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This month's issue features results of the PURE global dairy study, and breastfeeding and antibiotic-resistant bacteria.

More Dairy Means Lower Cardiovascular Disease Globally

- **Four-fifths of the world's cases of cardiovascular disease occur in low- and middle-income countries, yet relatively few studies are conducted in these contexts.**
- **A new analysis of dairy intake and cardiovascular disease across 21 countries finds that total dairy consumption is associated with lower disease risk, especially with lower risk of stroke, across world regions.**
- **When different types of dairy were considered separately, researchers found higher intake of milk and yogurt were most clearly linked to lower cardiovascular disease risk.**
- **Given the low levels of dairy consumption in much of the developing world, and the rising risk of cardiovascular disease in those places, the findings suggest that promoting dairy products could be a worthwhile public health program.**

For many years, researchers have been gathering and analyzing different sources of data to figure out definitively whether consuming dairy products has a net positive or net negative influence on cardiovascular health. Naively, the fact that dairy contains saturated fat suggests the proposition that it might raise the odds of having a heart attack or a stroke. However, the diversity of dairy fats, alongside a host of other health-promoting molecules found in milk, cheese and yogurts, has led many researchers to suspect the opposite might be true. A consensus has been forming that dairy products either have no noticeable effects or have protective effects on the cardiovascular system, though this has rested upon data drawn heavily from a few wealthy countries. A new study known as "PURE"—"The Prospective Urban Rural Epidemiology" —studyhas just filled in this gap [1]. Taking in data from five continents, it reports that higher dairy consumption is linked to lower cardiovascular disease the world over.

The mounting evidence in this field has been frequently covered in *SPLASH!* Back in 2013, for example, Welsh researchers concluded that eating dairy has a small, protective effect against stroke and heart disease [2]. This built on work conducted in Japan, the Netherlands and Sweden [2]. More recently, a meta-analysis combined data from three large cohorts in the United States [3]. The analysis found a neutral association between dairy and cardiovascular disease. In September this year, *SPLASH!* reported on a piece of research that was impressive for the period of study as opposed to the diversity of the population that it followed: A 21-year clinical trial found that dairy fat was not associated with cardiovascular disease among elderly people in the United States [3].

However, dairy consumption tends to be lower, and—depending on the place in question—often healthier in low- and middle-income countries. Butter consumption is so low in China, Malaysia and Pakistan, for example, that it was deemed by researchers involved in the new study to be not worth including in food questionnaires. Moreover, in much of the Middle East, fermented dairy products are common. Understanding the role of dairy in cardiovascular disease in lower- and middle-income countries is important—80% of the world's cases of cardiovascular disease are found there.

Differences are also seen in patterns of disease burden. Whereas in North America and Europe, strokes are rarer than coronary heart disease, the opposite is true in East Asia and Africa [1]. Importantly, temporal trends have been diverging as well. An analysis of global cardiovascular disease burden between 1990 and 2015 found the age-standardized death rate to be reducing in high-income countries [4]. The same could be said for a few middle-income nations. Yet no shifts were detected in sub-Saharan Africa, in much of Oceania, nor in Pakistan, Kyrgyzstan and Mongolia—implying that the rise of environmental contributors (smoking, drinking, unhealthy food and excessive bodyweight) has kept pace with public health improvements. In Bangladesh and the Philippines, deaths from cardiovascular disease have been straightforwardly increasing.

The new study ran between the beginning of 2003 and July of this year, and recorded the dietary intakes and cardiovascular outcomes of more than 136,000 people, aged between 35 and 70, across 21 countries. The researchers were primarily interested in the risk of a "composite outcome," which is a single measure that includes deaths from cardiovascular causes, as well as heart attacks, strokes and cases of heart failure that do not end in death (heart failure typically involves the gradual weakening of the heart muscle over time [5]). For this composite outcome the results were clear: Consuming two servings of dairy per day, compared with no dairy, was associated with a highly significant lower risk. Similarly, drinking at least one serving of milk each day, or consuming one of yogurt, was linked to a lesser chance of the composite outcome.

As ever, there are many details and caveats to the results beyond these headline findings. The composite outcome aside, consuming dairy was separately associated with a lower probability of death from cardiovascular disease, death from other causes, getting a diagnosis of cardiovascular disease and the risk of stroke. But the results were not quite statistically significant for heart attacks on their own. Similarly, the data on cheese consumption did not imply any clear link with the composite outcome. And the countries for which there were data on butter suggested that high levels of butter consumption, compared with not having butter, led to a higher (though not statistically significant) risk of the composite outcome of cardiovascular disease.

But for the field at large, the most important result is the consistency of the findings across regions. Within countries with low dairy consumption, and within countries of dairy aficionados, the patterns linking consumption and disease are broadly the same. The authors conclude by suggesting public health advice. Across much of Africa, and especially for countries such as China where the risk of hypertension is high yet consumption of milk, yogurt and so on is low, efforts to encourage people to have more dairy could lead to broad improvements in cardiovascular health.

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Breastfeeding May Help Protect Babies from Antibiotic-Resistant Bacteria

- **Antibiotic resistance is a major global public health challenge, and more than 200,000 infants are estimated to die every year due to resistant infections.**
- **A new study assessed how the milk and gut microbiota of mothers shape the antibiotic resistance of bacteria in the infant gut.**
- **The study found that breastfeeding reduced the amount of antibiotic-resistant bacteria in the infant gut, whereas antibiotic treatment of mothers during delivery increased the amount of antibiotic-resistant bacteria.**

Bacterial resistance to antibiotics poses a major challenge to global public health [1,2]. Babies lack a fully developed immune system and gut microbiome, and are particularly susceptible to infections by resistant bacteria [3–5]. More than 200,000 infants are estimated to die every year due to septic infections caused by antibiotic-resistant pathogens [4].

Bacteria often develop antibiotic resistance by receiving antibiotic resistance genes from other bacteria [6]. The infant gut microbiota has been shown to contain a high abundance of antibiotic resistance genes compared with adults [7–9]. "Infants carried a larger proportion of antibiotic-resistant bacteria in their gut than did adults, despite never having been treated with antibiotics," says Katariina Pärnänen, a Ph.D. student in Marko Virta's laboratory at the University of Helsinki.

This raises the question of where the antibiotic resistance genes in the infant gut originate, with some previous studies suggesting that they are shared between the guts of mothers and infants [10,11]. Another possibility is that antibiotic resistance genes are present in human milk, which is known to influence the infant gut microbiota [12-14].

In a new study, Pärnänen and her colleagues set out to investigate the origins of antibiotic resistance genes in the infant gut [15]. They sequenced DNA from the milk and gut of 16 mother-infant pairs over a period of 8 months to assess how the milk and gut microbiota of mothers shape the antibiotic resistance of bacteria in the infant gut.

"The biggest challenge was obtaining enough DNA sequence information from breastmilk to be able to study the antibiotic resistance genes," says Pärnänen. "This is because breastmilk has a lot of human DNA in it, and when the DNA is sequenced more than 90% of the sequence information is human," she says. Using the latest DNA sequencing technologies, the researchers were able to sequence sufficient DNA from the milk and gut microbiota to perform their analyses.

"We could observe that mothers transmit some of the antibiotic-resistant bacteria found in their gut to their infants, so past use of antibiotics of the mother might have an impact on which resistant bacteria end up in the infant gut," says Pärnänen.

The researchers also found that antibiotic resistance genes could be transferred through human milk to the infant gut. "Antibiotic resistance genes, which confer resistance to antibiotics in bacteria, were found in breast milk and thus are also likely transmitted to the infant," says Pärnänen.

"However, infants who were breastfed until the age of six months had less antibiotic resistance genes in their gut bacteria than infants who weren't breastfed at all or whose breastfeeding had been terminated earlier," she says. As a result, breastfeeding seemed to protect infants from resistant bacteria.

“This is likely because breastmilk promotes the growth of beneficial probiotic bacteria like bifidobacteria, which take over so that bacteria that often carry antibiotic resistance genes cannot grow efficiently,” says Pärnänen. “It is known that bacteria like *Escherichia coli* are more abundant in infants who are fed formula compared to breastfed infants, and *E. coli* is often associated with antibiotic resistance and many strains are also pathogenic,” she says. Indeed, a recent study by a different research group showed that high levels of *Bifidobacterium* in the infant gut microbiome are associated with significantly reduced levels of antimicrobial resistance in early life [16].

Mothers may need to receive antibiotic treatment during delivery—known as intrapartum antibiotic prophylaxis (IAP)—for various reasons, including to prevent the transmission of harmful bacteria living in the birth canal to the infant during delivery. Pärnänen and her colleagues evaluated the effect of IAP on the development of the infant gut microbiome and the transmission of antibiotic resistance genes.

“We saw that intrapartum antibiotic prophylaxis treatment given to mothers increased the abundance of antibiotic resistance genes in the infant gut even six months after treatment,” says Pärnänen.

The researchers hypothesized that antibiotics administered during delivery to the mother might eliminate all bacteria except those resistant to the drug, and the mother was likely to pass these resistant bacteria on to her child where they had a head start in establishing the infant gut microbiome.

Pärnänen is planning follow-up studies to investigate other factors that might influence antibiotic resistance in the infant gut. “Next I am planning to look more closely at the influence of different diets on antibiotic resistance of infant gut bacteria,” she says.

The researchers conclude that the number of antibiotic resistance genes present in the infant gut is influenced by factors that shape the overall infant gut microbiome, including the duration of breastfeeding and antibiotic treatment of mothers during delivery. The results suggest that mothers contribute to the antibiotic resistance genes in the infant gut microbiota by sharing genes from their gut and breast milk bacteria.

The study also adds to the known health benefits of exclusive breastfeeding for at least six months [17]. “We suggest that breastfeeding should be promoted not only for its other health benefits, but also for the reason that it has the potential to reduce the abundance of antibiotic-resistant bacteria in the infant gut,” says Pärnänen.

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Measuring Inbreeding Balances Efficient Selection with Sustainable and Healthy Herds

- **The genome of dairy cattle has been refined over many centuries, primarily through selective breeding.**
- **Scientists have begun to measure and model the changes in the genome that the increased use of selective breeding using genomic markers is having on herd genetics.**
- **Two recent studies on the use of genomic data measure changing genetic diversity in North American Holstein and South American Gyr dairy cattle.**
- **Looking at inbreeding in cattle, scientists conclude that while improvements in production can be accelerated, it is very important to monitor and manage changes to genetic diversity to ensure sustainable development of highly productive herds.**

Selective breeding has been used for many centuries—initially in a crude form by early farmers, but today using highly sophisticated genome analysis and complex algorithms. However, the goals have remained the same: to improve the efficiency of dairy production. This translates into breeding the healthiest, most productive cows suitable for the appropriate farming system and environment. New technologies have provided the capability to monitor the changes that occur with selection in great detail. Two recent papers explored the most effective methods to accomplish this and investigated changes in North American Holstein [1] and South American Gyr dairy cattle [2].

Genomic Breeding Values (GBV) are now part of many national programs for dairy herd improvement. GBV predict the value of using an individual bull or cow for breeding the next generation of cattle for the farm. They are the culmination of over 10 years of intensive international dairy science research investment in cattle genetics, and build on 30 years of nationalized production trait measurements and the previous system of estimating these breeding values. Implementation of precise genomic measures as a means of selection for herd improvement has led to a rapid rise in the rate of gain in many herds. It has also meant that the impact of selecting in this way can now be modelled and evaluated in great detail.

Selective breeding programs by their nature tend to reduce genetic diversity in dairy cattle populations. A similar effect can occur in nature, for example when the number of individuals in a species is markedly reduced, but it is more common in artificial selection, especially when selection is focused on a limited number of traits [3].

The reduced diversity may not be obvious in the way cattle perform in the short term but may eventually lead to an inadvertent increase in undesired or deleterious phenotypes, or traits, reducing performance of a herd or increasing the risk of health problems.

With this in mind, scientists have begun to measure and model the changes in the genome that the increased use of selective breeding using genomic markers is having on herd genetics.

A very useful way to measure genetic diversity is by calculating the level of inbreeding in a population. This has been previously estimated from pedigree data, but with the availability of detailed data on the genomes of many cattle, there is an expectation that more accurate measurement can be made. Two recent publications consider the North American Holstein [1] and South American Gyr dairy cattle [2]. The Holstein breed is the most widely used dairy breed in North America and many other countries. Gyr cattle belong to the *Bos indicus* subspecies of cattle. They originated in the Asian sub-continent, and were first imported from India to Brazil early in the 20th century for mixed use but have since been selected for milk production. The Brazilian Gyr has also become a source of dairy genetics for other countries where these animals are suited to warmer climates.

The scientists participating in both studies were interested in changes to the level of inbreeding in the cattle under study. In both the studies reported, they compared methods of estimating the amount of autozygosity in the herds. Autozygosity indicates how similar the DNA is within individuals and across the herd as a result of regions of DNA originating from a common ancestor. Put simply, offspring get one copy of their DNA from their mother, and one copy from their father. Autozygosity is the measure of how similar those sets of copies are to the originals. If the DNA of both maternal and paternal origin is identical, then the offspring would be fully autozygous. There are many strains of laboratory mice, for example, that have been selected to be identical in all but their X and Y sex chromosomes, which are referred to as fully inbred. In cattle this is not a likely outcome, but there are degrees of inbreeding that can be measured as the sharing of identical stretches of DNA derived from sire or dam. The scientists were able to detect where sections of the genomes were identical using DNA sequence and molecular marker data. Technically these regions of the genome are referred to as runs of homozygosity (ROH) [4-9].

Using different ways of measuring ROH, Forutan et al. [1] were interested in how accurately they could predict autozygosity using computer simulation. They then compared these results to actual data from over 40,000 dairy cattle born over a period of 25 years. For North American Holsteins, the effect of selective breeding using molecular methods has been most pronounced in the past 5 years. The introduction of genomic estimated breeding values has accelerated the rate of genetic gain without increasing the level of inbreeding per generation. This is because the molecular data provide more precise selection and can be used to avoid increased inbreeding by selecting a wider range of bulls. The acceleration in production gains arises significantly from the fact that the process of selection using molecular methods is much faster than traditional methods, allowing bulls to be used for breeding from a younger age. However, this has the consequence of an overall increase in the level of inbreeding when examined at herd level.

In the Gyr cattle, the focus of the study was a bit different. The purpose was to determine the level of inbreeding from ROH, and to consider the consequences this may have on expanding Gyr herds being used in dairy production [2]. Peripolli and her colleagues found that the limited number of founder animals imported into Brazil had affected subsequent population structure, as may be expected. The scientists found that using the ROH method could accurately detect and describe the level of autozygosity in these cattle. They also focused on specific regions in the DNA that were affected. Selection leaves a signature in the genome where the genes controlling a trait are located and the surrounding regions that hitchhike because they are found in the same linkage block [10]. They were interested to know which genes were in those regions and what function they may have. Indeed, they found that the most prominent regions of increased ROH were those containing genes that are known to be involved in dairy production traits.

These studies emphasize the growing accuracy that genomics provides for evaluating selective breeding programs. They show that, although improvements in production can be accelerated, it is very important to monitor and manage changes to genetic diversity to ensure sustainable development of highly productive herds. Using the new tools available to measure ROH is an effective approach to achieve this goal.

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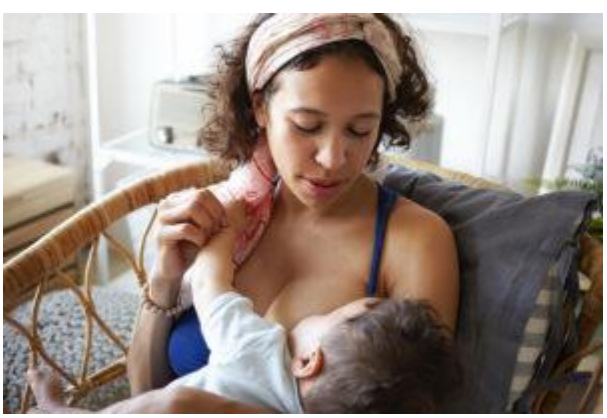
Breastfeeding May Lower Risk of Stroke Later in Life

- **Stroke is a major cause of death among US women aged 65 and older, particularly among Hispanic and non-Hispanic black women.**
- **Breastfeeding may protect against stroke, and a new study investigated the association between breastfeeding and stroke and how it differs by race and ethnicity.**
- **The study found that breastfeeding was associated with a lower risk of stroke among postmenopausal women, and this association was strongest for non-Hispanic black women.**

Stroke is a leading cause of death in US women aged 65 and older [1,2]. It is particularly deadly among Hispanic and non-Hispanic black women, due to their increased rates of risk factors such as hypertension, obesity, and diabetes compared with non-Hispanic white women [3-6].



One factor that may protect against stroke is breastfeeding. Breastfeeding is known to have protective effects on maternal health, such as a reduced risk of breast and ovarian cancer, reduced likelihood of hypertension and diabetes, improved cardiovascular health, and reduced maternal postpartum weight [7-22].

“It looks like breastfeeding has really important effects on the ways mothers recover from pregnancy,” says Professor Eleanor Schwarz at the University of California, Davis, who has also written a commentary on breastfeeding and maternal cardiovascular health [23]. “Moms who are not able to breastfeed end up with higher blood pressure and more risk of diabetes that requires treatment, and both of those factors affect vascular disease, whether that's heart attacks or strokes or other changes in the blood vessels,” she says.

Both the American Academy of Pediatrics and the World Health Organization recommend exclusive breastfeeding for 6 months, and continuation of breastfeeding for 1 year or longer [24,25]. However, exclusive breastfeeding rates are relatively low in US women, and even more so among Hispanic and non-Hispanic black women [26-29].

“The fact that we do have these very dramatic disparities in the rates of breastfeeding is actually a really big issue, and not everybody makes the links to the longer-term health consequences both for mothers and for infants,” says Schwarz.

Hispanic and non-Hispanic black women have lower breastfeeding rates and are at higher risk for stroke compared with non-Hispanic white women, suggesting that there might be a link between breastfeeding and stroke. However, there have so far been few studies examining the association between breastfeeding and stroke and whether this association differs by race and ethnicity. “I think that where breastfeeding fits in understanding multiple health disparities is a really important piece of the story,” says Schwarz.

A new study by Professor Lisette Jacobson of the University of Kansas School of Medicine addressed whether breastfeeding might protect against stroke, and whether its effects differ by race and ethnicity [30]. Jacobson and her colleagues found that breastfeeding was associated with a lower risk of stroke among postmenopausal women, and this association was strongest for non-Hispanic black women.

The new study analyzed data from a large racially and ethnically diverse cohort of women who participated in the Women’s Health Initiative, a longitudinal national health study that focused on strategies to prevent chronic disease in postmenopausal women [31-34].

The researchers found that after adjusting for multiple stroke risk factors and lifestyle variables, women who reported ever breastfeeding had a 23% lower risk of stroke compared with women who had never breastfed. This association was strongest for non-Hispanic black women.

In addition, breastfeeding for even a relatively short duration of one to six months was associated with a 19% lower risk of stroke, and this association became stronger as breastfeeding duration increased. Longer duration of breastfeeding was associated with a lower risk of stroke in all women studied and among non-Hispanic white and non-Hispanic black women.

“All of that to me is very consistent with the prior literature,” says Schwarz. “I think it's understood that breastfeeding affects risks of high blood pressure and high sugars, and those are two things that are bad for women's vasculature,” she says. “It does seem that moms who aren't able to breastfeed are at greater risk,” says Schwarz.

The researchers point out that their study did not establish a causal relationship between breastfeeding and the risk of stroke, but they found that the association between the two remained statistically significant even after adjusting for various confounding factors.

The researchers conclude that breastfeeding is associated with a lower stroke risk among postmenopausal women, and they suggest that promoting breastfeeding along with other healthy lifestyle behaviors could be helpful in mitigating the risk of stroke. Given that stroke is one of the leading causes of death among Hispanic and non-Hispanic black women, and these populations also experience low breastfeeding rates, the researchers suggest that increasing breastfeeding duration among these women may be particularly beneficial in helping to guard against stroke.

“The challenge is that breastfeeding is a very time-sensitive health behavior,” says Schwarz. “It does appear to have lifelong effects for both women and their babies, but to some extent there's no point in talking about it once a woman's milk has dried up, really all we can know at that point is that perhaps she's at higher risk and we need to modify her other risk factors as best we can,” she says.

The researchers recommend follow-up studies to confirm the epidemiologic evidence that breastfeeding positively influences the risk of chronic diseases such as stroke, and to assess dose-response relationships. Understanding the risk factors for stroke may help researchers develop intervention programs to reduce stroke risk, particularly in populations that are most at risk.

“There's many, many reasons that we already know that breastfeeding is good for mothers and babies, and so I think really where we need to focus our energies is how to support mothers who want to breastfeed in doing so,” says Schwarz. “Some of that has to do with things like paid maternity leave, so probably changes such as those would have the biggest effect on our public health,” she says.

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