



### SPLASH! milk science update

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This issue of *SPLASH!* explores dairy, breastfeeding, and their metabolic impacts on the consumer. Articles cover the topics of [obesity and dairy consumption](#), differences in [appetite regulation](#) in breastfed and formula-fed babies, the relationship between [type 2 diabetes and dairy consumption](#), and a recently discovered link between milk and [neonatal growth](#). It's a great lineup.

Enjoy!

## Evidence for Thinner Dairy Consumers

- **Links between dairy consumption and obesity are inconclusive, but a notable proportion of studies indicate an anti-obesity effect.**
- **Two components of dairy—calcium and whey protein—are the main suspects for the association of dairy with lower body weight.**
- **Among consumers with moderate-to-high dairy intake, those whose genetics halt lactose production in adulthood have slimmer waistlines than lactase producers.**



Does dairy make you fat? Being rich in lipids, it should, right? But some evidence suggests that the calories in dairy are somehow easier to burn up than they should be. While the effect is subtle (and certainly not apparent in every set of data), it is sufficient for physiologists to wonder about potential biochemical explanations.

The evidence comes from epidemiological studies. These are hard to interpret because they often present a tangle of cause and effect.

The first tangle is called 'inverse caution bias', which describes a situation where obese people eat lots of low-fat dairy as part of an attempt to lose weight. Any researcher arriving at the door with a questionnaire might then note that obese people often eat low-fat dairy products, implying a cause of obesity where none exists. This problem is overcome by prospective studies.

A 2011 review by Anestis Dougkas and colleagues describes 13 epidemiological studies, of which seven are prospective. In all but one case they either report a significant decrease in body mass with higher dairy consumption, or find no statistical significance.

The second tangle of cause and effect arises from the nature of the mechanisms that might be at play. If the girths of dairy lovers are to be compared fairly to those of dairy avoiders, logic dictates that individuals in both groups should ingest the same amount of energy overall. Otherwise you could be comparing piggies and pickers. However, one theory proposes that dairy products exert a slimming effect by fooling the body's appetite sensors, leading their consumer to crave less food.

When researchers did ensure that their study's subjects, all obese, were eating equal numbers of calories, there was no sign that dairy enhanced weight loss in three out of five studies. But dairy helped in two of the five. The most striking insight from these studies, however, is that dairy appears to protect against the loss of lean body mass—in other words, muscle—when fat people go on diets.

For example, in one study, three fat-free yogurts per day over the course of a three-month calorie-restriction diet led to an 81% greater loss of belly fat (compared to dieters who didn't eat yogurt). That kind of finding catches physicians' attention because there is a [well-established association](#) between abdominal fat and metabolic disorders, including type 2 diabetes.

The trunk-fat-fighting effect of dairy has also been demonstrated among rural, middle-aged Swedish men, who are, on the whole, a bit chubbier than the medical ideal. Over 12 years, 15% of the men in this study developed abdominal obesity. The main predictor of who joined this category was how much dairy fat they reported eating on a daily basis at the beginning of the study. Men who normally ate larger amounts of dairy fat were much less likely to spend the next dozen years watching their midriffs expand.

The link between dairy and belly fat also holds true for adolescents. A team of Portuguese researchers has reported it among teenagers in the Azores—*islands that lie far out in the Atlantic*. After statistically removing all other lifestyle factors and nutritional variables from their results, this team found that adolescent boys who eat at least two servings of milk or yogurt per day are less likely to have excess fat around their waists. The waistline effect was not as strong for girls, but an association between milk consumption and adolescent girls' overall body fat was significant.

On the whole, Europeans eat a lot of dairy compared to the participants in studies conducted elsewhere. Which begs the question: Are all of these conclusions relevant for populations with different dietary preferences? Two surveys of populations that consume little dairy—the Nunavik in northern Canada and Japanese women—suggest a threshold level of dairy consumption is necessary before any benefit can be measured.

A third, very large population is beginning to show the same effect. Indians, too, don't drink much milk—or at least that has been the case historically. But this is changing. Between 1980 and 2003, India's per capita annual dairy supply rose from 39 kg to 70 kg. That still isn't quite enough to place India in the list of the top 100 per capita dairy-consuming countries, but it represents a huge leap. And the result is evident among Indian factory workers. Surveys of this sector in four Indian cities show that the odds of obesity and of a disproportionately large waist circumference are lower for Indians who have at least one portion of milk each day than for those who don't consume any.

Similarly, a threshold effect has also been put forward to explain results regarding the potential benefits of dietary calcium. The best-fit line from Dougkas's meta-analysis yields the insight that consuming about 400 mg of dietary calcium per day—for an average person who otherwise eats normally—gives a BMI of 25.6 kg/m<sup>2</sup>. If daily calcium consumption rises to 1200 mg, the average person slims by 1.1 kg/m<sup>2</sup> and drops to within the accepted healthy range.

Calcium may promote a slimmer body through various mechanisms. It is known, for example, that low dietary calcium increases the blood concentration of several hormones and causes calcium ions to move into cells. Inside cells, this higher calcium level promotes the creation and storage of fat. But whether this mechanism has much influence on obesity is doubted because most fat accumulation in humans comes from food, not from *de novo* synthesis inside the body's cells. Another theory is that high dairy calcium somehow increases fat oxidation. A more accepted idea pins calcium's slimming effects on calcium ions in the gut reacting with dietary fat to form insoluble soapy blobs. These are then excreted, effectively preventing some dietary fat making its way from the gut lumen into the body.

What is clear, however, is that calcium's benefits depend, to some extent, on other components of dairy products. Zemel et al., for example, showed more extensive weight and body fat loss in obese people who got their calcium through dairy products as part of a calorie-controlled diet than in those who received calcium as a supplement.

### Dairy genes

Dougkas's meta-analysis, like the vast majority of studies, treated all participants equally—which of course, they aren't, at least in the eyes of geneticists. A rather neat study conducted in Spain has identified a tiny patch of the genome that appears to have huge sway in how the body responds to a high dairy diet.

A little way upstream from a gene that encodes the enzyme lactase, which breaks down the milk sugar lactose, lies a region of DNA that governs how long the lactase gene keeps working. Lactase is produced during infancy so babies can breakdown the lactose in their mother's breast milk. But whether the cells along the villi of the small intestine continue to produce it into adulthood depends on the DNA sequence of this upstream region.

Dolores Corella and her colleagues examined the lactase gene region of DNA of elderly people living near the city of Valencia in the west of Spain. They found that participants with two copies of the 'C' version of the gene have lower BMIs and smaller waists than participants with two 'T' versions, or with one 'T' and one 'C'. The double 'C' genotype

ensures that lactase production halts in adulthood. Details of the results further hint at lactase's functional role: the differences in body mass and midriff fat were only significant among participants who had moderate or high dairy intakes. So whether you have the 'CC' genotype or not makes no difference to your BMI—unless you love dairy.

Although the calcium and lactase data are persuasive, other components of dairy may also influence body weight. Whey proteins have been singled out in the literature because they can be broken down into the bioactive peptides, casokinins and lactokinins, which act to inhibit the production of the hormone angiotensin II. And that, in turn, dampens down fatty acid production. Furthermore, whey proteins seem to stimulate insulin secretion, consequentially suppressing appetite.

In surely one of the most careful examinations of post-breakfast hunger ever, Veldhorst et al. report that people who eat whey protein devoid of glycomacropeptide (a particular sort of whey protein) at breakfast consume more calories at lunch than people who eat the same breakfast, but in which the whey protein contains natural levels (21%) of glycomacropeptide.

Although these details are fiddly and the degrees of difference are small, the stakes are rather big. This planet is currently home to 1.6 billion overweight people who may suffer associated health impacts later in life. It would serve them well to swap dairy into their diets.

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## How Breastfed Babies Control Their Own Appetite

- **Breastfeeding on demand leads to successful lactation and better infant appetite control.**
- **Factors involved in appetite control that are present only in breastmilk, such as leptin, appear to influence regulation of milk intake in breastfed infants.**
- **Breastmilk appetite control factors likely influence physiological processes such as hypothalamic development and gastric emptying.**
- **The mode of feeding affects milk intake and appetite regulation such that bottle feeding allows greater milk consumption and lower appetite control compared to breastfeeding.**

'Slow down, Mama!' – In contrast to breastfeeding, which allows infants to feed on demand, bottle feeding enables parents to provide set volumes of milk to babies. Latest evidence shows that breastfed babies control their appetite better than formula-fed babies, and although the mechanisms through which this occurs are not yet clear, it has been shown that this has long-term effects on appetite regulation and weight control into adulthood. Perhaps it is time to start seriously considering breastfeeding as an intervention window against the obesity epidemic.



### The facts

Exclusively breastfed infants self-regulate their nutrient intake<sup>1,2</sup>. Breastfeeding on demand facilitates this. In 1986, a study demonstrated that when mothers stimulated an increase of milk supply by daily milk expression, their babies did not consume the extra milk after cessation of the stimulation phase<sup>3</sup>. We have shown that breastfed infants rarely consume 100% of the available breastmilk, with the average consumption being 67% of available breastmilk<sup>4</sup>. Ultrasound imaging studies of milk ejection in the breast of lactating women have shown that in 39% of the mothers who had multiple milk ejections, the infant terminated the breastfeed during a milk ejection even though milk was readily available<sup>5</sup>, demonstrating active short-term appetite control.

In addition, breastfeeding results in long-term appetite control not otherwise seen in formula-fed infants, with a significant body of evidence demonstrating that breastfed infants have a lower risk of becoming obese in childhood and adulthood<sup>6,7</sup>. A number of large epidemiological studies in different areas around the world have reported a negative, dose-response relationship between the duration of breastfeeding and the incidence of obesity later in life, after controlling for confounding factors<sup>8-10</sup>. These findings are quite remarkable considering that the only nutritional measurements made were whether the infant received breastmilk and the duration of breastfeeding, hardly acceptable measures of dietary intake in light of the large variation between mother/infant dyads in daily milk production, intake, and composition<sup>4,11-13</sup>.

### Appetite control factors in breastmilk

The consistent beneficial effects of breastfeeding on short- and long-term appetite control in babies are bound to be multifactorial and are not yet well understood. One piece of the puzzle may be found in the components of breastmilk, which are absent or present in lower amounts in artificial formula. In 1994, leptin was discovered, a signalling peptide regulating energy intake and expenditure in adults<sup>14</sup>. Since then, a series of other bioactive factors involved in adult energy metabolism have been identified, including adiponectin, an orexigenic (stimulating food intake) peptide; ghrelin, which stimulates food intake and has an adipogenic activity; resistin, a cytokine secreted by adipocytes, and many others. What is fascinating is that many of these factors that control appetite in adults are also present in breastmilk! As can be expected, studies are emerging linking them with appetite regulation in breastfed babies.

Increasing leptin concentration in breastmilk has been associated with lower infant weight, still within the normal range, at two years<sup>15</sup>. Moreover, animal studies have shown that leptin contributes to the development of neural circuits associated with appetite regulation<sup>16</sup>. Other hormones in breastmilk may also confer appetite control in breastfed infants. Breastmilk adiponectin has been shown to positively correlate with the incidence of being overweight at two years of age<sup>17</sup>. Breastmilk IGF-I positively correlates with BMI in the first five months of life<sup>18</sup>. Although these and many other appetite control factors are present in breastmilk, they have only recently been identified, and their role in neonate physiology, infant growth, and short- and long-term appetite control is elusive, thus deserving close attention. In addition to these hormones, other components of the nutrition the infant receives early on may regulate appetite. Protein intake is a serious candidate.

### Protein intake

The protein content of a food is known to influence appetite and its regulation<sup>22,23</sup>. The protein content of mature human milk is very low, three times less than that of bovine milk<sup>24</sup>, yet it is optimal for the growth requirements of the human term infant. Noticeably, this is the period of maximal growth rate across the total lifespan. Animal milk-based artificial formulas typically contain higher amounts of protein, different ratios of protein types (e.g., caseins versus whey proteins), as well as a different composition of protein, all of which may affect infant development and appetite regulation. Therefore, it becomes clear that further knowledge on how the specific composition of the early infant nutrition influences

development of appetite mechanisms in the infant is paramount. In this connection, factors such as the maternal diet and BMI, which may affect breastmilk composition in appetite controllers, merit further investigation.

### Infant suckling and gastric emptying

Whilst breastfed infants display good appetite regulation, there may be other influencing factors apart from the vast array of appetite control factors in breastmilk. A recent study suggests that the 'container' from which milk is delivered (breast or bottle) may also play a role. Li et al. (2012)<sup>19</sup> showed that bottle feeding is positively associated with increased weight gain in the first year of life irrespectively of whether breastmilk or formula was fed. The researchers speculated that infants are more active in controlling the volume of milk taken during a breastfeed and that changes in breastmilk composition occurring during a breastfeed, such as the increase in fat as the feed progresses, may provide a signal that the feeding is nearing completion. Bottle feeding in comparison, is more likely influenced by the caregivers who are more likely to lengthen the feed if they believe the infant has not consumed enough of the milk in the bottle.

Interestingly, breastfed infants display a wide range of feeding patterns and volumes that may also relate to breastmilk composition in terms of appetite regulating factors. For example, the main source of leptin in the first six months of life is breastmilk where it is absorbed from the stomach and enters the infant's circulation. In contrast, there is little to no leptin in artificial formulas. This may explain in part why breastfed infants feed more frequently and consume less milk than their formula-fed counterparts.

In addition to feeding patterns, differences exist in how food is processed by the infant's gastrointestinal tract depending on whether it is breastmilk or formula. Formula, being bovine milk-based, empties slower in the stomach because of its higher casein-whey ratio compared to breastmilk<sup>20</sup>. Moreover, preliminary evidence supports the notion that appetite control factors, such as leptin, which are present in breastmilk but are absent in formula, may also influence gastric emptying<sup>20, 21</sup>. These differences in gastric emptying and nutrient processing may not only influence growth and appetite regulation in the short-term, but may also have appetite programming effects and thus long-term consequences.

### Breastmilk as a model for optimum nutrition in later life

Popular opinion and accumulating evidence suggests that the 'window' of early feeding has an impact on adult health by influencing functional programming. Indeed, given the enormous increase in obesity and obesity-related diseases, the breastfeeding period is an important public health initiative and an opportunity to influence long-term health<sup>25</sup>. Whilst breastfeeding is often shown to be protective against obesity, a proportion of infants still become overweight later in life despite being breastfed. This indicates that the weaning period may also be critical to appetite control. The transition from consuming breastmilk at a frequency and quantity largely of the infant's choosing to being encouraged to consume food to meet the expectations of the parents and health professionals is a period which, if not well managed, may have detrimental effects on the infant's appetite control mechanisms that developed during breastfeeding. Thus, in addition to investigating how appetite is regulated during the breastfeeding period, we should perhaps start thinking of the composition of human milk as an optimum guide for the introduction of solid foods in infancy and the lasting effects into adulthood.

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## On Diabetes and Dairy

- **Consumption of low-fat dairy lowers the odds of developing type 2 diabetes by about 10% for each additional serving per day.**
- **High-fat dairy products, as a group, show no significant association with type 2 diabetes, although some studies suggest that cheese may be preventative.**
- **Whey protein and vitamin K2 may provide protection against type 2 diabetes.**



Type 2 diabetes describes a condition where cells that would normally respond to insulin by absorbing glucose from the blood stop doing so, allowing blood glucose to rise to unhealthy levels. It is closely associated with obesity. Various studies link the regular consumption of low-fat dairy products to reduced odds of developing type 2 diabetes. Not every study finds this effect, but in those that do, the question is: why?

Funny enough, the answer is whey, at least in part. Dairy proteins contain two main categories of protein, caseins and whey proteins. Typically during the development of type 2 diabetes, the number of functional insulin receptors sitting on the surface of fat and muscle cells decreases over time. Therefore, the signal these cells receive for any given amount of circulating insulin slowly wanes.

Experiments with both mice [1] and people [2] show that eating whey protein stimulates the insulin-producing cells in the pancreas to work harder than they normally would. They simply make greater amounts of insulin. In other words, the body's internal message relaying that it's time to remove glucose from the blood gets communicated more loudly. And this counteracts the lessened 'listening' ability of those cells whose job it is to pick up blood sugar.

One study [3] on type 2 diabetics reported that when whey protein is added to a meal of easy-to-digest carbohydrates, blood insulin levels are hiked by 57%. More importantly, the blood glucose levels of the diabetics in the study were 21% lower than they were after they ate a control meal.

Whey's benefits are also implied by studies that link the consumption of dairy products to an overall lower likelihood of developing diabetes. Many studies have looked for this effect; some have found one, others have not.

A meta-analysis [4] conducted in 2011 by researchers at Soochow University in Suzhou, China, brought the results of seven cohort studies together. They report a 14% reduction in the risk of type 2 diabetes in people with high dairy consumption compared to people with very low dairy consumption. This dose-dependent effect implies a 10% reduction in the odds of getting type 2 diabetes with each additional daily serving of low-fat dairy.

Perhaps the most instructive individual cohort study is the one that followed its participants for the longest time. The Nurses Health Study involves some 120,000 female registered nurses. They began enrolling in the study in 1989 and have filled in biennial lifestyle questionnaires ever since. These women have also been asked to recall their dairy intake during high school [5].

The results are intriguing. They confirm that consuming dairy products as an adult offers modest protection against type 2 diabetes. However, the really significant benefit comes from eating lots of dairy as an adolescent. This suggests the mixed results from other cohorts might boil down to when and for how long the researchers tracked the participants.

Whey is not the only constituent of dairy that could help prevent diabetes. Another component was brought into the spotlight by a closer analysis of the particular kinds of dairy products that are good for diabetics. The place to study such a topic is Europe, where high dairy consumption is combined with strong national preferences. The French, for example, eat a lot of cheese, meanwhile the Swedes and Dutch get through large quantities of yogurt.

Eight European countries, 340,000 people in total, are taking part in EPIC InterAct, a study that aims to unpick the genetic and lifestyle factors that contribute to type 2 diabetes risk. The researchers running EPIC InterAct have not found any statistically significant anti-diabetic benefit to drinking lots of milk [6]. But, after statistically correcting for all sorts of risk factors, including obesity, they have reported that a diet rich in fermented dairy products, including cheese, is protective.

Why fermented dairy? No one is completely sure. But one explanation is that a vitamin called K2 is causing the effect [7]. K2 is not made in mammalian bodies, so it isn't present in all dairy. It is manufactured, however, by the bacteria used to seed the dairy fermentation process. K2 reduces inflammation, which, it is thought, raises insulin sensitivity.

Although many questions remain unanswered, this research is heartening, particularly for people with a family history of type 2 diabetes. Like obesity, diabetes can have devastating medical consequences over time—indeed, it is the primary non-traumatic cause of blindness and kidney failure in developed countries. As a result of these consequences, diabetes is also an expensive burden on society.

The University of South Australia, Adelaide, has put numbers on this. Researchers James Doidge and colleagues [8] asked how much increasing the consumption of dairy in Australia could cut the national healthcare bill. For the financial year 2010-2011, they came up with the figure AUD \$2.0 billion (USD \$2.1 billion), an amount slightly greater than total public health spending in the country the year before. Whether they are correct or not, the ballpark their calculation landed in is surely worthy of attention.

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## Talking the TORC

- **Milk provides bioactive molecules that stimulate growth.**
- **Nutrients in milk are sensed by the baby's cells, which turn on mTORC.**
- **Inside cells, mTORC initiates the to-do list for making things needed by growing cells.**
- **This knowledge could lead to new ways of measuring the health impact of milk.**

Milk has evolved to sustain life through supporting the growth and healthy development of infants. A recent article in the prestigious journal *Science* reported a breakthrough in our understanding of what lies behind the cellular mechanism of the growth "switch".

In order for the tissues in our body to grow, nutrients need to be converted into structural proteins and lipids, molecules important for energy storage and cell membrane maintenance. Two key events associated with milk production that rely on these critical nutrients are the growth of the mammary gland during pregnancy as it prepares for lactation and, of course, the growth of the baby that consumes the milk. Milk is not only a source of calories, but it also provides bioactive molecules that stimulate growth by switching on the appropriate physiological systems. We refer to this process of activation as an anabolic effect.



### What causes growth?

Growth happens at the level of individual cells; growth and proliferation of cells leads to overall developmental growth of organs and tissues. Fundamentally, all cells respond to signals that are generated by nutrients (e.g., milk proteins), hormones (e.g., insulin), and the availability of energy.

We refer to cells as sensors for this purpose, and when there is a demand for growth, and the cells detect that conditions are just right, they switch on the cellular machinery that provides the building blocks for new cells and tissues. The sensing function works because of receptors attached to the outside of the cell that generate a message that travels to the inside of the cell. The "wires" that telegraph these messages are in fact molecules that link with one another. At the heart of this interaction is a molecule called mTOR, and when it is linked with its partners, it is called mTORC1.

## How can mTORC1 send a signal?

Much work has focused on the messages that stimulate the formation of mTORC1, and one key element is the amount of the essential amino acid, leucine, that is present in the circulation. Leucine is a key indicator of amino acid “status”, and there are therefore specific receptors that cells use to detect levels of leucine (1). However, the effect that mTORC1 has on other molecules that control the sensor function and complete the messaging system are still emerging.

### The missing link

A new study by Robitaille and colleagues from the University of Basel (2) has provided a major step forward in understanding this system. Robitaille et al. used a combination of test tube analysis and laboratory mouse model systems to find the molecules that were activated by mTORC1. First, they identified 1398 proteins that were affected by mTORC1 and then applied a computer-based method to aid some excellent detective work. Just like Sherlock Holmes, they came up with a brilliant deduction! There were groups of phosphoproteins that had not been previously observed, and when they followed the trail of interactions, it provided the missing link to a molecule called CAD. This link we now know plugs the mTORC1 complex into two well-known anabolic mechanisms known as the “de novo pyrimidine synthesis pathway” and the “pentose phosphate pathway”. In other words, mTORC1 initiates the cell’s instructions for making things needed for growth. Interestingly, these are biochemical pathways that we recognise from studies of mammary gland biology and lactation (3-5). By making this connection, Robitaille and colleagues have solved a riddle and for the first time connected nutrient sensing to the switch to anabolic capacity in cells.

### Why is this important?

Both maternal and neonatal factors are crucial for the immediate healthy growth of the newborn, and what is becoming abundantly clear is that nutrient quantity and quality during neonatal growth has an impact on lifetime health. The anabolic switch is a key regulator of neonatal growth. Furthermore, the mammary gland itself depends on anabolic growth to achieve a level of production that can generate adequate amounts of milk. Evolutionary determinants of milk composition have provided a tuned and balanced nutrient source for regulating the anabolic switch.

The groundwork has been completed for us to find ways to monitor the cellular proteins at the centre of these events. The development of this approach will provide an efficient tool to measure the health impact of milk.

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