



### SPLASH! milk science update January 2015 Issue

This month's issue explores dairy's effect on mortality, vouchers to incentivize mothers to breastfeed, clues from seals to solve premature milk loss, and improving infant formula with bovine osteopontin.

#### Milk and Mortality

- **A prospective study of 61,433 Swedish women and 45,339 Swedish men found that higher milk intake was associated with higher mortality.**
- **Higher intake of cheese and yogurt among the Swedes was associated with lower mortality.**
- **A prospective study of 94,980 Japanese men and women found that higher milk intake was associated with lower mortality.**
- **Correlation studies of two factors, "A" and "B," do not show "cause and effect"; there is likely a "C" or third factor involved.**
- **For the Swedish study, the different genetic backgrounds of study subjects is a possible third factor.**
- **The totality of the evidence suggests that milk is beneficial for bone health and cardiovascular health.**

A research article published in the British Medical Journal on dairy intake and mortality is causing a lot of fuss [1]. So far, the journal has published 45 rapid responses to this article compared with an average of 3 responses to other articles in the same issue. What's all the fuss about?

Researchers followed 61,433 Swedish women and 45,339 Swedish men for 20 years, recording death outcomes and fracture events [1]. They also estimated milk consumption based on a food frequency questionnaire. Surprisingly, they found that women who drank more than three glasses of milk per day had more hip fractures than women who drank less than one glass of milk per day. High milk intake was also associated with higher all-cause mortality in both men and women.

Meanwhile, published in the same month, a study of 94,980 Japanese men and women followed for a median of 19 years came to opposite conclusions [2]. The investigators found that higher milk intake was associated with lower all-cause mortality.

How could these studies come to opposite conclusions? First, the people in the two studies drank very different amounts of milk. The Japanese people were asked whether they drink milk "never," "1-2 times per month," "1-2 times per week," "3-4 times per week," or "almost every day," and 43.6% reported that they drink milk almost every day. The Swedish people drank up to 6 glasses of milk per day (1-2 glasses per day on average). Second, the two study populations had completely different genetics and environment, which is a fancy way of saying that everything about them was different.



At the end of the day, neither of these studies tells us anything about cause and effect. Just because "A" is associated with "B," does not mean that A causes B. Often the real cause of B is a third or "C" factor, that is linked to both A and B. In a classic example, increased ice cream consumption is associated with increased shark attacks. Do sharks especially love humans who have just eaten ice cream? Fleshy outside with a creamy center? No, it just so happens that ice cream intake and shark attacks are both correlated with a third factor—warm weather.

Occurring less often than a third factor—though also possible—is a phenomenon called "reverse causation," where "A" and "B" are linked, but "B" causes "A." The authors of the Swedish study acknowledged that it is possible that women who were at higher risk of bone fracture may have responded by drinking more milk to prevent it [1].

In nutrition research, identification of a causal factor through observational studies is particularly impossible because nearly every diet component is correlated with every other component in the diet. If one food component is increased, another is necessarily decreased. In the Swedish study, high fluid milk consumers may have eaten less cheese and yogurt. Likewise, some food items often co-occur. The six glasses of milk that some Swedish people partake may not be a problem, but what about all of the cookies that go with the milk?

One might wonder why scientists ever bother to conduct observational studies of human nutrition when the results are suspect and tell us nothing about cause and effect. Randomized controlled trials are very expensive, especially if they are to span human lifetimes. Observational studies in humans, when paired with plausible mechanisms, provide at least some evidence on which to base dietary recommendations.

The authors of the Swedish study were motivated by the theory that galactose—a breakdown product of lactose—may have detrimental health effects [1]. On the face of it, this sounds unrealistic considering that babies have been exposed to loads of it 24/7 since the beginning of human time. Putting that thought aside, the data of the Swedish study doesn't really support the galactose theory. The researchers found that a higher intake of cheese and yogurt was associated with lower mortality [1]. Given that cheese and yogurt contain galactose at levels similar to those in fluid milk [3–4], the negative effects of fluid milk, if there are any, cannot be explained by galactose.

Is there a “third factor” that could explain the milk and mortality associations among Swedes? Possibly, genetics. The DNA mutation that allows some people to drink milk into adulthood provided such a strong survival advantage that it spread rapidly in geographically isolated populations [5–7]. When a DNA mutation is highly favorable, its selection enables nearby deleterious mutations to persist [8]. This “hitchhiking” of deleterious mutations has even been observed near the lactase gene [9]. Thus it is expected, on principal, that those who can consume lactose will have a different disease risk from those who cannot, independent of whether they actually drink milk [10].

In the Swedish study [1], the genetic background of the study subjects is unknown. If they had a similar incidence of the 13,910\*T allele—the lactase persistence allele—to that of Swedes in other studies [11], then it could be expected that 60.5% of the subjects had an excellent ability to break down lactose (T/T), 32.9% of them had a moderate ability to break down lactose (C/T), and 6.6% of them had no ability to break down lactose (C/C). It is likely that a higher proportion of Swedish subjects drinking 0 or 1 glass of milk per day would be C/C or C/T (with fewer hitchhiking deleterious mutations), compared with subjects drinking more glasses of milk per day. It's also likely that this subset of the study population consumed more fermented milk products. Therefore, genetic background is a possible “third factor.” If milk consumption is correlated with lactase allele incidence and lactase allele incidence is correlated with disease risk, then milk consumption will be linked with disease risk even though milk consumption is not a causal factor. While it has not been proven and is admittedly just a hypothesis at this point, it is possible that the Swedish subjects' “genetic background” could be like the “warm weather” for ice cream and shark attacks.

What's the bottom line? In the absence of better evidence, the dietary recommendations—three glasses of milk per day for U.S. adults [12]—will not change. The totality of the evidence suggests that milk is beneficial for bone health and cardiovascular health. Consumers can relax and enjoy their ice cream without fear of sharks.

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## Should Breastfeeding Mothers be Paid?

- **A pilot study in poorer areas in northern England is testing whether offering new mothers shopping vouchers helps increase breastfeeding rates.**
- **The results so far suggest that the scheme does achieve this aim.**
- **Opinion is divided, however, as to whether this would be a good use of public finances.**

Is offering vouchers to mothers, who are statistically unlikely to breastfeed, bribery—and thus a misuse of public funds—or is it smart public health policy? Since November, this question has been debated in the north of England, prompted by a short summary of a study that appeared in medical journal *The Lancet*[1].

The logic behind the scheme is simple. Breast, as the saying and the evidence goes, is best. Breastfeeding lowers the odds that infants will develop various illnesses, and in some studies has been linked to benefits that run into adulthood, including higher IQ and lower chances of becoming obese. But women living in poorer neighborhoods of developed countries tend to have especially low breastfeeding rates. These women seem likely to have a strong desire for vouchers that can be spent at supermarkets. The idea is therefore to raise breastfeeding rates in these neighborhoods—giving kids born in them a better start in life—by using vouchers to reward mothers who hit breastfeeding milestones.

So far, only a small, pilot study is underway in England, although plans are afoot for a randomized, controlled trial at a later date. In the pilot, vouchers are awarded for reaching two days' breastfeeding, 10 days, six to eight weeks, three months, and six months. To confirm that the milestones have been reached, signatures are required from both the mothers and healthcare professionals.

The pilot study has been taking place in three neighborhoods in the counties of Derbyshire and Yorkshire, where 58 of 108 eligible women have joined the scheme. Historically, breastfeeding rates have hovered in the region of 21%-29% at six to eight weeks in the areas from which the enrolled women come. That is low compared to the average of 46% for all of England[2], in 2013-2014. It is also low given the World Health Organization's advice to breastfeed exclusively for the first six months of an infant's life[3].

Crucially, 21-29% also looks low next to the 34% of the 108 eligible women who claimed vouchers corresponding to having breastfed for six to eight weeks. This implies—because some women not enrolled probably hit this milestone, too—that the actual breastfeeding rate at this stage is even higher. (Another way to think of this statistic is that 64% of those who enrolled managed to breastfeed for six to eight weeks.) To be sure, the sample size of the pilot study is small and the data are still coming in, but the initial signs show that the strategy works.

Could this work elsewhere? If so, how is it likely to be received? It has already been tested in Quebec, Canada, where mothers were paid \$55 Canadian for each month of breastfeeding.



In the UK, as in Canada, health costs are pooled across the whole country, with all citizens able to receive medical care that is free at the point of use via a national health system. By improving infant's health through increased breastfeeding, this scheme potentially reduces the wider financial burdens on the healthcare system. As a result, payment for breastfeeding is likely easier to justify to British and Canadian taxpayers than to those of many other countries, such as the US. Not that everyone in England thinks it is a good idea. One fairly well known writer went so far as to call the scheme "patronizing" and "naïve", claiming, "no woman in

history has ever successfully breastfed without being convinced in her heart that it was right for her and her child"[4]—clearly forgetting the entire history of wet-nursing.

Yet the Centers for Disease Control's data suggest that this sort of program could have important health benefits in the United States as well. Breastfeeding rates in less well-off states are very low: the CDC's PRAMS surveys[5], reveal that women in Mississippi are less than half as likely to still be breastfeeding four weeks after giving birth as are women in wealthier states like Washington, Colorado, Oregon, and Utah.

The disparity is the same in many countries. There tends to be pressure on poorer new mothers to go back to work sooner than if they had a bit more in the bank, or to take informal work where the basic legal minimums of employment law are not upheld. In short, it is typically harder for them to breastfeed for many weeks compared to richer women. Voucher schemes for breastfeeding should not be evaluated by what people choose to buy with their vouchers, as some wealthy commentators may be tempted to focus on. Instead, what matters is whether they deliver public health gains for kids in relatively deprived areas at little cost.

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## Protein for Babies: Too Much of a Good Thing

- **When milk production stops, the mammary gland regresses.**
- **Scientists have searched for the factors controlling this process for decades.**
- **Seals have evolved a mechanism for preventing milk production from switching off.**
- **Comparison of seals and other species identifies the milk protein alpha-lactalbumin as a key switch.**

Removing the suckling drive is quickly followed by changes that we refer to as involution, which returns the mammary gland to a pre-lactating state. There is an element of pre-programming involved here, but sometimes milk production just stops, and that suggests that specific milk or mammary factors play a role.



Scientists have been searching for the involution factor in milk for many years, and even gave the mysterious unknown factor a name, FIL, which stands for “feedback inhibition of lactation” factor. What is the factor? There has never been an adequate description or identification of the factor, but evolution has provided us with experiments of nature that may have provided an answer.

Evolution has generated a great diversity of physiological solutions to deal with circumstances that benefit survival strategies for different species. This includes reproductive and lactation strategies. A fascination with this species diversity has led scientists to study comparative lactation, which in turn has provided insights into the physiological mechanisms of mammary gland biology. An intriguing insight into what may be triggering involution comes from the study of seals [1].

There are three groupings of seals, but only the fur seals and sea lions have evolved a strategy that allows them to leave newborn pups on land while the mother spends days, or even weeks, foraging for food at sea [2,3]. Clearly there is no suckling during these trips and production of milk is essentially stopped. However, lactation resumes when the mother returns to shore and an intense period of suckling before returning to sea to repeat the cycle. In other words, fur seals are resistant to a trigger that, in most mammals, would result in involution. This seemed like a great system to search for clues into the factor controlling involution.

Milk commonly contains protein, lipid (fat), and carbohydrate (mainly as lactose or milk sugar). Carbohydrates provide energy for growth and a healthy gut. However, the amount of each component varies between species, and the composition of fur seal milk is notably different. Analysis of fur seal milk shows that there is no lactose. This provided the lead, because the production of lactose is dependent on a milk protein called alpha-lactalbumin (LALBA).

A great way to study milk proteins is to look at the genes that encode them by examining the animal's genome. The challenge with the fur seal study was that they are not widely studied so no one had developed the research tools for studying their genomes. However, seals are most closely related to the canine family and so they began by using tools that were developed for studying dog genomics. The relationship to dogs turned out to be close enough for the use of canine gene expression analysis methods using micro-scale arrays, a way of analyzing thousands of genes simultaneously. They used this analysis to look for molecules in the mammary glands that were associated with programmed cell death (called apoptosis). When they compared the seal mammary gland to human, cow and mouse, what became clear was that there was an absence of a gene called LALBA. A closer examination of the genome revealed a mutation in the fur seal genome that essentially prevented the LALBA gene from making the protein alpha-lactalbumin. Was this the clue to the apoptosis-causing molecule that initiates involution?

To answer this question, Sharp et al [1] turned to cell culture experiments. They mixed varying concentrations of the bovine alpha-lactalbumin protein with mammary cells from cows, mice and seals. They found that when higher doses of alpha-lactalbumin were added, the cultured mammary cell structures became disrupted and died. This was a direct correlate of what happens in the mammary gland during involution, and is the best laboratory based model available. Similar results were found independently in cultured bovine mammary cells by Riley et al. [4].

There was one major question raised by this finding was, how can a milk protein act as a trigger if it is always present in milk? One of the key differences may be that particular forms of alpha-lactalbumin are required. Indeed when looking into this issue more closely, Sharp and her colleagues found that two molecules of alpha-lactalbumin combined (called a dimer) had the highest level of apoptotic activity. They also found that a small percentage of alpha-lactalbumin is usually present in this form. We know very little about what controls the levels of dimerization, or whether it increases during lactation, but it is a wonderful example from nature into how milk production may end, and how involution may be initiated.

The challenge is now to find if there are ways of modulating this effect, to improve our ability to help prevent or reverse involution, for example, when a mother prematurely stops producing milk.

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## Building Better Options: Bovine Osteopontin in Infant Formulas

- **Constituents added to formula can shift infant biology closer to breastfed infants.**
- **The protein osteopontin is highly concentrated in breast milk.**
- **Adding dairy-derived bovine osteopontin to formula shifts infant biology closer to that of breastfed infants.**

Cow's milk, wheat flour, and sugar mixed together was the first recipe whipped up by Henri Nestlé's in the mid-1800s marketed as "farine lactée." However, infant feeding-practices have been widely variable historically and cross-culturally for thousands of years, if not longer (1). Infants have been fed combinations of animal milks, cereal grains, meat broths, juices, tea, and a diversity of supplemental culturally specific infant foods (1). More recently, improved research instruments and techniques have yielded new information, leading to the reformulation of commercial artificial breast milks. Infant formula now typically includes long-chain polyunsaturated fatty acids (LCPUFAs) (2) and lactoferrin (3,4). Versions of formula that feature prebiotics and probiotics are also commonly available (5,6). Might bovine osteopontin be the next ingredient to be added to infant formulas?

Osteopontin is a protein that serves important biological functions in our bodies. The protein contributes to wound healing and inflammatory immune responses by stimulating the actions of immune cells (7,8). Osteopontin is also important for bone development and maintenance (7,8). The concentration of osteopontin in human breast milk is higher than in other body fluids, and, on average, ten times higher than the concentrations currently in infant formula (9). The high concentration of osteopontin in breast milk, even higher than in the maternal blood stream, indicates that up-regulation of osteopontin occurs specifically in the mammary gland. This could be because osteopontin serves specific purposes for mammary gland function and/or for biological effects when ingested by the infant.



Recently Donovan and colleagues expanded our understanding of how consumption of osteopontin during in early life affects infant biology (10). In an experimental monkey model, researchers evaluated numerous developmental systems in the context of breastfeeding, formula-feeding, and the differences between formula with and without bovine osteopontin (bOPN). Infants were reared either by their mother, or reared in an infant nursery using standardized methods (11). Within the nursery context, infants were fed either a standard control infant formula as commercially available, or supplemented with bOPN for the first three months of life. This is a particularly strong study design because there were “within nursery” comparisons. For over six decades, psychologists have demonstrated the numerous behavioral, psychological, and neurobiological differences that emerge when infants are nursery-reared (11). These differences cannot be explained solely by the different early life diet, because limited social environment, absence of maternal behavioral care, and restricted maternal microbial exposure are substantially different between nursery-rearing and mother-rearing conditions.

Importantly however, the breastfed and formula-fed groups showed many similarities. Infants in the three groups had similar body weight, body length, and bone mineral density. The three groups also had similar abilities to deliver oxygen to their organs as measured by red blood cell counts and hemoglobin concentration. On a macro-level, their immune systems were similar; all groups had the same total number of white blood cells, although there were some differences in the specific types of white blood cells between the formula-fed groups and the infants consuming mother’s milk. Breastfed infants had a higher percent of neutrophils— first-response immune cells to microbial infection. Accumulations of dead neutrophils at the site of an infection are more colloquially referred to as “pus.” Breastfed infants also had slightly lower percentages of lymphocytes, adaptive immune cells “programmed” to selectively target specific pathogens more commonly called “antibodies.”

A more nuanced investigation of the transcriptome of the intestinal tract revealed other important differences among the groups. Differences were present in the expression of genes that influence immune system, cell cycle, cell motility, neuronal development, and protein processing (among others). In all, over 1000 genes were differentially expressed between the breastfed group and the formula fed groups, with expression generally greater in the breastfed infants vs. formula-fed infants (88% vs. 12%). However, infants fed bOPN formula fell intermediate between the breastfed and control formula-fed groups on nearly half of the differentially expressed genes. These results demonstrate, in a controlled setting, that the addition of bOPN to formula shifted intestinal gene expression in infant monkeys toward the “typical” developmental patterns of breast-fed baby monkeys.

Given the major differences in early environmental contexts between the nursery and mother-rearing, that the inclusion of one milk constituent contributed to a partial “recovery” of typical infant development in the intestinal tract is incredibly gratifying. These results motivate further research beyond investigating the expression of these genes in cells in the intestinal tract, but expanding into other areas of the body, particularly the brain. Given the bidirectional communication along the gut-brain axis, we can predict that changes in gene expression in the gut may be paired with changes in gene expression in the brain.

As animal scientists continue to investigate the potential benefits of bOPN in formula, food and dairy scientists can identify and optimize dairy streams to recover these proteins for economical availability for use in infant formulas. The marriage of basic research in lactation biology with innovations in dairy science will continue to improve infant formula. Fortunately, the sophistication of the experimental “guess and check” has exponentially advanced since Henri Nestle took his crack at it nearly 200 years ago.

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