



## **SPLASH!® milk science update** **August 2016 Issue**



This month's issue features how dairy improves satiety, human milk improves long-term heart health for premature babies, human milk mercury levels are higher in the Amazon, and genomic selection improves the health and productivity of dairy cows.

### **Dairy Products Could Significantly Increase Satiety**

- **Obesity is a major global problem, and one potential solution involves using foods that increase satiety to help with weight loss.**
- **Studies on the effects of dairy products on satiety have had conflicting results, possibly due to differences in study design and type of dairy used.**
- **A new meta-analysis of published clinical trials finds that consumption of more than 500 ml, or about 2 cups, of dairy products significantly increased satiety.**
- **Although the exact mechanisms of this effect are unclear, some studies indicate that it could be related to the protein components of milk.**
- **The new study suggests that dairy consumption could play a role in controlling caloric intake by increasing feelings of satiety.**

Obesity is a major public health issue—with no easy remedies. One potential solution involves consuming foods that increase satiety, thus reducing appetite for later meals and helping with weight loss. So far, a variety of foods have been shown to affect satiety, including soda, fruit drinks, and milk [1-4]. Researchers have been particularly interested in using dairy for this purpose, but studies on how dairy products influence appetite have had conflicting results.

In a new study, researchers led by Leila Azadbakht at Isfahan University of Medical Sciences conducted a meta-analysis of published clinical trials to determine the effects of dairy products on satiety. The new study concludes that consumption of over 500 ml of dairy products significantly increases satiety [5].

“You get more feelings of fullness, and less hunger, consuming a dairy product than consuming a soft drink or some other product,” says G. Harvey Anderson at the University of Toronto, who has conducted previous research on dairy and satiety, and was not involved with the new study.

Previous studies have shown that dairy consumption can help control body weight [6]. “Epidemiologically, it’s shown consistently that people who consume more dairy products have better control of body weight,” says Anderson. Dairy products also appear to affect “postprandial” glucose levels, i.e., the glucose levels after a meal. “What we find consistently is that postprandial glycemia, which is an important aspect of glucose control, is much better after milk than any other beverage one might consume, and we see this with yogurt or cheese too,” he says.

Despite these promising signs, studies of the effects of dairy products on satiety have so far had conflicting results. Many studies have shown associations between dairy products and decreased appetite or increased satiety [7-11], but others did not show such an association [12,13]. This variability between studies could be due to a number of reasons, including differences in study design or the type of dairy products tested.



In the new study, the researchers conducted a meta-analysis of 13 eligible clinical trials published before February 2015 to determine the effects of dairy consumption on satiety. They found that consumption of more than 500 ml, or about 2 cups, of dairy products significantly reduced hunger and significantly increased satiety. Consumption of 500 ml of dairy products also significantly reduced later food consumption.

“There’s no doubt about that, you drink 500 ml of dairy and you’re going to feel fuller,” says Anderson. In a previous study, Anderson and his colleagues found that in both kids and adults, dairy increased post-meal satiety and decreased postprandial glucose. “The overall effect is reduced appetite,” he says.

Anderson points out that consuming any beverage other than water will add calories to the meal, but in the case of milk, this increase in calories could be counteracted by its effects on satiety and postprandial glucose. “Because you’ve got greater satiety and less post-prandial glucose, you’re probably going to get the benefit later,” he says. “Maybe you wouldn’t have that afternoon donut, and would come out ahead for the day,” says Anderson. “But the jury’s still out, nobody’s done the experiment,” he says.

The mechanisms behind the effects of dairy on satiety are still unclear. Previous studies have suggested that dairy consumption may affect appetite-regulating hormones such as ghrelin, or the neuropeptide glucagon-like peptide-1 (GLP-1) [7]. “Perhaps the satiety itself is from this increase in gut hormones that produce satiety and also benefit post-prandial glycemia,” says Anderson. “The hormones slow down stomach-emptying, which means you also feel fuller and don’t eat as much,” he says. One possible mechanism involves the activation of gut hormones and GLP-1 by peptides produced by the digestion of milk proteins.

Consuming foods rich in protein has been previously shown to produce feelings of satiety [14,15]. Researchers have suggested that the effects of dairy products on satiety could be due to the proteins in milk, namely whey and casein. “Absolutely, it is the protein,” says Anderson. He and his colleagues previously studied the effects of the components of whole milk—milk proteins, fat, and lactose—on satiety, and found that the milk proteins had the greatest effect on increasing postprandial glucose and satiety [16]. “The surprising thing was that whole milk gave you more than the sum of its components, so there’s an interaction between the components as they are in milk and the benefits you get from milk,” says Anderson.

The limitations of the new meta-analysis include the limited number of studies that fit their inclusion criteria, and the fact that most of these studies had small sample sizes and differed in the type of dairy products studied, which included milk, yogurt, cheese, and chocolate milk. More long-term studies will be needed to figure out how different types of dairy products vary in their effects on satiety, and to dissect the mechanisms by which they affect satiety. But the results suggest that dairy consumption could play a role in helping to control caloric intake by increasing satiety. “We have to also remember that dairy products are full of nutrients, and we derive other benefits from them compared to an awful lot of other beverages,” says Anderson. “There are so many advantages of milk as a pre-meal or within-meal beverage,” he says.

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## Premature Babies Fed Breast Milk Have Stronger Hearts as Adults

- **A new study finds differences in the hearts of adults who were born premature and fed formula, from the hearts of adults also born premature but fed breast milk from birth.**
- **In general, both of these groups had less well functioning hearts compared with hearts of people who were born at full term. However, those fed breast milk as preemies had far more “normal” hearts.**
- **The study adds to other evidence making the case for premature infants to receive breast milk in their first weeks of life, either expressed by their own mother, or donor milk.**

Thanks to improving knowledge and standards of care in hospitals, babies born several weeks before their due dates are more likely than ever to survive. This trend has come with the loose assumption that, once through early life, individuals born premature grow like children born at term, living just as long and as healthily.

But in the past few years, evidence has come to light showing that preterm infants grow in subtly different ways from infants born at term. In 2013, for example, Adam Lewandowski of Oxford University and his team of medical scientists demonstrated that, as young adults, those who were born early tend to have hearts that are a bit heavier than hearts of individuals born at term, though with smaller chamber volumes and weaker functioning.



In their most recent study, published in June 2016 [1], the same team considered why preterm babies' hearts might develop differently. They thought that the nutrition provided in the neonatal intensive care unit (NICU) might be a factor. Specifically, the team wanted to know if preterm infants who were fed only breast milk during their stay in the NICU have more “normal” hearts as adults compared with those who were fed infant formula during the same period of their lives.

To figure this out, the researchers set about re-analyzing data from their 2013 studies [2,3] taking into account early feeding regimes. In these studies, the team contacted people born between 1982 and 1985 who had originally participated in a clinical trial that investigated the effects of early diet on cognitive development. As

such, these individuals had weighed less than 1,850 g at birth, and spent the first weeks of their lives in one of five NICUs in the UK. While they were in the NICU, some had been randomly assigned to exclusively receive breast milk, and others to receive infant formula.

The results of the new data analysis come with a dose of caution. Only 102 of the 926 people who were enrolled in the original trial as preterm infants could be contacted and convinced to spend a day in Oxford having their heart scanned by an MRI (magnetic resonance imaging) machine. For this reason, Lewandowski and his team urge tentative interpretation of their findings. Nonetheless, the size of the effects and reasoning that has been put forward to explain them are noteworthy.

Compared with healthy adults of the same ages, sizes, and sexes who were born full term, the individuals born early had slightly different heart structures—as described in the 2013 studies. They also had higher blood pressure, and altered blood biochemistry profiles. But the differences were relatively slight for individuals who were premature and, while in the NICU, had exclusively consumed breast milk. For example, both milk-fed and formula-fed preemie groups had smaller left ventricle volume as adults than those born at term. But the reduced size for the milk-fed group was 9%, whereas that of the formula fed group was 18%.

There were various other differences between the breast milk- and formula-fed groups. The formula-fed individuals had bigger pulmonary artery diameters, and their ejection fractions from their right ventricle—a measure of how well the heart pumps blood out of it and around the lungs—were smaller. Meanwhile the ejection fractions of the right ventricle of the breast milk-fed group were no different from those of individuals born at term. Moreover, the overall chest cavity dimensions of the formula-fed group were smaller than those of the breast-milk fed group—and again, the breast-milk-fed group was no different by this measure from those of the full-term-born group.

The finding about chest cavity differences is important because it hints at a mechanistic explanation for the overall differences. The heart's physiology is intimately connected with that of the lungs. Out of the right ventricle, blood is carried around the lungs to pick up oxygen. It then travels back to the heart, where the powerful muscular walls of the left ventricle pump it around the body.

Lewandowski and his coauthors write that those who were fed formula as premature infants did not receive the growth factors—such as vascular endothelial growth factor—that are present in breast milk. And for this reason, they probably had slightly abnormal vasculogenesis (the development process that gives rise to the heart and blood network) and angiogenesis (remodeling and expansion of that network) during early development. These two processes have also been linked to poor lung development in preterm infants. Hence, the finding of greater differences with preemie feeding regime between the right side of the heart and the left: the right ventricle's power must be commensurate with lung size and

function, so as to push blood around the lungs at the appropriate pressure. If the formula-fed individuals have less well-developed lungs, their right ventricle growth would be restricted.

Although the study didn't test this, the differences identified are probably noticeable in the participants' physiological performance, during peak exercise, and as they cope with the effects of age and modern living on their cardiovascular systems. It is only logical that the lower end-diastolic volumes and stroke volumes—essentially, the lesser pumping abilities—of the hearts of adults who were fed formula in the NICU will lower their maximal exercise capacity throughout adult life. And maximal exercise capacity is itself an independent predictor of mortality and cardiovascular health into old age.

So, while the number of adults evaluated in this study was indeed small, and infant formulas have improved substantially since the early 1980s, the policy implications of this research are clear and simple. Babies in the NICU should be fed breast milk whenever possible, including donor milk if their own mothers have problems expressing, or do not wish to express.

Commenting on the paper in the British Medical Journal, Russell Viner, a professor at University College London's Institute of Child Health, said that this research adds to other studies that have concluded the same policy recommendation. "For premature babies who are born before they are physically ready for life outside the womb, breast milk is incredibly important. It protects an already vulnerable baby from infections and leads to a range of later beneficial effects on the brain, blood pressure and bone strength," he said [4].

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## Mercury in the Amazon, and Lysozyme C

- **Recently, Brazilian researchers set about measuring the mercury levels of breast milk from women in several communities along a tributary of the Amazon.**
- **In one community in particular, some of the women were found to have breast milk with mercury levels higher than the World Health Organization's recommendations.**
- **The research team found that mercury in breast milk is almost entirely bound to just one enzyme, called lysozyme C—a finding that may lead to a means of removing the mercury.**

Mercury can accumulate in the bodies of animals, humans included. When it does, it has been known to have harmful effects. But for remote communities living where mercury has occurred naturally at high levels for thousands of years, responding to new knowledge about the chemical is far from simple. Recently, researchers from several city-based universities in Brazil travelled to small settlements along the Amazon River's largest tributary to measure levels of mercury in women's breast milk [1]. This research is noteworthy because it has identified the enzyme in breast milk that mercury can become associated with—which is a first step to understanding how to remove it.

The Amazon region has been known to have high levels of mercury in many of its watercourses for decades. Responsibility for this has been laid squarely at the feet of gold miners, who have used and continue to use mercury to extract gold from soils. But while gold mining has certainly accentuated the problem, the region appears to be naturally high in the element, says study author Bruna Cavecci of São Paulo State University, "The rock formations of the Andes have mercury, so it is not only human action."

Other activities, such as the construction of hydroelectric power plants, have also been thought to influence local mercury levels by disrupting river sediment and creating the conditions for chemical change. Upstream of many reservoirs, the mercury in sediments and plankton tends to be in its inorganic form, but the concentration of the organic form often increases over time in the deep water parts of reservoirs near to dam walls. Both forms are considered toxic, but this matters because it is the organic form of mercury, often taken in by eating fish, that is more easily absorbed by the human body, where it can accumulate over time.

Cavecci and her colleagues chose the Madeira River for their study in part because a hydroelectric complex along its course has led to concerns about local organic mercury levels. The first phase of their research involved travelling to six



communities situated along the river's edge, from which the researchers took hair samples from the nape of the necks of lactating women who had lived in the community for at least a year and reported eating fish often [1]. These hair samples allowed the team to create a rough map of the relative mercury exposures of the six communities. Returning to the communities with the highest exposure, the researchers then asked to take samples of breast milk from individuals whose hair had registered a significant mercury concentration.



Back in the lab, it soon became clear that 4 of the 18 women's breast milk samples had mercury concentrations higher than the World Health Organization's reference standard of 6.0 mg per kg. The maximum found was 9.9 mg per kg, which was in breast milk from a woman in the community of Fortaleza do Abunã. The second-highest concentration found also came from a woman in that community. Cavecci noted that the geographic pattern of mercury levels in the communities did not appear to implicate the hydroelectric facility; Fortaleza do Abunã is, in fact, upstream of the dam.

But Cavecci and her colleagues wanted to know more than the concentration of mercury in breast milk. They were interested in the biochemical details of how mercury came to be incorporated into it, and therefore, exactly how infants and young children consuming the milk might be exposed. So they set about a two-step chemical analysis of the milk sample that contained the highest mercury level.

First, the investigators separated the constituent proteins in the breast milk sample using a technique called gel electrophoresis. Then they looked for big and heavy atoms associated with each kind of protein, using a machine called an atomic fluorescence spectrometer. This analysis showed that most of the mercury in the breast milk—87% of it—was bound up with just one protein, the enzyme lysozyme C, and that one mercury atom was chemically associated with each molecule of the protein.

This kind of knowledge has the potential to help exposed communities. Simply replacing breast milk with formula comes with potential health costs to infants and young children because they miss out on many of breast milk's health-giving ingredients, which even the best formulas lack. Some of these, such as oligosaccharides that help good bacteria to flourish in the gut and also help fight viruses, are especially important in environments with questionable hygiene.

In the short term, at least, communities along the Madeira that have high levels of mercury are lucky to be situated in the country that has probably the most extensive national breast milk banking system in the world [2]. Using donor milk could be an alternative to breastfeeding for some women because there is one such milk bank in the state capital of Porto Velho, four hours' drive from Fortaleza do Abunã. Another option would be for new mothers to avoid eating fish that eat other fish, which are more likely to contain high levels of mercury.

However, knowing that mercury is almost entirely bound to one kind of protein also suggests how to target new methods to remove it from breast milk. "The binding of mercury to lysozyme C causes deactivation of [the enzyme's] bactericidal effect, but there are other proteins that protect the baby who breastfeeds," says Cavecci. In other words, removing lysozyme C from breast milk should, in theory, result in milk that is almost as effective as the original at helping infants fend off germs in the first few months of life. That is a significant advance—and Cavecci says that her group is due to have more studies published soon.

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## Genomic Selection Accelerates Improvements in Health and Productivity of Dairy Cows

- Sequencing the bovine genome has made genomic selection of dairy cows possible.
- Incorporating genomics into herd improvement schemes has markedly increased productivity and health traits.
- Rates of genetic change increased by 50–100% for milk production traits.

- **Between 2008 and 2014, genomic selection resulted in a 3–4-fold change in the rate of improvement in health and productive lifespan.**
- **Genomics will continue to have a major on-farm impact.**

The introduction of genomic selection into dairy cattle selective breeding programs has been greatly anticipated and is a remarkable example of the benefits of genomic technology [1,2]. Made possible because the systems for selective breeding were already well developed in dairy, and the widespread use of artificial insemination meant that new developments could be delivered quickly. First introduced in the USA in 2008, there has now been sufficient time to generate enough data to assess its impact.

Genomic selection is based on the identification of breeding animals from the composition of their genome [3]. Each individual, aside from identical twins, has a unique genome. Although the number of regions shared among individuals within a cattle breed is much greater than that in a diverse population like humans, it is these differences that make a highly productive dairy cow, or one that is not so great.

Until recently, the selection of breeding animals was based on a process of testing bulls by observing the performance of their daughters. Commonly, this involved thousands of cows and took many years to complete. The potential major advantage of genomic selection is to dramatically reduce the time for the selection process. This is possible because the genetic composition of the bulls and cows can be completed at an early age, rather than waiting for the lengthy process required to infer the genetic value of the animals. Effectively, this means that the age of the parents of offspring is younger. The potential gain from this effect was predicted from theoretical modeling [3-5] and has now had sufficient time in practice to reveal the true impact.

A recent paper published by Dr Adriana Garcia-Ruiz et al. [6] analyzed the data from the US National Dairy Database to compare the effect of selective breeding programs before genomic selection was introduced and after its implementation. To do this, the researchers focused on genetic trends, that is, the rate at which the improvement in traits was changing. This is possible due to frequent measurements of dairy production traits through herd recording programs, which is an integral part of the industry. They followed an established procedure for analysis, which took into account the four possible routes of genetic change between parents and offspring. The results of the study overwhelmingly endorsed the predictions and clearly demonstrated that the rate of gain in significant traits has accelerated.

As predicted, there was a marked reduction in generation interval. This reflects the improvements in the accuracy of the process and the use of younger breeding pairs, particularly younger bulls. The introduction of genomic selection in 2008 produced a 37% reduction in generation interval in six years. This change underpinned a major contribution to all other changes in rates of gain. The analysis revealed that there was about a 50% increase in the rate at which genetic improvements were contributing to improvements in milk, fat and protein yield following the introduction of genomic selection. When the figures were compared directly between 2008 and 2014, the comparable improvement was 71%, 111%, and 81%, for milk, fat and protein, respectively, for the three production values.



Apart from the milk production traits, other factors that affect the health of cows and the many factors that influence the productive life of a cow have been difficult to change through selective breeding. The reasons for this are complicated, but mostly it is because the traits have very low heritability. Theoretical predictions have predicted that these low heritable traits will benefit from genomic selection. This was borne out by the study [2]. The researchers analyzed data for fertility, mastitis, and longevity. Fertility in dairy cattle is crucial to farmers as they manage cows through timed calving and periods of lactation. Over many years, as cows have been selected to produce more milk, there has been a steady decline in fertility. The factors contributing to this decline have been difficult to pinpoint, but it has become an issue in herd management. The low heritability affects accuracy for measuring breeding values,

and has made it difficult to influence with genetic selection. Genomic selection has the advantage of improving the accuracy of genetic measurement, and simultaneously incorporating multiple selection traits. This was reflected in the analysis of fertility since the introduction of genomic selection, which showed marked improvements in fertility gains.

One of the most significant health issues in dairy cows is mastitis—another trait with low heritability. Not only does it affect the wellbeing of individual cows, collectively it has a very large economic impact on the dairy industry. The number of cells in milk is used as an indicator of when mastitis may be present or developing. When analyzed, this trait was found to be improved by genomic selection by an astounding change of over 300%.

Finally, the longevity or productive lifespan of cows was analyzed. The capacity of a dairy cow to remain healthy and productive is highly valued by farmers. There is a great deal of investment and management time in raising a cow through to her first lactation, and consequently, the productive lifespan of the cows in a herd has a major impact on the economic output of the farm. Previously, there was no trend for improvement in productive lifespan of cows. However, since the

introduction of genomic selection methods, the annual improvements have been between 5- and 16-fold. Once again, these results show the greatest benefits for those traits that are difficult to measure and with low heritability.

Clearly, the introduction of genomic selection is having an overall impact on the efficiency of production by the dairy industry, even though it is still in its infancy. Farmers now have the best available genetic tools to implement the genetic improvements more rapidly. The greatest advantage is being seen in traits that have been difficult to measure or influence, which means that new generations of dairy cows will have longer and healthier productive lives.

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**Funding provided by California Dairy Research Foundation and the International Milk Genomics Consortium**

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