



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



This month's issue features how high-fat yogurt lowers the risk of depression in women, how breastfeeding may help infants at risk of autism, how human milk helps preterm infants at risk of retinopathy, and how more serotonin in cows diminished milk fever.

### **Eating High-Fat Yogurt is Associated with a Lower Risk of Depression in Women**

- **Previous studies have shown a link between diet, and particularly the consumption of prebiotics and probiotics, and mental health.**
- **In a large-scale longitudinal study of Spanish university graduates, researchers examined the effects of consuming prebiotics or probiotic yogurt on depression.**
- **The new study found that eating whole-fat yogurt was associated with a lower risk of depression in women, but consuming low-fat yogurt or prebiotics was not significantly associated with depression risk.**
- **It's not clear from this study why a lower risk of depression was associated with high-fat yogurt but not low-fat yogurt or prebiotic consumption, or why the association was only significant in women.**
- **More observational and interventional studies in different populations will be needed to understand the causal mechanisms behind this association and reach broader conclusions about whether eating high-fat yogurt can help with depression.**

Over the past few years, researchers have found several intriguing links between diet and mental health. For example, unhealthy diets have been associated with a higher risk of developing depression, while healthy diets may instead have a protective effect [1–6]. These effects are thought to be at least partly mediated by the gut microbiome and may be influenced by both prebiotics and probiotics [7–9].

“Some animal studies have shown an association between prebiotic and probiotic consumption and mental health,” says Aurora Perez-Cornago at the University of Navarra. “We wanted to see what happens in humans,” she says.

Along with Miguel Angel Martínez-González and colleagues at the University of Navarra, Perez-Cornago conducted a longitudinal study of Spanish university graduates over more than nine years to examine the effects of consuming probiotic yogurt or prebiotics on depression [10]. The researchers found that eating high-fat yogurt was associated with a lower risk of depression in women.

“Previous studies have determined foods and also dietary patterns or lifestyles that have been related to lower depression rates,” says Perez-Cornago. “This is the first prospective study that has analyzed the association between yogurt and prebiotic consumption and depression risk,” she says.

Perez-Cornago emphasized that the study only shows an association, not cause and effect, and more studies will be needed to make any broader conclusions about whether eating high-fat yogurt can help with depression. “This is very novel area of research, and we need many, many more studies before recommendations can be given to people concerned about mental health,” she says.

Studies have shown that commercial yogurt lowers the risk of diseases such as obesity and metabolic syndrome that have been associated with depression [11–14]. Commercial yogurt that contains a high enough concentration of live beneficial bacteria also serves as a probiotic and could influence mental health through its effects on the gut microbiome.

“There is a hypothesis that the association between diet and depression might be driven at least partially by the gut microbiota and gut health,” says Perez-Cornago. “That’s what promoted us to do this research looking at these specific food groups that are important for gut health,” she says.

The researchers used food-frequency questionnaires to assess the consumption of high-fat yogurt, low-fat yogurt, and prebiotics among 14,539 Spanish university graduates. They then analyzed the association between yogurt or prebiotic consumption and depression.

Perez-Cornago and her colleagues found that consuming high amounts of high-fat yogurt was associated with a lower risk of depression, and this association was only significant among women. There was no association between prebiotic or low-fat yogurt consumption and depression risk.

“We were surprised that we saw differences between high-fat and low-fat yogurt because our hypothesis was that the beneficial bacteria in the yogurt might be the ones that result in this association between yogurt consumption and lower depression rates,” says Perez-Cornago. “Because low- and whole-fat yogurt don’t differ in bacterial composition, this



probiotic hypothesis does not appear to fully explain the association that was found in this study,” she says.

It’s still not clear why the association was specific to high-fat yogurt and not low-fat yogurt or prebiotics. “We need more studies to determine why there is a low- and full-fat yogurt difference in this association,” says Perez-Cornago. “We were also expecting to see an association between prebiotics, and we didn’t find an association,” she says.

More studies will also be needed to figure out why the association between high-fat yogurt and lower depression risk was only significant among women. “Women have a higher incidence of depression than men in general, so they are more likely to suffer depression, but we don’t have any data to explain why women and not men had lower rates of developing depression if they consume high-fat yogurt,” says Perez-Cornago.

Follow-up studies could try to tease apart the associations between yogurt and depression and get at causal mechanisms. “What we think needs to be done are randomized controlled trials with people with depression, to give these participants yogurt to see if it actually decreases depression,” says Perez-Cornago.

Perez-Cornago also pointed out that her study was conducted in a specific Spanish population, and suggested that similar large-scale studies should be conducted in other populations. “Before any recommendation can be given to a general population, especially women concerned about their mental health, we think that we first need to know why there is a difference between low and full-fat yogurt and also need to repeat this in other populations,” she says.

“I think this is a very promising field, but it’s still in its infancy,” says Perez-Cornago. “We need many more studies before any conclusions can be reached.”

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## Breastfeeding Molds Eye Contact in Infants at Risk of Autism

- **A variant of a gene called CD38 is associated with an increased risk of autism.**
- **The increased risk is associated with a tendency to produce low levels of the hormone oxytocin.**
- **Among infants with this particular gene variant, low oxytocin levels appeared to be “topped up” by their mother’s breast milk and somewhat functionally corrected.**
- **This “topping up” was evidenced by an experiment that measured the attention that infants paid to different sets of eyes conveying emotions.**

There is a version of a gene called CD38 that has a curious association with human behavior. This is because CD38 activity influences the release of the hormone oxytocin, occasionally nicknamed the “love” hormone but more broadly understood as a modulator of empathy and trust. Oxytocin is also found in breast milk. For this reason, a recent study [1] reports that the longer infants who are genetically predisposed to produce low levels of oxytocin are exclusively breastfed, the more they behave as though their brains made normal amounts. With additional research, this insight could offer a means of reducing the odds of developing autism among people born with this particular genetic risk factor.

The CD38 gene sits on chromosome four. It is made up of eight sections, known as exons, of which one occasionally appears in a version called rs3796863. This is also called the “C allele.” When an individual has two copies of the C allele—one on each pair of chromosome four—cells in the brain release less oxytocin than they would if there were two copies of the A (normal) allele—or, for that matter, one copy of the C allele and one of the A.



Autism, like most complex behavioral disorders, has various genetic risk factors. Nonetheless, research supports a correlation between having two C alleles of CD38 and a higher-than-usual risk of autism. In one such study [1], which looked at [Israeli families](#) with a history of autism, individuals diagnosed with autism spectrum disorders had much lower CD38 expression levels than unaffected members of their immediate families.

The reason low CD38 expression—and thus low oxytocin levels—confers a risk of autism seems to have something to do with how we learn to pay attention to important social cues during development, especially to emotions conveyed by the eyes. A key study published in [Nature in 2013](#) [2] tested how much attention infants pay to the eyes of caregivers. Those who were later in life

diagnosed with autism showed a normal level of eye attention during at least their first month or two of life. Then, between two and six months of age, this tailed off—these individuals made less eye contact with their caregivers compared with infants who did not go on to be diagnosed with autism. In other words, the study suggested that development of autism begins in infancy.

Subsequently, in 2015, a group of researchers including [Simon Baron-Cohen](#), director of Cambridge University’s Autism Research Centre, in England, found they could increase eye contact in adult men with autism (as well as in men without autism) by administering a [nasal spray containing oxytocin](#) [3].

Together, these threads of new knowledge suggested that a widespread, external source of oxytocin for infants—breast milk—might, unbeknownst to science, be having essentially the same effect as an oxytocin nasal spray. If that were the case, it would mean that breastfeeding is especially important in the development of infants with two CC alleles of CD38, since it “top-ups” their naturally low oxytocin levels. This is exactly what [Kathleen Krol](#), of the University of Virginia, Charlottesville, and her colleagues set out to test [4].

Krol’s team designed an experiment to measure the attention paid to emotional eyes by 98 seven-month-old infants. First, they tested whether their young participants spent more time looking at eyes conveying fear, anger, or happiness rather than a neutral expression. As other scientists had previously shown, they found that the infants in their study displayed a stronger bias for staring at fearful eyes than at eyes conveying other emotions, which is understood to be an evolutionary adaptation to help infants notice danger in their environment. And in general, infants spent more time looking at a picture of eyes conveying any emotion, compared with a picture displayed next to it that showed emotionless eyes.

The researchers then picked apart these data using information about each infant’s CD38 genotype—that is, whether they had CC, AC, or AA alleles—and records about each infant’s exclusive breastfeeding period. This revealed the startling finding the researchers had originally hypothesized.

Among infants at greater risk of developing autism—the CCs—breastfeeding increased their preference for looking at happy eyes and reduced their preference for looking at angry eyes. In other words, the longer that the at-risk infants consumed only breast milk, the more similar their behavioral development was at seven months of age to infants with AC and AA genotypes.

This finding is extraordinary because it suggests that oxytocin in breast milk goes some way to “correcting” the early developmental consequences of having a CD38 genotype that puts one at risk of autism. Many questions remain, however. At present, it’s unclear whether the breastfeeding effect permanently alters CC infants’ path of development, or merely adjusts it temporarily. And, as previously mentioned, many [other genes](#) are thought to alter the odds of developing autism spectrum disorders. Still, rarely does science come up with such a simple advice for families in which the condition is common: if at all possible, do not cut short the World Health Organization’s recommendation for six months exclusive breastfeeding, and if you can, keep up breastfeeding beyond that, as you introduce your infant to other foods. It may have an important impact on your infant’s development.

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## Human Milk Lowers Risk of Retinopathy Among Preterm Infants

- **Retinopathy of prematurity occurs as a result of the stopping and starting of blood vessel growth that often occurs in the retinas of very young preterm infants.**
- **A new meta-analysis finds that feeding preterm infants human milk reduces their risk of them developing the disease.**
- **Human milk's protective effects are likely due to specific chemical constituents that help to regulate the restarting of blood vessel growth in the retina.**
- **The policy advice that this study offers—to give preterm infants human milk—may have a particularly important impact on the incidence of retinopathy of prematurity in developing countries.**

Retinopathy of prematurity (ROP) is a common affliction of very young preterm infants that can lead to blindness. It occurs when the blood supply to the retina develops abnormally. In some cases, this problem is so severe it can cause the retina to detach from the back inner wall of the eye. Decades ago, medical researchers demonstrated a difficulty in the care of the tiniest preterm infants: supplying these infants with lots of oxygen improved their chances of survival, while at the same time increasing their risk of ROP. A recent meta-analysis, however, offers more straightforward advice to neonatal intensive care units: Providing human milk to a very young preterm infant—whatever amount is available—significantly reduces the risk of the disease.

The authors of the meta-analysis, which was recently published in the *Journal of Perinatology* [1], carefully selected relevant studies with data on both the frequency and severity of ROP among preterm infants that were and were not fed human milk. Of the 1,701 infants in these studies who received human milk, 509 (29.9%) developed ROP of any level of severity. Meanwhile, of the 760 infants in these studies who were not fed human milk, 310 (40.8%) did. The meta-analysis's authors—neonatologist Salim Bharwani of Pediatrix Medical Group and The Woman's Hospital of Texas, in Houston, and his colleagues—found those differences to be statistically significant.



Normally, as a healthy fetus develops in utero during the third trimester, molecules present in its environment are thought to guide retinal development. But this aspect of development can suddenly stop if the infant is born early. Not only are those chemical factors now absent, but the moderate, consistent supply of oxygen that is delivered via the placenta is interrupted, and replaced—at least initially—by room air, which has a much higher oxygen pressure than the inside of the uterus. ROP then emerges as the infants' body tries to compensate for these sudden changes.

The sudden jump to a higher oxygen environment prompts the growth of blood vessels in the retina to halt. This, in turn, leads to the development of hypoxia in the retinal cells, because they are still metabolically active and no longer being supplied with sufficient oxygen by the bloodstream. Cells raise the alarm by producing two

molecules to come to their rescue: erythropoietin and vascular endothelial growth factor (VEGF), which both stimulate blood vessel growth in the retina. However, these new blood vessels, erected in haste, tend to be leaky, and their growth can create fibrous scars. Because of the slap-dash nature of this compensatory blood vessel growth, retinal detachment becomes a risk [2].

Why should consuming human milk prevent any of this? Although the recent meta-analysis did not investigate this question, its authors do offer some suggestions. In short, they argue that some of the chemical constituents of human milk act to regulate the hurried restarting of blood vessel growth that can cause ROP.

Firstly, human milk contains many antioxidants, some of which are preferentially accumulated in the eyes. By reducing oxidative stress, these chemicals reduce the amount of VEGF that is produced by retinal cells, and hence the rapid proliferation of blood vessels within the retina. Human milk's high content of IGF-1 (compared with cow's milk [3], for example), is thought to have a similar effect: IGF-1 is another VEGF regulator.

A third VEGF regulator is an omega-3 long-chain polyunsaturated fatty acid called docosahexaenoic acid (DHA) [4]. DHA's importance in the proper development of the retina is implied by the simple fact that a healthy human has a higher concentration of the compound in the outer segments of their retinal photoreceptors than in any other bodily tissue [5].

A developing fetus or preterm infant cannot make its own supply of DHA. As such, a fetus depends on its mother's body sending DHA through the placenta, and a preterm infant does not receive any DHA unless supplemented. Human milk, by providing some DHA, compensates in part for the interruption in the placental supply.

The history of ROP is often described as a series of three epidemics. The first epidemic appeared in rich countries in the 1940s and 1950s, as infants of very low weight or younger than 32 weeks gestational age started surviving. Understanding of the complications of providing high oxygen to preterm infants then pushed the ROP incidence back

down. The second epidemic occurred in the 1970s, as rich countries again lowered the age of survival for preterm infants—and again new methods of ROP detection and treatments reduced its impact [6]. Since the 1990s, ROP has been an emerging problem in poorer countries as their ability to care for preterm infants catches up—but neonatal units often lack the equipment to continuously monitor infants placed on supplemental oxygen. This has been called the third ROC epidemic [7].

In the midst of the third epidemic, tens of thousands of infants each year are becoming blind early in life. The kind of clear advice provided by this meta-analysis offers hope not only for premature infants cared for in high-tech neonatal intensive care units in the developed world but also for those cared for elsewhere.

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## Happy Cows to Reduce Milk Fever

- **Milk provides a rich source of calcium.**
- **The calcium in milk is redirected from the diet and other sources in the body.**
- **About 5–10% of dairy cows do not keep pace with balancing calcium, resulting in milk fever.**
- **Serotonin affects mood but has also been found to influence calcium levels.**
- **Treatment of dairy cows with serotonin helps to restore a balanced use of calcium.**

Serotonin is best known to us as a brain factor that affects mood, with high levels associated with euphoria. However, it has much wider effects in the body, influencing gut motility, blood vessels, and osteoporosis. To scientists, this points to an interaction with calcium, and as we all know, calcium is an important component of milk and dairy products. So does serotonin influence milk calcium, and could the mood of cows affect milk production? Recent research by scientists in Wisconsin suggests that serotonin has an effect on regulating calcium in the important transition period from late pregnancy through lactation [1].



Calcium demand is at a peak during pregnancy and lactation. Maintaining a steady balance of calcium intake through the diet, and having the necessary biological mechanisms in place to control and regulate the way in which it is utilized, are essential. However, sometimes the demand outstrips the supply, and the hormones that regulate calcium can't keep up. This can happen in many species but is a special challenge in dairy cows that produce relatively large offspring, and large volumes of milk. When cows are noticeably affected, it is referred to as milk fever. Estimates of the prevalence of milk fever in the USA are between 5–10%, and maybe greater than 20% if based on low concentrations of calcium in the blood of animals [2], so it is a condition that animal scientists have been studying for some time.

Calcium is found in high concentrations in milk and is actually an essential component of its micro-architecture. In addition, calcium is known to contribute to good health and is particularly well known for its role in promoting strong teeth and bones. But calcium is also critical for many other normal functions in the body. For example, it is found inside cells where it binds to proteins and is essential to the internal machinery of the cell. It is also found in the fluid that bathes the cells and keeps them healthy and functional. For some roles, it even has specialized micro-compartments so it can be available for rapid mobilization as required. A good example is how it is involved in allowing muscles to do work. Muscles are made from many muscle cells, or fibers, that are able to work together in an orderly manner to cause muscles to contract. They achieve this by sliding thousands of filaments made up of two long protein chains and found in every muscle cell, over one another. The sliding filaments are actually a very large number of overlapping, grab-pull and release

events that happen so quickly they result in a smooth contraction of the muscle. The key initiator of the contraction is calcium. Calcium unlocks a site on the proteins, allowing one to grab the other and complete one cycle of the sliding motion. So every time a muscle does any work, holding a posture, or walking, or even moving a finger, or turning an eye, calcium is involved.

What happens when there is not enough calcium to supply all of these events? One of the first signs is a collapse due to the inability of the muscles to function. This is what happens to some dairy cows in the period following calving when she has been challenged to provide lots of calcium to the developing calf during pregnancy, and then has the additional challenge of providing calcium for producing milk. The condition is treated by giving an injection of calcium, but the farmer needs to first find the cow and quickly respond, and can be a risk to the animal. So researchers have been investigating ways in which this condition can be best managed and prevented from happening.

Calcium is regulated by hormones, and particularly the hormone produced by a tiny gland found in the neck of the animal, the parathyroid gland. The gland produces parathyroid hormone (PTH) that controls the way in which calcium is absorbed, distributed and recycled in the body. The scientists who study hormones have been working on the issue of milk fever for some time, and the recent research by Weaver et al. [1] found an association between calcium levels and serotonin.

Serotonin is best known as a brain factor that is associated with mood and targeted in the treatment of depression. However, serotonin is also released in other parts of the body and has been found to influence a molecule that is similar to PTH, known as PTH-related protein (PTHrP). This control system influences calcium regulation at the level of the mammary gland and is important for calcium control during lactation [3–5]. However, most of these studies have previously been done in laboratory mice or rats, and there has been very little attention paid to the system in dairy cows. Weaver and colleagues set out to address this issue in two breeds of dairy cows, Holstein and Jersey [1]. Their approach was to directly infuse the cows with serotonin for a short period during late pregnancy.

What happened? The scientists monitored calcium levels in milk and in the blood of the cows and also measured hormone levels. They found that the levels of calcium were altered by the treatment with some differences between Holstein and Jersey cows. The pattern was generally a reduction in calcium levels in the blood in the period of infusion or immediately after the infusion, which was proposed as the stimulant for mammary gland PTHrP release and better regulation of calcium during the onset of lactation. The differences noted between Jersey and Holstein cows may be a focus for continued study. The data suggests that serotonin could be used to prevent milk fever, either by treating animals or looking for natural variants with higher serotonin levels. Whether the cows have naturally elevated levels of serotonin, or are treated with a synthetic form, the future application of this research should be conducive to happier cows and happier farmers.

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