LETTERS

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MILK AND MORTALITY

Milk and mortality: raw versus pasteurised milk

A serious flaw in Michaëlsson and colleagues' study is that it did not distinguish between raw and pasteurised milk.[1] These two entities are completely different in structure, content, nutritional benefits, and disease associations, and referring to both as "milk" underestimates this difference.

Whole raw milk, from grass fed cows, is an enhanced source of nutrients, including beneficial bacteria such as *Lactobacillus acidophilus* and high levels of vitamins (A, B, C, D, E, K), enzymes, calcium, and conjugated linoleic acid, in a package that optimises absorption of all its contents.

Pasteurisation reduces contamination with pathogens but also kills the beneficial lactobacilli that produce vitamin K_2, improve absorption of nutrients, and normalise gut function. Pasteurisation denatures the fragile and nutritious milk proteins and enzymes, and it reduces the vitamin content. In addition, contamination can occur after pasteurisation and lead to outbreaks of serious infection.[2] Pasteurisation also negates the reduction in childhood asthma and atopy associated with consumption of raw milk.[3]

The authors also did not measure the fat content of the milk. This is important because deficiencies in fat soluble vitamins A, D, E, and K are associated with decreased bone mass and osteoporosis.[4] Most health conscious people try to limit their intake of saturated fat, which is widely accepted to be associated with heart disease, although this is controversial.[5]

In conclusion, even though legislation mandates the pasteurisation of milk, raw milk from grass fed dairy cows is still available in Europe and North America and is widely available in less developed countries with an agrarian economy, such as Colombia.

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Full response at: www.bmj.com/content/349/bmj.g6015/rr/778957.

1 Michaëlsson K, Wolk A, Langenskiöld S, Basu S, Warensjö Lemming E, Melhus H, et al. Milk intake and risk of mortality and fractures in women and men: cohort studies. *BMJ* 2014;349:g6015. (28 October.)
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Vitamin D status, bone fracture, and mortality

Two recent Swedish studies support a seasonal effect on fracture risk. The first study in a very large population sample showed a significant seasonal variation in hip fracture, with a lower risk in summer (37.5% in men; 23.5% in women) compared with winter.[1] The second study in a smaller sample found a seasonal variation in the incidence of indoor fractures in community dwellers, with the same seasonal trend.[2]

There are several possible reasons for this seasonal variation. One is the serum and plasma 25-hydroxyvitamin D (25(OH)D) concentration, which shows marked seasonal variation in Sweden, with the highest values reported in summer and the lowest in winter. Circulating 25(OH)D is a well established determinant of bone health and is associated with fracture risk in numerous case-control and prospective cohort studies.[3] Michaëlsson and colleagues' study would have benefited from including 25(OH)D measurements or season (or both) as confounders in the analysis.[4] Such information would have been additionally useful in light of the recent meta-analysis supporting a strong association between 25(OH)D concentrations and all cause and cause specific mortality.[5]

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Competing interests: None declared.

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Cite this as: *BMJ* 2014;349:g6995

Galactose content in fermented dairy products was wrong

Michaëlsson and colleagues' proposed mechanism for the effect of milk intake on the risk of mortality and fractures is based on the assumption that fermented dairy products (which had the opposite effects to those of non-fermented milk) are free of galactose.[1] For most fermented dairy products, however, this is untrue. The paper quoted by the authors shows a decrease in lactose from 4.8 g/100 g to 2.3 g/100 g (loss of 2.5 g/100 g) in yoghurt compared with milk,[2] with an increase in galactose of 1.3 g/100 g. Because lactose is composed of glucose and galactose, which have equal molecular weight, this decrease in lactose would lead to 1.25 g/100 g of galactose formed (equal to the 1.3 g/100 g in the quoted paper). Yoghurt therefore contains the same amount of galactose as milk (and in lactase non-persistent people may lead to even higher galactose intakes).

The galactose content of (semi)hard cheeses is somewhat lower because the curd is washed during production, but cheese is not usually free from galactose.

Overall, the galactose intake from fermented dairy products (soured milk and yoghurt in the paper) is equal to that from regular dairy products, which makes the authors' proposed mechanism highly unlikely.

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1 Michaëlsson K, Wolk A, Langenskiöld S, Basu S, Warensjö Lemming E, Melhus H, et al. Milk intake and risk of mortality and fractures in women and men: cohort studies. *BMJ* 2014;349:g6015. (28 October.)
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Milk and mortality: effects of modern milk production

Modern industrial scale milk production involves administration of various synthetic substances to dairy cows to enhance production. The milk contains residues of these synthetic substances such as hormones, antibiotics, and analgesics.[1] Sadly, Michaëlsson and colleagues did not discuss these negative aspects of mass produced milk.[2]

For instance, cohorts were recruited to the study between 1987 and 1997. But until the European-wide ban in 2000, recombinant bovine somatotropin was used to enhance milk production. This hormone can affect hormonal and metabolic growth factors, including human serum insulin-like growth factors (IGF), which in turn can increase the risk of cancer.[3 4] A large European cross sectional study showed that intake of dairy products was an important dietary determinant of serum IGF-1.[5]

Analysis of milk for the presence of these substances would have provided a more plausible explanation for the effect on mortality.

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Competing interests: None declared.

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Unaccounted sex differences undermine the association

Michaëlsson and colleagues overstate their findings.[1] The large sex differences are not accounted for or mentioned in the abstract and key points.

The hazard ratios for mortality are very different in men and women. The hazard ratio in men is small. Statistical significance is meaningless with such a large denominator. Such a small hazard ratio cannot be called a signal because it is easily caused by residual confounding. The hazard ratio in women is large enough to be a true signal, comparable to the mortality risks of smoking or morbid obesity. But why was a true signal found in women but not men? In Bradford Hill's criteria of causation, this is a serious consistency problem, which undermines any causal interpretation.

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1 Michaëlsson K, Wolk A, Langenskiöld S, Basu S, Warensjö Lemming E, Melhus H, et al. Milk intake and risk of mortality and fractures in women and men: cohort studies. *BMJ* 2014;349:g6015. (28 October.)

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Authors' reply

We thank all authors for their views on our article and would like to clarify some points.[1 2]

In response to Kerr, few people in Sweden use raw milk because pasteurisation of commercially sold milk has been mandatory since 1937.[3] We could therefore not compare risk estimates for raw and pasteurised milk. The fat content of milk did not seem to explain our associations. In fact, we found higher rates of mortality with low fat (≤0.5%), medium fat (1.5%), and high fat (3%) milk, with only modest differences in risk estimates.

Hill suggests confounding by vitamin D status.[4] We did adjust mortality and fracture risk estimates for vitamin D intake and hazard ratios were not attenuated, but serum 25-hydroxyvitamin D (25(OH)D) levels were not available. However, we adjusted our estimates for serum 25(OH)D levels in the biomarker substudies in an updated analysis and the results were similar (see figure on thebmj.com). In addition, vitamin D intake has only a modest effect on the occurrence of osteoporotic fractures in Sweden[5]—fewer than 5% of such fractures in older women and men are attributable to a low serum 25(OH)D.[6 7] Moreover, serum 25(OH)D values do not seem to be low in Scandinavia, even during the dark season.[8-10] Rigorously performed meta-analyses have found no reduction in mortality rates with vitamin D supplementation.[11 12] Admittedly, perhaps few people were truly vitamin D deficient and the studies might have been too short or the vitamin D dose too low.[13] Randomised controlled trials with higher doses of vitamin D are ongoing.[14] It is difficult to attribute disease occurrence and mortality to low serum 25(OH)D in observational studies like ours because of the relation between ill health or frailty and low vitamin D status.[15-17] More studies are needed, but high milk consumption seemed not to be driven by frailty or ill health in our studies.

Hettinga finds our galactose hypothesis highly unlikely.[18] We stated that "Separating milk intake from the consumption of other dairy products may be of importance since a less pronounced induction of oxidative stress and inflammation in humans is expected with cheese and fermented dairy products (for example, soured milk and yogurt) because of their lower or non-existent lactose and galactose content, possible probiotic antioxidant and anti-inflammatory effects, and effects on gut microbiota." Effects of galactose can therefore be counteracted by probiotic effects of fermented dairy products. Our reference 14, not reference 15 as Hettinga quoted, indicates that total galactose content is lower in fermented milk products than in milk, but this depends on time since production, bacterial strain, and the use of the Leloir pathway.[19-22] This reference is from 1980, however, and its relevance now is uncertain. Because of the lack of data in this field, a Swedish University of Agricultural Sciences' project is set to examine the concentration of different carbohydrates in dairy products. According to our reference 15,[23] Hettinga's claim that "the galactose content of (semi)hard cheeses is somewhat lower" is as an understatement. Hard cheeses would not be recommended for people with galactosaemia if they had only "somewhat lower galactose"—most of these cheeses have undetectable levels of galactose.[23] Our galactose hypothesis might be proved wrong, and we cannot provide evidence for such a hypothesis with our study design, but it is still a possible explanation for our findings.

Sundar suggests synthetic substances in milk as an underlying explanation for our findings.[24] We did discuss this possibility in our discussion, but if these factors were causes, we ought to have seen similar associations with different dairy products.

We suggest that Bonneux reads our discussion and sensitivity analysis about differential associations in women and men.[25] The most likely explanation is methodological, with the larger number of outcomes and repeat dietary assessments in women improving the precision and reducing the total error in the female cohort analysis. In addition, the men were on average 10 years younger than the women at end of follow-up. We also previously found a weak tendency for a higher risk of fracture in women with high milk consumption[26];

this earlier analysis was based on a single questionnaire and the number of fractures was similar to that in the current male study.

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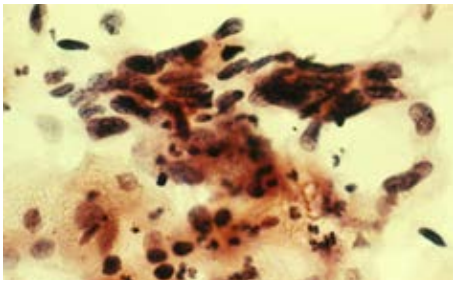
CERVICAL PRE-CANCER

Using term pre-cancer creates new disease out of risk factor



The articles published under the Too Much Medicine banner are a welcome counter to the prevailing wisdom, which is driving doctors and patients in the opposite direction. So I was dismayed to discover that a print issue illuminated by Heath's essay on overdiagnosis and overtreatment also contained an editorial entitled *Safety of Modern Treatment for Cervical Pre-cancer*.[1 2]

The use of pre-cancer (like pre-diabetes, subclinical hypothyroidism, osteopenia, and sundry others) creates a new disease out of a risk factor—exactly the kind of thing that the Too Much Medicine series is trying to combat. The oddest aspect is that the term never appeared in the wise and helpful body of the text, which refers to cervical intraepithelial neoplasia throughout. Was the title the work of someone on the editorial staff? Of course journals should reflect a range of views, but the degree of inconsistency shown here is depressing.

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Competing interests: None declared.

1 Heath I. Role of fear in overdiagnosis and overtreatment—an essay by Iona Heath. *BMJ* 2014;349:g6123. (24 October.)
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Authors' reply

Cervical cancer screening differs from other cancer screening programmes in that it prevents invasive cancer. Screening programmes in the UK, Nordic countries, and elsewhere have been highly successful—finding and eradicating pre-cancerous lesions. Such lesions are not only epidemiological risk factors but virally infected tissues with a strong biological potential to develop into invasive cancers unless treated.

It is a great challenge for colposcopists to select, among all women with cervical intraepithelial neoplasia, those who have true pre-cancerous lesions—the ones that should be treated. We chose the established term pre-cancer in the title of our editorial to illuminate this. The editorial discusses the important problem of overtreatment and the possible harm of eradicating too much cervical tissue in too many fertile women. It is not a part of *The BMJ*'s Too Much Medicine campaign, but we are pleased that Jewell includes it in that discussion. Overdiagnosis and overtreatment with physiological and psychological side effects are part of all screening programmes, including cervical screening. These unwanted consequences must be challenged, monitored, and minimised.

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TESTOSTERONE REPLACEMENT

Testosterone replacement and cardiovascular events

In February 2014, *The BMJ* published a personal view by Sidney Wolfe of Public Citizen—a US anti-pharmaceutical pressure group trying to obtain black box warnings for testosterone products.[1] The article presented summaries from two recent papers that claimed increased cardiovascular risk with testosterone replacement therapy (TRT).[2 3]

In July 2014, the Food and Drug Administration published a detailed response to Public Citizen, explaining why it rejected every aspect of the case and concluding that the credible medical literature tended to support a reduction in mortality with TRT.[4] The FDA reported the glaring errors in the two papers that hundreds of readers had identified. The first paper did find an increase in cardiovascular events with TRT, but the authors recently had to modify their data to explain why more than 1000 men were omitted because their event occurred before TRT, while also admitting that more than 100 women had been included in a male only study. The second study looked only at non-fatal events in the first three months after starting TRT. However, treatments such as testosterone that reduce mortality from cardiovascular events inevitably increase the rate of non-fatal events because more people survive.

SPL

A recent long term study of 6355 men aged over 69 years and more than 19 000 controls showed no increase in coronary events overall but a reduction in the cohort at greatest risk.[5] The treated group also had low baseline testosterone and high rates of erectile dysfunction, both proven markers of cardiovascular risk.

In the name of medical integrity, having provided a platform for pressure groups with a private agenda, *The BMJ* should publish outcomes that are considered conclusions based on the highest levels of medical evidence.

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Competing interests: I am an occasional speaker and researcher for Bayer, Lilly, and Menarini.

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Author's reply

In a response to my column,[1] Hackett criticises the study by Finkle et al, which investigated about 55 000 men prescribed testosterone, considerably more than any previously published study assessing the cardiovascular risk of testosterone products.[2] It found a significantly increased rate of non-fatal myocardial infarction in the three months after initial testosterone prescription compared with the previous year.[3]

Hackett challenges the validity of using non-fatal myocardial infarction as the primary outcome because testosterone's ability to reduce mortality from cardiovascular events would increase the rate of non-fatal events as more men would have survived. This is rebutted by a recent meta-analysis of 27 randomised testosterone trials, which identified 33 cardiovascular related deaths (22 testosterone arm and 11 placebo arm), for which the odds ratio was similar 1.42 (95% CI 0.70 to 2.89) to the estimate for all cardiovascular related events. In 14 trials not funded by the drug industry the risk of a cardiovascular related event on testosterone therapy was greater (2.06, 1.34 to 3.17) than in drug industry funded trials (0.89, 0.50 to 1.60).[4]

Hackett also mentioned the US Food and Drug Administration's rejection of our petition for a black box warning about cardiovascular risks but disregarded the Canadian government's

contrasting action the same day: "Health Canada is advising patients and healthcare professionals of new safety information regarding testosterone hormone replacement products and a risk of serious and possibly life-threatening cardiovascular (heart and blood vessel) problems . . . Health Canada has recently completed a safety review on testosterone replacement products. This review found a growing body of evidence (from published scientific literature and case reports received by Health Canada and foreign regulators) for serious and possible life-threatening heart and blood vessel problems such as heart attack, stroke, blood clot in the lungs or legs; and increased or irregular heart rate with the use of testosterone replacement products."[5]

Perhaps this makes Health Canada, as Hackett characterises us, an "anti-pharmaceutical pressure group." Thus far, neither the FDA nor the European Medicines Agency has acknowledged the serious cardiovascular risk of testosterone products.

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Competing interests: None declared.

1 Wolfe SM. Increased heart attacks in men using testosterone: the UK importantly lags far behind the US in prescribing testosterone. *BMJ* 2014;348:g1789. (27 February.)
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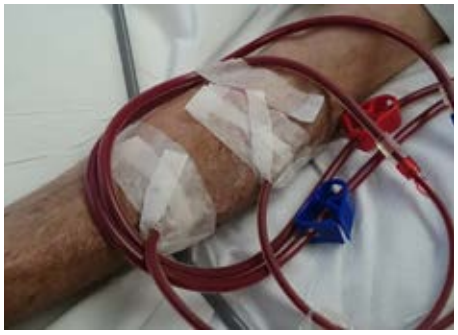
ARTERIOVENOUS FISTULAS

Alternatives to arteriovenous fistulas

In their review, Siddiky and colleagues suggest that arteriovenous fistulas for haemodialysis "offer the best short, intermediate and long term options for renal replacement therapy."[1] Although they have many advantages, one of the few rigorous systematic reviews in vascular access emphasises the often overlooked complication of primary non-function (the fistula never works).[2] This occurs in about a quarter of patients, and only 60% of fistulas still function without intervention at one year. Many clinicians see fistula surgery as a minor operation, but these poor outcomes have an extremely negative effect on the patient experience and morbidity.

For some patients, fistula creation is not possible or is precluded by informed patient



choice. With the right care both arteriovenous grafts and tunnelled lines are acceptable alternatives.[3 4] A recent well designed study suggests that in certain patient groups, particularly older people and those with diabetes, the three approaches are clinically equivalent.[5] This diversity of options is important if we wish to provide individualised care, rather than a one-size-fits-all approach, in modern healthcare.

In the absence of randomised controlled trials in vascular access, clinical guidelines have relied on observational studies, often with inherent selection bias. In particular, many studies fail to deal adequately with the confounding burden of comorbidity, which often precludes the creation of native vascular access.

Clinicians and policy makers must not ignore the absence of clear evidence to support decisions about vascular access. Nor should they overlook the need for work to define the causes of early fistula failure alongside the design of novel interventions to improve both clinical outcomes and the patient experience.

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Competing interests: None declared.

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Authors' reply

We appreciate Corbett and colleagues' response to our article. Our brief was to provide an overview of arteriovenous access, with a focus on simple autologous vein fistulas rather than on tertiary access or complex access in the presence of central vein disease.

Primary non-function is a recognised problem, but ideally no more than 10-15% of radiocephalic and brachiocephalic arteriovenous fistulas should fail within the first hours after surgery. By six weeks a further 10-15% may have failed or shown signs of failing to mature.[1] We believe that figures above this reflect a combination of poor choice of access creation, along with limited preoperative imaging, postoperative surveillance programmes, and appetite for salvage.[2]

Poor outcomes certainly affect the patient's experience and morbidity and repeated access creation can be soul destroying for the patient. But Corbett and colleagues fail to recognise the serious morbidity and mortality associated with long term use of a central venous catheter. The resultant central venous pathology reduces access options, including the use of grafts, given the high incidence of venous hypertension that develop secondary to central stenosis or occlusions.[3 4] Dialysis adequacy over time is also better if dialysis is on a fistula or a graft.[5]

Access teams should tailor their approach to each patient on the basis of individual needs and options available. That is certainly our approach—fistula first is not always attempted and graft first may be the best or only option.

Evidence that early failure may be driven by uraemia is growing.[6] Early referral and creation of access is therefore imperative. More work is also needed to better understand perianastomic disease.

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Full response at: www.bmj.com/content/349/bmj.g6262/rr/780206.

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