

# EDITORIALS

## Milk and mortality

Genetic studies could help us interpret a biologically plausible but preliminary association

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Clinical guidelines are increasingly based on experimental evidence from trials. Few randomized controlled trials give the effect of diet or nutrients on major health outcomes. Dietary guidelines or recommendations tend to be based on observations from prospective cohort studies, possibly describing the eating habits of people who happen to live longer for a multitude of reasons rather than the effects of a particular diet or nutrient.

Dietary guidelines may also be designed to provide recommended intakes of specific nutrients, sometimes based on the lowest level of evidence (that is, opinion) and reflecting the assumption that normal intakes in Europe or North America represent those that are optimal.<sup>1</sup> As such, it is hardly surprising that dietary guidelines are not always confirmed by experimental evidence from trials, such as the harmful effects of saturated fats<sup>2</sup> or the benefits of calcium.<sup>3</sup> In a linked paper (doi:10.1136/bmj.g6015),<sup>4</sup> Michaëlsson and colleagues question the role of milk, an item that often features in dietary guidelines.<sup>5</sup> Based on observational evidence, Michaëlsson and colleagues raise the possibility that milk could increase the risk of particularly hip fractures among women and cardiovascular and overall mortality in both sexes.

In dietary guidelines, dairy products, including full or specifically low fat milk, are recommended as sources of protein and calcium for bone health, and in some diets as prevention against hypertension.<sup>6</sup> The prospective observational evidence available, mainly from cohort studies in Western countries, does not consistently show higher milk intake to be associated with lower risk of hip fracture, cardiovascular mortality, or death.<sup>7 8</sup> Diet is difficult to assess precisely, potentially obscuring any differences. Widespread use of low fat milk is relatively recent so less evidence about its role is available. Michaëlsson and colleagues did not distinguish between low fat and full fat milk. Yet concerns about the role of milk have existed for decades, with specifically lactose, for which milk is the main dietary source, previously hypothesized as a cause of ischemic heart disease.<sup>9</sup> Countries, mainly in Europe and North America, with higher rates of lactase persistence (the ability to digest milk after early childhood) and hence higher milk consumption also have higher rates of hip fracture<sup>9 10</sup> and ischemic heart disease.<sup>9</sup> Ecological studies do not provide strong evidence for a hypothesis, but these observations require some explanation.

Low milk consumption in countries with low rates of fracture and ischemic heart disease might be correlated with a protective factor, such as physical activity, or milk may act together with other unidentified factors.

Dietary guidelines do not clearly distinguish between milk and other dairy products.<sup>5</sup> Michaëlsson and colleagues are suggesting a signal of harm specifically from milk, but not from fermented dairy products with a low lactose content (including yogurt and cheese), where associations were in the other direction. The authors found that people who consume milk are similar to those who consume yogurt or cheese, making it less likely that the findings are the spurious result of other differences correlated with milk intake, such as alcohol consumption. Confounding would be even less likely if consumers of fermented milk products and consumers of milk had similar risks of death from a cause unrelated to dairy consumption, such as accidents. Future researchers should explore this possibility. Michaëlsson and colleagues found stronger associations of milk with risk in women than in men, perhaps due to differences in study design between male and female cohorts, or perhaps as a result of residual confounding.

Michaëlsson and colleagues suggest that milk is harmful because a metabolite of lactose, D-galactose, mimics aging through inflammation and oxidative stress in animal models. The authors show that milk, but not fermented dairy products, is positively associated with a biomarker of oxidative stress (8-iso-PGF<sub>2</sub>α), but they could not test whether the positive associations of milk with hip fracture, cardiovascular mortality, and death were specifically mediated by D-galactose. D-galactose relates to bone metabolism in animals<sup>11</sup>; evidence concerning the cardiovascular effects of D-galactose is limited.

Lactase persistence has evolved independently several times and shows signs of preferential selection,<sup>12</sup> indicating that lactase persistence may promote survival to adulthood or fertility but not necessarily longevity. Inability to process D-galactose, galactosemia, is associated with reproductive abnormalities,<sup>13</sup> suggesting that D-galactose or its metabolites could have reproductive effects. However, a theory stands or falls according to how its predictions withstand testing and not according to the plausibility of its mechanism. Tests in humans to confirm

or refute the role of milk and D-galactose or its metabolites in early survival, fertility, and longevity are not available.

Michaëlsson and colleagues raise a fascinating possibility, about the potential harms of milk with an interesting inner mechanism involving D-galactose, which is consistent with ecological evidence<sup>9 10</sup> and animal studies.<sup>11</sup> Their findings should be interpreted cautiously though because the authors rely on observational not experimental evidence, potentially reflecting correlation not causation.

As milk features in many dietary guidelines<sup>5</sup> and both hip fractures and cardiovascular disease are relatively common among older people, improving the evidence base for dietary recommendations could have substantial benefits for everyone. Comparing the health of adults with and without genetic lactase persistence in a setting where milk intake is discretionary and reflects only lactase persistence might be the most expeditious way forward, although randomized controlled trials, if feasible and ethical, would be most convincing.

As milk consumption may rise globally with economic development and increasing consumption of animal source foods, the role of milk in mortality needs to be established definitively now.

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