Countries Study, Ancel Keys established that animal fat was an important risk factor for IHD on the basis of a study of dietary factors for men between the ages of 55 and 59 years and incidence of CHD in seven countries. However, when the Seven Countries Study was being conducted, John Yudkin, a British diabetes expert, suggested that dietary sucrose was a more important risk factor than was animal fat. Keys and Yudkin had a spirited debate, which Keys eventually won.

Examining the data in the work of Segall and other studies is worthwhile to evaluate which dietary factors are most strongly correlated with risk of IHD. Therefore, I obtained dietary supply data for 1961–63 from the Food and Agriculture Organization for use with data for IHD circa 1972 in the work of Segall. The data were used in linear regression analyses with SPSS version 13 (Chicago, IL, USA). Table 1 gives the results of that analysis. Although milk and its components have a high correlation coefficient, that of animal fat is higher. Had Segall considered animal fat in addition to milk, he might not have concluded that milk was a risk factor for IHD.

After I found that total energy and fat supply were the primary risk factors for Alzheimer’s disease, with fish and cereals reducing the risk, I evaluated dietary risk factors for CHD. I used mortality rate data for acute myocardial infarction and other IHDs for males and females for 33 countries in 1986 and dietary supply data for earlier periods. In the first study, animal fat supply for 1973 had the highest correlation for males of all age ranges, whereas added sugar for 1983 had the highest correlation for females of all ages; both factors together gave higher regression coefficients. Had women been included in the Seven Countries Study, Yudkin might have been able to make a better case for the role of sugar as a risk factor for CHD.

After completing the first study, I found similar analyses by Stephen Seely. He used CHD mortality rates for men for 1975–78 for 24 countries and dietary supply data for 1967. For men, the highest correlation was with milk and milk products ($r = 0.91$), followed by added sugar ($r = 0.84$), animal protein ($r = 0.81$) and animal fat ($r = 0.76$). For women, in a multiple linear regression analysis with data for 21 countries, he found that milk proteins represented the dominant risk factor, with sugar, saturated fats and geographic latitude also contributing, with a combined correlation coefficient, $r$, of 0.93.

I conducted a second ecologic study of IHD and dietary factors with the addition of milk and its components. I used IHD mortality rate data for 1968–69 for 30 countries and those for 1986 for 32 countries. In this study, lactose from 1983 had the highest correlation with mortality rates for men older than 35 years and for women older than 65 years, whereas added sugar had the highest correlation for women aged 35–65 years. However, for dietary data from around 1970, animal fat had a higher correlation than lactose. Influenced by the work of both Seely and Segall, I emphasized the lactose finding rather than the animal fat finding. I now realize that doing so was an error, partly because IHD arises after years of an unheathful diet and partly because observational studies have not confirmed the non-fat portions of milk to be risk factors for CHD.

One interesting finding in my study was that added sugar was the most highly correlated risk factor for women younger than 65 years. This finding has important implications. Menopause is a highly likely candidate for the transition of the serum lipid relation to
dietary factors for women, with atherosclerosis and arterial clogging leading to CHD taking 10–15 years after oestrogen levels decrease. The established journal literature supports this interpretation. The risks related to post-menopause are due mainly to the abrupt interruption of oestrogen, which indirectly protects lipid, glycemic metabolism and directly affects vessel function. Female sex hormones were significantly inversely correlated with low-density lipoprotein cholesterol and positively associated with high-density lipoprotein cholesterol. These hormones slow the progression of subclinical atherosclerosis as defined by carotid artery intima-media thickness in post-menopausal women. For women younger than 65 years, probably because they needed to be able to deal with fat for reproduction and lactation in the child-bearing years, oestrogen helps store dietary fat in the fatty tissues rather than in the arteries, so until some time after menopause, they are protected against fatty build-up in the arteries. Sugar is stored in the body as triglycerides (triacylglycerol). High-carbohydrate diets increase triglyceride levels and decrease high-density lipoprotein levels. Carbohydrates, especially simple ones, are known CHD risk factors. Looking at CHD mortality rate trends in European countries that have reduced the amount of animal fat in national diets, one finds more support for the role of animal fat as an important risk factor for CHD. In 1972, the Finnish launched what evolved into a national-level programme to change diet and other behaviours to prevent cardiovascular disease. Strongly rooted in theory and using comprehensive approaches, the initiative relied on community-level organization and participation. Behavioural changes reduced total cholesterol and blood pressure, reducing IHD mortality by 73% in North Karelia and by 65% for Finland as a whole for 1971–95. In Eastern Europe, CHD mortality rates decreased significantly when animal fats were replaced to some extent by increased consumption of rapeseed oil, of which oils rich in α-linolenic acid are an important component.

Despite the missteps in applying the ecologic approach to the study of CHD, properly designed and executed ecologic studies can be useful. They can quickly identify important risk-modifying factors for chronic diseases at a small fraction of the cost and time of conventional observational studies. Findings of the Alzheimer’s disease study, for example, were generally confirmed in observational studies 5 years later. The classic ecologic diet–disease study by Bruce Armstrong and Richard Doll identified animal fat as the primary dietary risk factor for many types of cancer, yet cohort studies had difficulty in confirming the results of this study. However, the discrepancy seems to be nearly resolved with the realization that much of the risk for cancers such as breast cancer may come from dietary factors early in life.

Another example is that an ecologic study was the first to generate the hypothesis that solar ultraviolet-B irradiance, through the production of vitamin D, reduces the risk of cancer. The number of cancers so linked is now about 15, and the evidence for beneficial roles of ultraviolet B and vitamin D with respect to cancer appears to be strong. From the results of a post hoc analysis of a randomized controlled trial of vitamin D and calcium supplementation for post-menopausal women, 1100IU of vitamin D3/day reduced the risk of all-cancer incidence by about 35%. Interestingly for this commentary, there is now strong observational evidence that vitamin D also reduces the risk of CHD and cardiovascular disease incidence and mortality rates. Latitude, used by Seely, is a useful index of solar ultraviolet B dose and vitamin D production.

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**References**

Commentary: Lactose and ischaemic heart disease: a sweet hypothesis...but nothing more!

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In 1964 John Yudkin and colleagues published a report on sucrose intake by patients with vascular disease and control subjects. The mean sugar intake of the patients was nearly twice as high as that of the control subjects. This led to the hypothesis that sucrose, and by extension lactose, might be a risk factor for cardiovascular disease.

However, subsequent studies have not supported this hypothesis. A meta-analysis of 24 countries showed no significant association between lactose intake and coronary heart disease mortality. Similarly, a study of 21 countries found no association between milk drinking and ischaemic heart disease.

The lack of evidence for a causal relationship between lactose intake and cardiovascular disease is consistent with the hypothesis that milk and dairy products do not increase the risk of cardiovascular disease. This supports the view that the public health implications of dairy consumption are not as significant as previously thought.

In conclusion, while the hypothesis that lactose is a dietary risk factor for cardiovascular disease remains unproven, the evidence supports the view that dairy products are generally safe and have potential health benefits.