SPLASH!® milk science update March 2017 Issue

This month's issue features mother's milk that "trains" infant immune cells, dairy fat and lower risk of diabetes, sex-specific mother's milk, and protective properties of dairy cheese on blood vessels.

Twin Study Suggests Moms Make Sex-Specific Milk

- **A new study comparing growth in twins reports breastfed same sex twins are taller and heavier than breastfed opposite sex twins during adolescence and early adulthood.**
- **Differences in body size between twin types were attributed to access to sex-specific milk by same sex twins during infancy.**
- **This new study provides indirect evidence to support the hypothesis that human mothers tailor milk composition to produce different ingredients or quantities of ingredients for male and female offspring.**

Lactation biologists have long known that human milk synthesis varies across and within mothers. In the search for sources of this variation, the spotlight has been primarily directed at maternal factors. But it takes two to nurse, and human infants are not simply passive consumers of milk. Infant characteristics, from low birth weight [1] to illness [2], are known to affect milk synthesis, primarily through an increase in the very ingredients needed to improve infant health, growth, or cognitive development. Human milk appears to be tailored to specific infant needs—one milk does not fit all.

Illness and birth weight are temporary characteristics that are associated with short-term alterations in milk composition. But what about something permanent, like infant sex? Do human mothers produce milk with different types or quantities of ingredients for boys compared with girls? Maybe—there have only been a handful of studies that compared human milk composition for boy and girl infants, and not all found evidence for sex-specific production [3–5]. However, the results of a new study [6] on growth in twins push that “maybe” closer to “yes.” Kanazawa and Segal found that same sex (SS) twins were taller and heavier than opposite sex (OS) twins but only if they were breastfed [6]. Could access to sex-specific milk be responsible for the growth advantage to SS twins?

Recipe for success?

Many parents raise their children emphasizing that they can do and become whatever they want, regardless of their sex (or gender). Breaking “gender norms” may be possible with respect to human culture, but natural selection and human biology are not so gender-neutral. Evolutionary success or fitness is measured by how well an individual passes their genes on to the next generation; what it takes to be an evolutionary successful female is not the same as what it takes to be an evolutionary successful male.

To relate evolutionary success to milk production, just look at differences between the sexes in growth patterns [7]. Human males are generally larger than females at birth and during infancy, have a later age at puberty, later start of the adolescent growth spurt, and cease skeletal growth as much as five years later than females [7]. Larger body size during infancy and throughout the life course may correlate with more energetically dense milk production for boys (including greater quantities of fat as an energy source and protein as a growth substrate), while an earlier puberty (and adolescent growth spurt) in females may favor production of milk components, including calcium and phosphorus, that aid in skeletal maturation.

Indeed, these are the very differences evolutionary biologist Katie Hinde identified in rhesus macaques milk [8–10]. Mothers of sons produced milk with higher fat and protein (and thus total calories) than those of daughters, while daughters received greater quantities of milk with higher concentrations of calcium. However, these signatures of male and female milk were more pronounced in first time mothers compared with those that already had offspring. Hinde suggests that first time mothers, who may still be growing and have fewer energetic resources than more experienced mothers, “cut corners” with daughters and produce lower quality milk because body size is less important for reproductive success in females than it is in males [8–10].

Human females may also produce higher energy milk for males. In a sample of 25 American mothers, those with sons (aged 2–5 months) produced milk with 25% more energy than those with daughters [3], and mothers of 4-month-old sons (n = 25) in Singapore produced milk with more fat, including more polyunsaturated fatty acids, compared with those with 4-month-old daughters (n = 25) [4]. Neither of these studies, however, measured milk volume or controlled for first versus later born offspring. In contrast, Quinn [5] failed to identify any significant differences in milk fat, protein, or total energy content relative to infant sex (or maternal experience) in her sample of over 100 Filipino mothers. In addition, sons and daughters (both first- and later born) nursed with similar frequency, suggesting they received similar quantities of milk [5].

Thus, it is not clear from available data on milk composition if there is a recipe for success for boys versus girls. If the data from rhesus macaques are included to look at an overall pattern in primates, sex-specific milk production may be limited to first time mothers and/or may involve differences in quantity of milk rather than simply milk energy, factors that have not been systematically investigated in humans.

A double take

Evolutionary psychologist Satoshi Kanazawa at the London School of Economics and Political Science and his colleague Nancy Segal at California State University, Fullerton, decided to tackle the issue of sex-specific milk production using a novel approach. Rather than collect and compare milk samples, they focused on growth data from twins [6]. They reasoned that if mothers were tailoring milk production to optimize the growth and development of boys or girls, mothers of OS twins would be in a biological pickle—they could not simultaneously produce milk tailored for a boy and a girl. Milk for OS twins could either be tailored for one sex or for neither sex. As a result, breastfed SS twins were predicted to have a growth advantage over breastfed OS twins [6].

To test this prediction, Kanazawa and Segal [6] utilized growth data from the National Longitudinal Study of Adolescent Health (Add Health). Over 20,000 American adolescents were interviewed (and measured) at four time points (or waves) between 1994 and 2008 (between the ages of approximately 15 and 29 years). From the larger sample, 779 individuals had either an SS twin (n = 546) or OS twin (n = 233). Data on breastfeeding came from interviews with mothers and were analyzed in the statistical models as never breastfed or ever breastfed, with the latter category including all individuals who were reportedly nursed for at least three months.

In addition to the categories of SS or OS twin and ever or never breastfed, the authors included several other variables that could potentially influence height and weight during adolescence, as these could potentially confound their results. These included birth weight (larger babies may be larger adolescents); sex (a female from a female/female twin pair was compared with a female from a female/male twin pair); age at time of measurement; and finally, zygosity, or whether the twins were identical (one fertilized egg) or fraternal (two fertilized eggs), a trait that may influence body size [6].

At the first wave (mean age = 15.6 years), no significant differences were found in height or weight between breastfed OS and SS twins. But at each of the other three waves (mean ages of 16.2, 22.0, and 29.1 years), breastfed OS twins were significantly shorter (nearly an inch) and lighter (by about 12 pounds) than breastfed SS twins. This finding alone is suggestive of tailored milk production, but the researchers found something even more telling.

"The original analysis only included the breastfed same sex and opposite sex twins, and demonstrated that the same sex twins were taller and bigger than opposite sex breastfed twins," explains Dr. Satoshi Kanazawa. "But my friend, the great developmental psychologist Jay Belsky, told me that the best demonstration of causality is to make it disappear."

Remembering the advice of Dr. Belsky, Kanazawa compared never breastfed twin groups. "If breastfeeding was causing the advantage enjoyed by same sex over opposite sex twins, then this advantage should disappear when you take breastfeeding away." When the data were analyzed to compare never breastfed twin pairs, no significant differences were found in body size between SS and OS twins. In fact, SS twins tended to be slightly shorter and lighter than opposite-twins [6]. "It was a reverse of the pattern found in breastfed twins," continued Kanazawa. "I was glad that I listened to Jay's words."

From infancy and beyond

Although the focus of the study [6] was sex-specific milk production, the results highlight another amazing feature of lactation—the effects are not short-term and limited to infancy. But when do growth differences between twin types first begin? Are breastfed SS twins always larger than breastfed OS twins? Unfortunately, the Add Health dataset only provides metrics from age 15, so it is not clear when the observed differences in height and weight first appear, or if it is a general pattern throughout infancy and childhood.

However, the lack of significant differences in weight or height at the first measurement time point suggests that SS twins might not always enjoy a size advantage. "This was an unexpected finding of our study," says Kanazawa. "We fully anticipated that we would observe an effect in all waves." It is interesting that SS twins were taller and heavier at ages 16, 22, and 29 but not at 15, and the findings are difficult to explain without any data points during late childhood or early adolescence. One possibility is that the benefits (in both weight and height) of sex-specific milk on growth are not fully realized until the completion of the adolescent growth spurt. Perhaps the measurement at a mean age of 15.6 years was catching many—but not all—females at the end of their spurt and fewer males, who end their growth spurt at least a year later. Another possibility is that breastfed OS twins started their growth spurts earlier than breastfed SS twins. Thus, at the first time point OS were relatively the same size as SS twins who were still growing, resulting in similar weights and heights. Whatever the explanation, it is quite remarkable that breastfeeding, perhaps for as little as 3 months, can be linked with patterns and rates of growth experienced over a decade later.

Sex matters

Differences in body size between ever breastfed OS and SS twins (and a lack thereof between never breastfed twin types) indirectly support the hypothesis of sex-specific milk production. However, could there be another explanation for the reported results [6]? What else could be specific to identical twins of either sex but not OS twins that would result in attaining higher stature and body mass? Kanazawa and Segal propose alternative explanations but find none of them satisfactory [6]. Kanazawa believes that the results strongly suggest SS twins can benefit from tailored breast milk whereas OS twins “may be at a developmental disadvantage.” When it comes to milk production, sex matters.

As an evolutionary psychologist, Kanazawa is interested in ultimate explanations or identifying adaptations produced by natural selection. Mothers who produced milk with ingredients that best facilitate and support sex-specific patterns of growth and development would have greater reproductive success and leave more progeny that would, in turn, carry genes for sex-specific milk production. Just how mothers know the sex of their offspring is up for debate, but it is likely that because of human’s invasive placenta, hormones or other signals of infant sex communicate with the mammary gland prenatally [11]. Kanazawa believes that OS twins are unable to take advantage of tailored milk composition and thus “may be evolutionarily selected against.” Selection against OS twins actually begins much earlier than during lactation, he explains. “Twin researchers have always assumed that dizygotic twins were just as likely to be same sex as opposite sex. But in large population samples in the US and the UK, there are actually significantly more same sex than opposite sex dizygotic twins.” Assuming the rates of conception of SS and OS dizygotic twins are the same, this would mean that SS twins have a better survival rate in utero than do OS twins.

Are the issues with fetal survival and milk production somehow linked? Although purely speculation, it is certainly tempting to suggest that human gestation (and concomitant mammary gland development) operate most successfully when receiving information from just one sex. “Mixed signals” from OS twins may affect fetal growth patterns or result in the production of low quality milk, which could have lower energy or reduced immune components, growth hormones, probiotics, or any number of factors that relate to growth, development, and health.

The hypotheses stated above are testable and hopefully lactation biologists will continue to investigate milk production for evidence of a specific recipe for boys and girls. Thus far, much of the research has focused on macronutrients in milk. However, milk contains numerous bioactive ingredients, including hormones that influence skeletal growth and body composition. Expanding comparative studies to include a larger number of ingredients (and measures of volume) may reveal patterns that can help explain Kanazawa and Segal’s findings.

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Dairy Fatty Acids Serve as Markers for Lower Diabetes Risk

- **Most prospective studies of the causes and preventative behaviors associated with common lifestyle diseases suffer from uncertainty over whether participants are completely truthful in questionnaires.**
- **A team of researchers has found a way of measuring the levels of certain fatty acids in blood instead of asking people how much dairy fat they eat.**
- **The blood fatty acids measure has been employed in two prospective trials and suggests that eating dairy fats confers a lower risk of developing type 2 diabetes.**

Ask an average citizen how much fatty food they eat, and the response is likely to be a sugar-coated version of the truth. Many studies that search for links between dietary habits and complex diseases face this problem. But what if there were particular molecules that hang around in blood, which could be used to diagnose how much of a relevant foodstuff an individual typically consumes? It would mean that the disease risks attached to eating the food could be stated with greater certainty. This is exactly what Mohammad Yakoob of Harvard Medical School and his colleagues have identified in three fatty acid constituents of dairy products. Analyzing measurements of levels of these fatty acids in the blood of thousands of people enrolled in prospective studies has led these researchers to conclude that dairy fats reduce the risk of diabetes [1].

The idea that dairy foods lower the odds of developing cardiovascular problems and type 2 diabetes is tantalizing to anyone interested in public health because it suggests cheap and actionable guidance for those at risk. In recent years, studies of the effects of low-fat dairy products such as yogurt tend to be straightforwardly positive: eating low-fat dairy as part of a balanced diet appears to lower the risk of diabetes. But, intriguingly, the results for cheese are not consistently different. As a high-fat food, conventional medical wisdom suggests that eating lots of cheese should be bad for long-term metabolic fitness. Yet some large studies have even shown cheese has a protective effect against diabetes [2,3]. How could this be?

One explanation for these results relates cheese consumption to the production of insulin. Whey protein—a constituent of dairy products—has been demonstrated to stimulate pancreatic cells to this effect. Another idea, favored by Yakoob and his team, proposes that similarities in the chemical structures of a dairy fat called trans-palmitoleate, and another fat that is made inside the human body, called palmitoleic acid, leads to interference with regulatory feedback loops [4,5]. This interference reduces the amount of fat the body synthesizes and increases the signal strength of insulin to muscle cells, causing glucose uptake into muscle tissue.

Yakoob and his team focused on three fatty acids: pentadecanoic acid, heptadecanoic acid, and the aforementioned trans-palmitoleate. Researchers working in the early 1990s on two large prospective studies, the Nurses' Health Study and Health Professionals Follow-Up Study, had measured the levels of these fatty acids in both the blood plasma and red blood cell membranes of study participants and also tested whether the participants had diabetes. Presumably, since most people are creatures of culinary habit, the study participants maintained the same dietary tendencies over time. The participants were retested for diabetes in 2010. Roughly two decades on, 8% of those who had been diabetes free before had since developed the disease.

The task for Yakoob and his team was to figure out the role of dietary dairy, if there was one at all, in this change in diabetes prevalence. Taking the blood fatty acid data, along with swathes of information about the participants' other diabetes risk factors, the researchers set about statistical modeling. They calculated that participants with blood plasma levels of pentadecanoic acid in the highest quartile had a 44% lower risk of diabetes than those in the lowest quartile (that is, after removing the influence of other diabetes risk factors, including body mass index). For heptadecanoic acid, the difference was 43%. For trans-palmitoleate, it the risk difference was 52%. When the levels of these fatty acids in red blood cell membranes instead of blood plasma were considered, the results were similar. They were also similar for men and women.

The upshot of this work is therefore that either the fatty acids themselves act to lower the risk of diabetes, or that some other constituent of dairy fat does. And unlike previous prospective studies that have tried to put a number on diabetes risk, sugar-coated memories of what participants snacked on throughout the day have not biased the results. Of course, the study also suggests a new diagnostic for diabetes risk. All things being equal, the higher the levels of these fats in your blood, the less chance you have of developing diabetes.

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Mothers “Train” Their Babies to Fight Disease

- **Components in milk with broad-spectrum antimicrobial activities protect suckling young from infectious diseases, particularly in the gut.**
- **Mother’s milk contains immune cells that fight specific pathogens in suckling offspring.**
- **Immune cells in mother’s milk “train” offspring immune cells to fight diseases experienced by the mother (*Maternal Educational Memory*).**

Mothers transmit more than genes to their offspring. Some intergenerational maternal influences can impact newborns through their ingestion of milk, which can enhance their chances of optimal growth and survival. Currently, the accepted opinion is that most of these maternal influences do not persist beyond weaning. However, there are scattered and tantalizing pieces of evidence suggesting there may be some exceptions to acceptance of that opinion [1–3].

Immune components of milk

Milk is more than a nutritional supplement exquisitely formulated to suit the exacting growth requirements of the newborn of mammalian species. Milk also contains a variety of immunoactive components that help protect newborns from diseases [3–6].

Some milk components, including protein peptides, complex sugars and proteins, have a multitude of nonspecific antimicrobial activities—the first defensive line against infections. These components primarily function in the newborn gut where they remain active because the gut digestive processes are immature and slow to act.

In a second defensive line against infections, ingested maternal antibodies protect the young from pathogens common in the environments of both the mother and offspring. The antibodies function in the newborn’s gut and also cross into the blood. There, these antibodies protect against specific pathogens throughout the body [6]. The antimicrobial components in ingested milk do not persist in weaned offspring, hence their protective functions are lost.

Maternal educational immunity

A recent investigation by scientists from The University of California, Riverside and the University of Tasmania demonstrated that immune cells in milk from mothers independently vaccinated against two disease-causing organisms can “train” the offspring’s immune cells to recognize and potentially defend against these specific organisms [7]. Importantly, the immune cell responses to these specific organisms persisted in the offspring well beyond weaning. Life’s scientific surprises never cease to amaze!

This form of acquired immunity is termed “maternal educational immunity” [7]. The study expanded upon previous research by the same group that demonstrated persistence of lactationally transferred immunity in offspring to adulthood [1]. The authors of the current report proposed a mechanism accounting for this previous observation.

The investigators used a mouse model with a foster nursing experimental design. They demonstrated that mothers immunized with *Mycobacterium tuberculosis*, which causes tuberculosis, or *Candida albicans*, a fungus that causes candidiasis in humans, produced milk that contained immune cells sensitized to these disease-causing agents. Pups born from unimmunized mothers were nursed by either immunized or unimmunized (control) mothers. This smart experimental design eliminated the possibility of placental transfer of immune cells from mother to pup and it allowed distinction between foster mother- and pup-derived immune cells.

The investigators detected one specific type of maternal immune cell, T cells, in the thymus and spleen of the nursed pups [7]. These T cells were specifically sensitized to the pathogens in the maternal vaccine. How these maternal immune cells gained entry into the offspring blood and these tissues is unclear. T-cells are white blood cells—lymphocytes—that play a central role in cell-mediated immunity to disease agents.

The most striking result of the study was that pup-specific T cells sensitized to the maternal vaccine but not the maternal T cells were present in the pup spleen long after weaning (at least one year). The investigators’ intriguing conclusion was that the maternal T cells “trained” the development of the pup-derived T cells that were sensitized to the two pathogens. How this happened is still a mystery.

Implications

The animals used for the study were mice, therefore, investigations need to be extended to other species. However, there are important implications of this research. First, from an evolutionary perspective, there would be a large advantage to offspring survival if the highly specific immune cell responses of the mother acquired from her pathogen challenges were permanently transferred to her offspring. After all, maternal pathogen challenges are likely to be shared with the offspring as they both live in the same environment. Second, the immune system of a newborn is immature and often poorly responsive to vaccinations [8], hence they are susceptible to diseases. The investigators involved in the study suggest that some vaccines may be better delivered to newborns by vaccination of the mother prior to pregnancy with subsequent reliance on maternal educational immunity through nursing.

The possibility of using maternal vaccination prior to pregnancy opens new avenues for protecting the young from disease. Perhaps wet nursing, a practice prevalent in human populations of the recent past, unknowingly provided protection from disease through a similar means [9]. The old becomes the new. Our understanding of the roles of milk components in offspring is still far from complete. Many more surprises still await.

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Dairy Cheese Protects Blood Vessels from Sodium's Harmful Effects

- **Increased dairy intake is associated with lower blood pressure and better cardiovascular health outcomes, whereas increased dietary sodium is associated with higher blood pressure and increased cardiovascular morbidity and mortality.**
- **A new study investigated the interplay between dairy and sodium consumption by examining the effects of consuming a high-sodium dairy meal and two high-sodium non-dairy meals on blood vessel function.**
- **The researchers found that a high-sodium meal consisting of dairy cheese had a protective effect on sodium-induced impairments in blood vessel function, whereas high-sodium meals consisting of soya cheese or pretzels did not.**
- **Administering an antioxidant improved blood vessel function after ingestion of the non-dairy meals but had no further benefit on blood vessel function after the dairy meal.**
- **The results suggest that components of dairy cheese have antioxidant properties that protect against the adverse effects of sodium on blood vessel function.**

Diet plays a major role in influencing cardiovascular health. For instance, increased dairy consumption is associated with a decreased risk of cardiovascular disease and lower blood pressure [1–3]. On the other hand, an increase in dietary sodium—consumed primarily as salt—is associated with increased blood pressure and higher cardiovascular morbidity and mortality [4,5].

"If we look at the epidemiology literature, people who eat a lot of salt tend to have worse cardiovascular outcomes, but people who eat a lot of dairy tend to have better cardiovascular outcomes than average," says Anna Stanhewicz at Pennsylvania State University. "We're interested in understanding the interplay between these two things," she says.

In a new study, Stanhewicz and her colleagues examined the effects of a high-sodium dairy cheese meal and two high-sodium non-dairy meals on blood vessel function [6]. "Cheese is a high sodium food that your cardiologist might recommend that you avoid, but it's also a high-dairy food that might be beneficial," says Stanhewicz. Their results suggest that consuming higher dietary sodium in cheese may not have the same harmful effects on cardiovascular health as consuming the same amount of sodium from non-dairy sources.

The researchers gave 14 participants a meal consisting of either dairy cheese, soya cheese, or pretzels. "It was important to us that the study have real-world validity, which is why we used normal amounts of sodium that you would have in a regular snack," says Stanhewicz. "If you were sitting down and watching a football game, you could very easily consume that many pretzels just there in one sitting," she says. The researchers then examined the effects of the meals on skin blood flow under different conditions. "The skin has been validated as a model for what's happening with other blood vessels in the body," says Stanhewicz.

Eating the dairy cheese improved participants' blood vessel function compared with eating the non-dairy meals. "When they ate the high-sodium snack without dairy, they had a reduction in our measure of blood vessel function, but when they ate the equal amount of sodium in the context of a dairy snack, they had a better measurement of vessel function," says Stanhewicz. "What we took away from that is that something in the dairy itself is protecting the vessel from this sodium-induced reduction in function," she says.

Stanhewicz and her colleagues were interested in figuring out the mechanisms behind dairy cheese's protective effects. "The literature suggests that there are a number of potential protective mechanisms," says Stanhewicz. "In this study, the one thing we looked at was the antioxidant properties," she says. In animal models, dairy peptides have been shown to reduce markers of inflammation and oxidative stress [7–9]. "Some of the bioactive components of dairy have been shown to have antioxidant properties," says Stanhewicz.

To examine the role of antioxidants in dairy's protective effects, the researchers repeated their experiment after administering a non-specific antioxidant to the same sites where they measured blood vessel function. "We found that the antioxidant improved vessel function following sodium without dairy, but it had no further benefit after subjects had eaten the dairy cheese," says Stanhewicz. "We concluded that antioxidant components of dairy might be contributing to its overall protective effect," she says.

Stanhewicz and her colleagues are planning a longer-term follow-up study where participants will eat diets high in sodium, high in dairy, or both for seven days. "In this follow up study, we're taking some clues from what we found in terms of the antioxidant properties of dairy and really moving forward with more mechanistic enquiries into the specifics of how that might be working," says Stanhewicz.

These and other follow-up studies could provide answers to remaining questions about the relationship between dietary sodium and dairy. "If you ate a pretzel and a yogurt separately, how would that affect things? The short answer is we don't know yet," says Stanhewicz. "Depending on what we see in our follow-up studies, we should be able to answer some of those types of questions," she says.

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