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Across diseases, women are diagnosed later than men

On average, women are diagnosed with disease later in life than men

When men and women contract a disease, it is very different when this is discovered by the healthcare system. On average, women are diagnosed later in life than men. This issue has been studied and analysed by researchers from the Novo Nordisk Foundation's Center for Protein Research, the Faculty of Health and Medical Sciences, UCPH, in a comprehensive study where data from the entire Danish population have been in use. The new research results have been published in the scientific journal *Nature Communications*.

'When we look across all diseases, we see a tendency that women on average are diagnosed later than men. We have looked not just at diseases, but also at the course of the patient care. Our study zooms in on the areas where the differences are most pronounced - both for the individual diseases and for the course of the patient care. The message is that the national strategies that are established need to take a difference into account. We can no longer use the 'one size fits all' model. We are already heading in that direction with respect to personalised medicine,' says last author and Professor Søren Brunak, the Novo Nordisk Foundation Center for Protein Research.

The researchers analysed data from 6.9 million Danish people. The population was divided into two groups according to their sex. Over a 21-year period, from 1994 to 2015, the researchers have e.g. analysed the occurrence of all types of diseases, multimorbidity, where you suffer from more than one disease, and courses of patient care. They found that women on average are older when they are diagnosed compared to men. The entire sequence of the women's and men's patient care course was different and time-staggered.

In connection with ADHD, there was a difference of almost six years between the time when the two groups were diagnosed with the disease. The boys were about 14 years old, while the girls were about 20 years old. Here, according to the researchers, some studies point out that the reason for the difference is that women have a different subtype of ADHD, which manifests itself in a quiet and solitary manner as opposed to the externalising behaviour often seen in boys with ADHD.

Osteoporosis Was the Exception

Osteoporosis was one of the exceptions where women were diagnosed first. Here, women were typically diagnosed before they suffered a fracture caused by the disease, while the course for men was the opposite. They were typically not diagnosed until they turned up at the emergency room with a fracture.

Scientists do not yet know whether the differences are due to genetics, environment, diagnostic criteria or a mixture hereof. They are currently investigating this in their next step in collaboration with a research team from Finland. But they believe that there is a need to think about the sex right from the start of the research in tests with rats and mice.

'It has been surprising to see that there is such a big difference between the diseases that affect men and women and between their patient care courses in a society where otherwise, we have equal and uniform access to the healthcare system. Now we are trying to map out what really lies behind the differences we see. Can they e.g. be attributed to genetics or environment and culture?' asks first author and Postdoc David Westergaard, Novo Nordisk Foundation Center for Protein Research.

'But we need to think about the fact that there may be a sex difference right from the beginning at the hospitals and in the research. Traditionally, e.g. 50 men and women will be recruited for clinical trials. Afterwards you look at the overall effect for the test participants. But you forget to make a subanalysis, where you look

at the groups separately to see if there are differences. This has only been done during recent years,' says David Westergaard.

- ***In connection with 770 types of diseases, women were diagnosed later than men. There was an average difference of about four years.***
- ***In case of cancer, women were on average diagnosed 2.5 years later than men.***
- ***For metabolic diseases such as diabetes, women were on average diagnosed about 4.5 years later.***

http://bit.ly/2u73hTQ

UNH researchers identify role gender-biased protein may play in autism

One step closer to helping answer the question of why autism is four times more common in boys than in girls

DURHAM, N.H. - Researchers at the University of New Hampshire are one step closer to helping answer the question of why autism is four times more common in boys than in girls after identifying and characterizing the connection of certain proteins in the brain to autism spectrum disorders (ASD).

"Our study is the first to look at the gender-biased regulation of proteins in the brain and how they may play a role in affecting abnormal changes in the body that results in autism," said Xuanmao (Mao) Chen, assistant professor of neurobiology. "Our findings point to a new direction for autism research and suggest promising possibilities for creating novel treatment strategies."

In the study, recently published in the journal Frontiers in Cellular Neuroscience, the researchers looked at an enzyme called AC3 which is genetically connected to major depressive disorder (MDD), obesity, and autism spectrum disorders (ASD). However, not much is known about how AC3 functions in the brain. What is known is that many neurodevelopmental disorders or psychiatric diseases, such as depression and autism, exhibit profound differences between males and females, known as sexual dimorphism.

For example, females have a higher risk of depression, whereas autism affects more males, with a boy to girl ratio of four to one. The problem is that it is unclear what causes the differences.

The researchers took a closer look at the phosphorylation in the brain, a process when groups of chemicals called phosphates attach to proteins to regulate them, to see which were influenced based on gender.

They identified 204 proteins that were more highly regulated in females than in males. Of those, a large percentage (31%) were associated with autism.

"Our results suggest that proteins in the female brain, particularly autism-related proteins, are more tightly regulated than those in the male brain possibly helping to prevent the development of autism in females," said Chen.

The researchers point to evolution for possibly playing a part in how these proteins behave based on the key roles or functions of each sex. The female role has traditionally been multi-tasking several activities like childrearing, caring for the family, the home, and preparing meals whereas male tasks were more specifically focused on functions like hunting and gathering.

You can see this highly focused trait in autistic males who are very smart but tend to be fixated on one thing and not interested in, or cannot handle, other social interactions.

Chen says that this research is still in the early phase with mouse models and more studies are needed, but he is hopeful that it may open up a new research direction and one day could possibly lead to a new pharmacological treatment.

Contributing to these findings are Yuxin Zhou, doctoral candidate; Liyan Qiu, research scientist; and Ashley Sterpka, doctoral candidate, Feixia Chu, associate professor, all at UNH, and Haiying Wang, assistant professor at the University of Connecticut.

This work was supported by the National Institutes of Health (NIH) research funding, NIH COBRE program, and a Cole Neuroscience and Behavioral Faculty Research award.

http://bit.ly/2T2qt6r

What's for dinner? Sushi, with a side of crickets

While insects have been consumed for centuries worldwide, many people still haven't warmed to the idea of a creepy-crawly on the tongue.

But if your next dinner recipe involves raw fish, seaweed, wasabi and rice - the key ingredients for sushi - chances are you might enjoy some deep-fried crickets or beetles on the side.

For the first time, an international study led by La Trobe University and the University of Pennsylvania, has found that people who frequently consume sushi are more open to introducing edible insects into their diets.

This was particularly the case with the American sample - of the 82 per cent of participants questioned in the study who said they would be willing to eat insects, 43 per cent ate sushi on a regular basis.

Co-author Dr Matthew Ruby, Lecturer in Psychology at La Trobe University, said sushi could be considered a gateway food to insects.

"Until relatively recently, the idea of trying sushi - let alone having it become a mainstream menu item - was often thought of with disgust in many societies," Dr Ruby said.

"Just like eating sushi, eating insects will take some getting used to."

"It appears the more open you are to 'exotic' foods, the more willing you'll be to taste-test a grasshopper, or an ant, or even a spider."

The researched involved 476 participants - 275 from the United States and 201 India. In addition to the link between eating sushi and consuming insects, other key findings included:

- 82 per cent of American participants said they would consider eating insects in general, compared to 34 per cent of Indian participants

- 80 per cent of American participants said they would consider eating foods containing whole insects, compared to 48 per cent of Indian participants

- In both countries, a higher percentage of men than women were willing to eat insects, both whole and incorporated into other foods

- Almost 26 per cent of Indian participants felt that eating insects violated a protected value (meaning, they would not eat insects no matter how great the benefits, nor how minor the risks), compared to just 4 per cent of American participants

- 65 per cent of American participants agreed that rearing insects as food generates less pollution and greenhouse gas than rearing conventional livestock, compared to 28 per cent of Indian participants

Co-author Paul Rozin, Professor Emeritus of Psychology at the University of Pennsylvania, noted that 28 per cent of Indian participants and 65 per cent of American participants were willing to try food containing at least 1 per cent insect flour.

"Insect flour can be found as a protein-rich substitute for some standard grain flours in products like crackers, biscuits and protein bars," Professor Emeritus Rozin said.

"This could be another way to introduce insects into your diet, if the idea of crunching into a whole bug doesn't appeal to you."

There are over 2,000 edible species of insects throughout the world. Many species are non-toxic and can serve as a source of high-quality protein and micronutrients.

Furthermore, raising insects for food is typically much more environmentally sustainable than many commonly consumed animals in terms of food efficiency, water use, required farming space, and greenhouse gas emissions.

The research has been published in Food Quality and Preference.

http://bit.ly/2HhpOFU

Sepsis a leading cause of death in US hospitals but many deaths may not be preventable

Until now, the extent to which sepsis-related deaths might be preventable has not been studied

Sepsis is a major contributor to disability, death and health care costs in the United States and worldwide. A growing recognition of the high burden of sepsis as well as media coverage of high-profile, sepsis-induced deaths have catalyzed new efforts to prevent and manage the disease. While new initiatives have been beneficial in paving the road toward better detection and treatment of sepsis, the role of sepsis in associated deaths and their preventability remain largely unknown. To address this question, a research team at Brigham and Women's Hospital has comprehensively reviewed the characteristics and clinical management of patients who died with sepsis. The results are published in JAMA Network Open.

"It seems intuitive that all infections should be curable with antibiotics," said Chanu Rhee, MD, MPH, lead author and critical care physician at the Brigham. "But up until now, the extent to which sepsis-related deaths might be preventable has not been studied."

Rhee and colleagues retrospectively reviewed the medical records of patients who died in hospital or were discharged to end-of-life hospice care between January 2014 and December 2015. The study cohort consisted of 568 patients admitted across six acute-care hospitals -- three academic medical centers and three community hospitals. Using a standardized form, clinicians systematically reviewed medical records for presence of sepsis, clinical comorbidities, cause of death and indications of suboptimal sepsis care. The preventability of each sepsis-associated death was then evaluated in consideration of the above factors, and the patient's own goals of care.

The results confirmed the high prevalence of sepsis in hospital settings and its hefty contribution to mortality: sepsis was present in over 50 percent of terminal hospitalizations and was the immediate cause of death in 35 percent of all cases. However, analyses revealed that nearly 90 percent of deaths from sepsis were considered unpreventable from the standpoint of hospital-based care. Only one in eight of all sepsis-associated deaths were potentially preventable, and of these, only one in twenty-five were moderately or highly likely preventable. While there were no indications of suboptimal care in 77 percent of sepsis-associated deaths, the most common problems in the remaining cases were delays in antibiotic administration or in source control.

Why does the prevention of death from sepsis remain elusive despite high clinical awareness and delivery of care? The answer may lie in the underlying features of the patients themselves. Many patients were elderly with severe comorbidities, including cancer, chronic heart disease, and chronic lung disease. Additionally, many expressed goals of care which were not consistent with receiving aggressive treatment. Some patients were so severely ill from their sepsis by the time they reached the hospital that nothing further could be done at that point.

"Sepsis is a leading cause of death," said Rhee, "but since most of these deaths are occurring in very complex patients with severe comorbidities, many of them may not be preventable with better hospital-based care. For me, as a critical care physician, that resonated with what I see in my clinical practice. A lot of sepsis patients we treat are extremely sick, and even when they receive timely and optimal medical care, many do not survive. It was important for me to see that borne out of the more rigorous study we did."

In the future, Rhee and colleagues hope to replicate their findings in different hospital settings to further the generalizability of their results. In addition, they hope to investigate whether better preventative care prior to hospitalization could help reduce the prevalence of sepsis-related deaths.

"The point of this study is not to diminish the importance of sepsis quality-improvement issues in hospitals -- even one preventable death is too much," Rhee said. "In addition, since we only reviewed

medical records for patients who died, our study doesn't highlight all the other patients with sepsis for whom timely recognition and care in the hospital actually did prevent death. One of the takeaways, however, is that further innovation in the prevention of underlying conditions might be necessary before we can see a really large reduction in sepsis mortality."

Funding for this work was provided by the Prevention Epicenters Program of the Centers for Disease Control and Prevention (CDC) and the Agency for Healthcare Research and Quality.

Paper cited: Rhee, C et al. "Prevalence, Underlying Causes, and Preventability of Sepsis-Associated Mortality in US Acute Care Hospitals," JAMA Network Open, *DOI: 10.1001/jamanetworkopen.2018.7571*

http://bit.ly/2VUOuHC

A world full of copper helped animals colonise the Earth

An abundance of copper played an equally crucial role to oxygen in helping the rise and spread of the earliest animals 700 million years ago.

Scientists have analysed geological records to prove that the level of copper in the environment increased dramatically at the same time as the first animals started to emerge.

Copper is an essential building block of life, creating proteins that were crucial in helping early animal life—such as jellyfish and sea sponges—develop respiratory systems.

The relatively low level of oxygen in the environment during the Neoproterozoic period—when the first multicellular life began to emerge—has led scientists to investigate other factors that might have been involved.

By discovering a dramatic increase in the availability of copper during this period, geologists from the Universities of Aberdeen and Glasgow have revealed the crucial role it played in helping early life thrive.

Professor John Parnell, from the University of Aberdeen's School of Geosciences, led the study, published today in *Scientific Reports*.

He said: "Our research shows that across the planet, magmas from deep in the Earth brought copper-bearing volcanic rocks to the surface about 800 million years ago.

"These rocks were weathered to release abundant copper into the environment, just as animals were starting to appear.

"Animals use copper in several ways, but two critical functions of the metal give animals the strength to support themselves, and the ability to breathe oxygen from the air by making compounds called copper proteins, which are essential to the way they live.

"Oxygen in the air had the double role of weathering rocks to provide copper, and of letting animals breathe, which they could do using their copper proteins. Oxygen was actually toxic to earlier primitive life, but copper gave animals the means to cope with it and use it to their advantage—it was a clever bit of evolution."

Fellow author Professor Adrian Boyce of the University of Glasgow added: "It's no coincidence that some of the biggest copper ore deposits in the world, in Africa, formed just as the first animals were starting to emerge. Life and rocks were in harmony."

More information: *J. Parnell et al. Neoproterozoic copper cycling, and the rise of metazoans, Scientific Reports (2019). DOI: 10.1038/s41598-019-40484-y*

https://wb.md/2TNOxYq

Popular Spice Rivals Stimulant for ADHD

Appears to be as effective as the stimulant methylphenidate in treating symptoms

Batya Swift Yasgur, MA, LSW

The popular and expensive spice saffron (*Crocus sativus* L*)*, appears to be as effective as the stimulant methylphenidate (MPH) in treating symptoms in youngsters with attention deficit hyperactivity disorder (ADHD), new research suggests.

In a randomized 6-week trial, a team of investigators from Tehran University of Medical Sciences in Iran, found there were no significant differences in efficacy or adverse events in the saffron vs MPH group.

"From this preliminary study, the main point is that we can consider saffron as an alternative [to stimulants] in patients with ADHD," senior author Shahin Akhondzadeh, PhD, FBPhS, DSc, professor of clinical psychopharmacology, Roozbeh Psychiatric Hospital, Tehran University of Medical Sciences, Iran, told *Medscape Medical News*. "Short-term efficacy of saffron demonstrated the same efficacy as methylphenidate, although larger, controlled studies with longer treatment periods are necessary to verify the findings," he said.

The study was published online February 11 in the *Journal of Child and Adolescent Psychopharmacology*.

Empty Place

MPH, which is commonly used to treat ADHD, has many side effects, including loss of appetite, sleep disturbances, and nausea, the authors note. Moreover, approximately 30% of children do not respond to MPH, leading to a search for nonstimulant strategies.

"Many antidepressants have been used as alternatives to stimulants in patients with ADHD that cannot tolerate Ritalin or do not respond to Ritalin," Akhondzadeh said.

However, antidepressants are also associated with adverse events, with results that are "often unsatisfactory," the authors note.

This leaves an "empty place to be filled by alternative medications, in particular herbal medications," they add.

Saffron has traditionally been used for a variety of medicinal purposes, including its antispasmodic, antiseptic, anticancer, and anticonvulsant effects.

Saffron and its active constituents appear to increase the reuptake inhibition of dopamine and norepinephrine and are N-methyl D-aspartic acid (NMDA) receptor antagonists and GABA-α agonists.

"As you may know, my country is the main producer of saffron and about 90% of saffron is from Iran — indeed, saffron is a Persian herb with history as long as the Persian Empire," Akhondzadeh noted.

"There are solid documents in the Persian traditional medicine about the psychotropic effects of saffron, but we need evidence-based medicine in traditional medicine as well.

"My research group at Roozbeh Psychiatry Hospital has studied the psychotropic effects of saffron since early 2000, and we have documented its antidepressant effects," he added.

To investigate the question, the researchers conducted a randomized, double-blind pilot trial to compare the efficacy and safety of saffron capsules with MPH in a group of outpatient children (age 6 - 17 years).

Patients were required to have total and/or subscale scores on the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) of ≥ 1.5 standard deviations (SDs) above norms for the patient's age and gender.

The Parent and Teacher ADHD-RSI-IV was administered at baseline, and then at 3 and 6 weeks.

Patients (n = 54) were randomized to two parallel groups (n = 27 per group). Of these, 25 patients in each group completed the trial.

One group received MPH beginning at a dose of 0.3 - 1 mg/kg/day, which was titrated up during the trial.

The second group received saffron capsules at a dose of 20 - 30 mg/day, depending on the child's weight.

There were no significant differences in basic characteristics (eg, age and gender) between the two groups.

Cost a Concern

No significant difference was found in Parent ADHD Rating Scale scores at baseline between the saffron and the MPH groups (34.20 ± 4.69 vs 33.56 ± 6.48, respectively; mean difference [MD], 0.64; 95% confidence interval [CI], –2.58 to 3.86; $t = –0.400$; df = 48; $P = .691$).

Moreover, general linear model repeated measures also showed no significant effect for treatment (between-subject factor; $F = 0.672$; df = 1; $P = .416$). A time × treatment calculation showed a similar trend of the two treatment groups across time in both hyperactivity and inattention.

Moreover, a significant effect of both treatments on improving Parent ADHD Rating Scale scores was demonstrated ($P < .001$).

Post hoc comparisons of the Parent ADHD Rating Scale showed a significant reduction as soon as week 3 ($P < .001$) in both groups, and there was no significant difference between the treatment groups at endpoint ($P = .975$).

Similar findings were obtained in the Teacher ADHD-RS-IV scores, with no significant difference in baseline total scores between the saffron and the MPH groups (24.16 ± 8.32 vs 23.64 ± 8.16, respectively; MD, 0.52; 95% CI, –4.16 to 5.20; $t = –0.223$; df = 48; $P = 0.824$), time to improvement, and reduction in symptoms at study endpoint.

No serious adverse event was recorded in any of the patients, and non-serious events (eg, headache, dry mouth, insomnia, decreased appetite) were similar between the two groups.

"This study provides evidence for satisfactory outcomes with saffron in treatment of ADHD," the authors write. However, Akhondzadeh acknowledged that the cost of saffron is a concern.

"Although saffron is the most expensive spice, the daily dosage that we used in this study is equal to 60 mg pure saffron," he reported.

"Therefore any product from Iran is cheaper than common stimulants and from Europe is about €1 [$1.20] for each capsule," he said.

He noted that there are some saffron-based antidepressant products, based on his previous studies, available in Iran and in Europe.

Although saffron is available as a spice in the United States, "there is no guaranty that it will have the same medicinal effect if used in a meal, since the main component of our extract is crocin," he added.

Preliminary but Promising

Commenting on the study for *Medscape Medical News*, Patricia L. Gerbarg, MD, assistant clinical professor in psychiatry, New York Medical College, Valhalla, and Richard P. Brown, MD, associate professor in clinical psychiatry at Columbia University College of Medicine, New York, NY, called it a "credible" and "well-done randomized controlled trial."

The authors "appropriately note that this is positive preliminary evidence and that additional trials are needed to replicate these initial very positive findings," Gerbarg and Brown, who were not involved with the study, told *Medscape Medical News* via email.

The study was conducted in Iran, "where ethnic populations may have genetic variants that enable them to respond more positively or more robustly to saffron than other populations," which has been "noted with other herbs."

It is therefore "particularly important to replicate this study in a population that is not Iranian, to verify efficacy in other countries," noted Brown and Gerbarg, who are coeditors of *Complementary and Integrative Treatments in Psychiatric Practice* (Washington, DC: American Psychiatric Association Publishing; 2017), which has a chapter on saffron.

"Each practitioner must decide whether they feel that this evidence is promising enough to justify a trial of optimized saffron on a case-by-case basis [that] takes into account the observation that saffron is very low in side effects, so the risks are minimal," they said.

Moreover, "if the saffron is beneficial, it may be possible to reduce the dose or discontinue a prescription stimulant, which could spare the patient who may be experiencing side effects," Gerbarg and Brown add.

They warned that practitioners "should learn about what to look for in selecting the highest quality brands of saffron available."

The researchers acknowledge that more research is needed, including larger placebo-controlled studies with longer treatment periods in a "broader spectrum of ADHD patients, including those with comorbid mood and anxiety disorders, sleep problems, and ADHD patients with inattentive presentation."

The study was supported by a grant from Tehran University of Medical Sciences. Gerbarg, Brown, and Akhondzadeh and his coauthors have disclosed no relevant financial relationships.

J Child Adolesc Psychopharmacol. Published online February 11, 2019. Full text

http://bit.ly/2JbNsW9

Immigration is beneficial to economies, even after 100 years

A new study in the* Review of Economic Studies *finds that U.S. counties with more historical immigration have higher incomes, less poverty, and lower unemployment today.

An important issue in current American political discourse is the effect that immigrants have on the communities in which they settle. While this topic has received significant attention, the focus has generally been on the short-term effects of immigrants. We know much less about the long-run consequences of immigration.

Researchers studied the effects of immigration into the United States from 1850 to 1920, a period in which immigration to the country increased dramatically, and the immigration sources also changed. In 1850 over 90% of foreign-born people living in the United States were from Great Britain, Ireland, or Germany. By 1920, this figure was only 45%.

The authors found that immigration resulted in benefits that were felt soon after their arrival. Immigration resulted in more and larger manufacturing establishments, greater agricultural productivity, and higher rates of innovation. These findings are consistent with a long-standing narrative suggesting that immigrants contribute to economic growth by providing an ample supply of unskilled labor, as well as a smaller supply of skilled people, who bring with them knowledge and innovations that are important for development.

The size of the effects suggest that increasing the percentage of immigrants in a county by 4.9% results in a 13% increase in average per capita income today, a 44% increase in average manufacturing output per capita from 1860-1920 (and a 78% increase in 1930), a 37% increase in farm values, and a 152% increase in the number of patents per capita.

The researchers also found that these economic benefits did not have long-run social costs. Places with more historical immigrant settlement today have similar levels of social capital, civic participation, and crime rates.

"What is fascinating is that despite the exceptionalism of this period in US history," said the paper's lead author, Sandra Sequeira. "There are several important parallels that one could draw between then and now: the large influx of unskilled labor, the small but important inflow of highly skilled innovators, as well as the significant short-run social backlash against immigration. There is much to be learned from taking a longer perspective on the immigration debate."

The paper, "Immigrants and the Making of America" is available at: https://academic.oup.com/restud/article-lookup/doi/10.1093/restud/rdz003

http://bit.ly/2Fa4y2F

Mammoth moves: frozen cells come to life, but only just

The woolly mammal is unlikely to be walking among us soon

A team of scientists in Japan has successfully coaxed activity from 28,000-year-old cells from a frozen mammoth implanted into mouse cells, but the woolly mammal is unlikely to be walking among us soon.

The project by an international team took cell nuclei from a well-preserved mammoth discovered in 2011 in Siberian permafrost and placed them into several dozen mouse egg cells.

Of those, five displayed the biological reactions that happen just before cell division begins, said Kei Miyamoto, a member of the team at Kindai University in western Japan.

None, however, produced the actual cell division needed for a mammoth rebirth, the researcher told AFP.

The frozen carcass of a female mammoth on display in Yokohama a few years ago.

"This suggests that, despite the years that have passed, cell activity can still happen and parts of it can be recreated," he told AFP.

"Until now many studies have focused on analysing fossil DNA and not whether they still function," he added.

The research—published Monday in the journal *Scientific Reports*—doesn't provide much hope for Jurassic Park-style resurrection of long-extinct species just yet, he cautioned.

"We have also learned that damage to cells was very profound."

"We are yet to see even cell divisions. I have to say we are very far from recreating a mammoth."

The university has worked with other Japanese and Russian institutes to study and to possibly clone the mammoth and plans to study alternative methods to bring the prehistoric giant back to life.

"We need new technology, we want to try various approaches," Miyamoto said.

http://bit.ly/2T5lETf

Secrets of early life revealed from less than half a teaspoon of blood

Pioneering technology could pave the way for improved newborn vaccines

A global team of scientists have mapped the developmental pathway of a newborn's life for the first time. The research, published in *Nature Communications*, could transform our understanding of health and disease in babies.

Co-led by the MRC Unit The Gambia at the London School of Hygiene & Tropical Medicine, the new study included lifting the lid on what genes are turned on, what proteins are being made and what metabolites are changing in the first seven days of human life.

Newborn babies are the most vulnerable population when it comes to infectious disease. Establishing key pathways in early development could help measure the impact of factors such as diet, disease and maternal health, as well as key interventions like vaccines.

The study was conducted by the Expanded Program on Immunization Consortium (EPIC) research team, which includes MRC Unit The Gambia at the London School of Hygiene & Tropical Medicine, Boston Children's Hospital, the University of British Columbia, and the Papua New Guinea Institute of Medical Research.

The first week of a newborn's life is a time of rapid biological change as the baby adapts to living outside the womb, suddenly exposed to new bacteria and viruses, yet surprisingly little is known about these early changes. One of the biggest challenges in gathering data on newborn development has been sourcing a large enough blood sample for comprehensive profiling from a tiny newborn. The team overcame this with pioneering laboratory techniques applied on less than half a teaspoon of blood.

By using sophisticated software and new approaches they integrated different kinds of measurements to interpret the complex data derived from the precious samples. Thousands of changes over the first week of life were found including in gene expression and components involved in immunity.

Senior author Beate Kampmann, Professor of Paediatric Infection and Immunity from the London School of Hygiene & Tropical Medicine and Director of its Vaccine Centre, said: "Up to two thirds of newborn deaths can be prevented if effective health measures are provided at birth and during the first week of life. Of the 5.4 million under-five child deaths per year, about half occur during the neonatal period, i.e. the first month of life.

"Knowledge about key developmental processes during our earliest days remains sparse, but this study plugs some of those crucial gaps. This work is particularly important for vaccine research. Newborns have very limited protection from infection in early life and there is an urgent need to optimise protective measures, including vaccines, used in this age group."

Working closely with local communities, the research team recruited newborns in a health centre in The Gambia, West Africa. They took blood samples from the babies on the day of birth, and then again either on day one, three or seven.

The samples were processed in the collaborating laboratories in Africa and North America, where the researchers discovered dramatic molecular changes driven by development. The findings were then validated in a second group of Australasian newborns. The two independent cohorts were found to have common, highly dynamic developmental trajectories, suggesting that the changes do not occur at random, but instead follow an age-specific pathway.

Prof Kampmann said: "The MRC Unit in The Gambia has carried out important studies in newborns for a long time in order to optimize the use of vaccines. Given our excellent community relations and infrastructure, we were ready to partner with our collaborators to apply the new tools of systems biology to very small blood samples. We wanted to establish this work in a real world situation in order to gain insight into immune development in a setting where new interventions can have the biggest impact on newborn survival."

Ofer Levy, Director of the Precision Vaccines Program at Boston Children's Hospital and a senior author on the paper, said: "Most infections in the world occur early in life, and newborns have the greatest susceptibility and the worst outcomes. This work provides a valuable window into health and disease in the first week of life. Our exciting findings allows us to ask bigger questions about the differences between different populations and the impact of biomedical interventions such as vaccines on development.

"Currently, most vaccines are developed by trial and error. We seek deep molecular insight into vaccine function in early life so we can better develop infant vaccines for the future. We demonstrated that it's possible to recruit newborns in a resource-poor setting, obtain small amounts of their blood, process it, ship it, conduct systems biology assays and integrate the results -- turning big data into knowledge."

Going forward, the EPIC team is currently investigating the impact of different vaccines on this early developmental trajectory in a larger cohort in The Gambia and Papua New Guinea.

The authors acknowledge limitations of their study including validation in larger cohorts and increasing our functional insights into the discovered pathways.

This study was funded through core grants from the Medical Research Council and the National Institutes of Health.

http://bit.ly/2F0E9mw

Researchers create SAMβA, a new molecule to treat heart failure

This innovation has been developed by researchers based in Brazil and the US. It not only halts the progression of heart failure but also improves the heart's capacity to pump blood.

A group of researchers based in Brazil and the United States have developed a molecule that halts the progression of heart failure and improves the heart's capacity to pump blood.

Rats with heart failure were treated for six weeks with the molecule, called "SAMβA." The disease not only stabilized, as it usually does in response to conventional drug therapy, but actually regressed, thanks to an improvement in the contractile capacity of the cardiac muscle.

Heart failure may result from myocardial infarction, commonly known as a heart attack, when a blocked coronary artery prevents blood from reaching a section of the heart. The rest of the cardiac tissue is overloaded, and the heart's capacity to pump blood throughout the body gradually declines over time.

The researchers have applied for a patent on SAMβA and its use in the United States. The molecule may come to supplement or even replace the medications currently used to treat heart failure, most of which were developed back in the 1980s.

An article describing SAMβA has been published in *Nature Communications*. The name SAMβA stands for "selective antagonist of mitofusin 1-β2PKC association," referring to the molecule's capacity to inhibit the interaction between protein kinase C beta 2 (β2PKC), a common protein in heart cells, and mitofusin 1 (Mfn1), a key element of mitochondria, which are the organelles that produce energy for cells.

In this interaction, β2PKC inhibits Mfn1, preventing the mitochondria from producing energy and hence weakening the heart's blood-pumping action.

"This interaction was one of our main findings in this study. Its critical role in the progression of heart failure was previously unknown," said Julio Cesar Batista Ferreira, a professor at the University of São Paulo's Biomedical Science Institute (ICB-USP) in Brazil and principal investigator for the study. Ferreira began research in the field in 2009 when he was a postdoctoral fellow at the same university's School of Physical Education and Sports (EEFE-USP) with a scholarship from FAPESP - São Paulo Research Foundation.

Once the patent has been granted, Ferreira added, the molecule can be tested in connection with hypertension and other cardiovascular diseases.

"We suspect the interaction between these two proteins may be a factor in other degenerative diseases involving mitochondrial dysfunction," Ferreira told Office.

Clerk and managers

Previous research by Ferreira's group at ICB-USP showed that the inhibition of β2PKC, which is overproduced in the cells of failing hearts, improved cardiac function in these patients. However, the intervention prevented the protein from acting in other ways that benefit the heart.

The novelty of SAMβA is its selectivity: it inhibits only β2PKC's interaction with Mfn1 in mitochondria and does not affect the protein's other actions.

Ferreira offers an analogy to explain this selectivity, comparing a heart cell to a company office with several rooms. β2PKC is an office clerk who moves along the corridors and goes into the different rooms, interacting with the managers of the respective sectors to perform his/her duties. When he/she enters one particular room (the mitochondrion), however, the office clerk (β2PKC) prevents a particular manager (Mfn1) from doing his/her job.

With the first molecule developed by the group, it was as if the doors of all the rooms were closed. The office clerk no longer hampered the mitochondrial manager and did not enter any other rooms; the company (heart cell) did not function harmoniously.

However, all SAMβA does is prevent β2PKC from interacting with Mfn1 in mitochondria. "It's as if we only closed the door to the room the clerk isn't allowed to enter while leaving him free to go into all

the others, so the company can continue functioning properly," Ferreira said.

Infarcted rats

To arrive at SAMβA, the researchers performed tests with recombinant proteins, cells, animals, and samples of cardiac tissue from patients with heart failure.

Ferreira's group first conducted different in vitro experiments to test the interaction between β2PKC and Mfn1. They found six molecules that inhibited the interaction, but only SAMβA did so selectively without influencing other interactions.

Next, SAMβA was tested in human heart cells. In addition to halting the progression of the disease, which is already achieved by the drugs currently in use, the molecule boosted the cells' capacity to contract - an essential part of the job done by the heart in pumping blood throughout the body.

SAMβA also reduced the amount of hydrogen peroxide in heart cell mitochondria. The presence of this peroxide characterizes oxidative stress, which is a trigger of cardiac cell degeneration.

Finally, the researchers induced myocardial infarction in rats. One month later, the rats developed heart failure, and an osmotic pump was implanted under the skin of each rat to release small amounts of SAMβA or an innocuous substance (in the case of the control group) for six weeks.

Unlike the control rats, those that were treated with SAMβA stopped exhibiting heart failure, and their cardiac function improved.

"The drugs in current use halt progression of the disease but never make it regress. We showed that by regulating this specific interaction, we could both halt progression and make the disease regress to a less severe stage," Ferreira said.

The next step is to make SAMβA available to other research groups for testing against other diseases in different experimental models. It will also be necessary to test the molecule's interaction with the drugs now used to treat heart failure.

"Validation and reproduction of our findings by other groups are critical to the process of developing SAMβA for use in treating heart failure. We will be seeking partners in the private and public sectors for this purpose," Ferreira said.

Cardiovascular diseases kill 17.9 million people annually, causing 31% of all global deaths, according to the World Health Organization (WHO). Acute myocardial infarction with subsequent heart failure is a major cause of morbidity and mortality worldwide.

http://bit.ly/2J6v6Wu

Your body is your internet -- and now it can't be hacked

Researchers have protected your pacemaker, other medical tech from remote hacks before they happen

WEST LAFAYETTE, Ind. -- Someone could hack into your pacemaker or insulin pump and potentially kill you, just by intercepting and analyzing wireless signals. This hasn't happened in real life yet, but researchers have been demonstrating for at least a decade that it's possible.

Before the first crime happens, Purdue University engineers have tightened security on the "internet of body." Now, the network you didn't know you had is only accessible by you and your devices, thanks to technology that keeps communication signals within the body itself.

The work appears in the journal Scientific Reports. Study authors include Shreyas Sen, an assistant professor of electrical and computer engineering at Purdue, and his students, Debayan Das, Shovan Maity and Baibhab Chatterjee.

"We're connecting more and more devices to the human body network, from smart watches and fitness trackers to head-mounted

virtual reality displays," said Sen, who specializes in sensing and communication systems.

"The challenge has not only been keeping this communication within the body so that no one can intercept it, but also getting higher bandwidth and less battery consumption," he said.

Body fluids carry electrical signals very well. So far, so-called "body area networks" have used Bluetooth technology to send signals on and around the body. These electromagnetic waves can be picked up within at least a 10-meter radius of a person.

Sen's team has demonstrated a way for human body communication to occur more securely - not going beyond a centimeter off the skin and using 100 times less energy than traditional Bluetooth communication.

This is possible through a device that couples signals in the electro-quasistatic range, which is much lower on the electromagnetic spectrum. Sen's group is working with government and industry to incorporate this device into a dust-sized integrated circuit.

A YouTube video is available at https://youtu.be/NHqfT1vIe6E.

Through a prototype watch, a person can receive a signal from anywhere on the body, from the ears all the way down to the toes. The thickness of your skin or hair also doesn't really make a difference in how well you carry the signal, Sen says.

The idea would be to create a way for doctors to reprogram medical devices without invasive surgery. The technology would also help streamline the advent of closed-loop bioelectronic medicine - in which wearable or implantable medical devices function as drugs, but without the side effects - and high-speed brain imaging for neuroscience applications.

"We show for the first time a physical understanding of the security properties of human body communication to enable a covert body area network, so that no one can snoop important information," Sen said.

The technology has received multiple patents through the Purdue Research Foundation Office of Technology Commercialization.

This work was supported by the Air Force Office of Scientific Research YIP Award (FA9550-17-1-0450) and the National Science Foundation CRII Award (CNS 1657455).

The research also aligns with Purdue's Giant Leaps celebration, acknowledging the university's global advancements made in health, longevity and quality of life as part of Purdue's 150th anniversary. This is one of the four themes of the yearlong celebration's Ideas Festival, designed to showcase Purdue as an intellectual center solving real-world issues.

ABSTRACT

Enabling covert body-area network using electro-quasistatic human body communication

Debayan Das, Shovan Maity, Baibhab Chatterjee, Shreyas Sen

Purdue University, West Lafayette, IN, USA doi: 10.1038/s41598-018-38303-x

http://bit.ly/2HqCwVB

NUS study: Eating mushrooms may reduce the risk of cognitive decline

Researchers found seniors who ate more than 300 grams of cooked mushrooms a week were half as likely to have mild cognitive impairment

A team from the Department of Psychological Medicine and Department of Biochemistry at the Yong Loo Lin School of Medicine at the National University of Singapore (NUS) has found that seniors who consume more than two standard portions of mushrooms weekly may have 50 per cent reduced odds of having mild cognitive impairment (MCI).

A portion was defined as three quarters of a cup of cooked mushrooms with an average weight of around 150 grams. Two portions would be equivalent to approximately half a plate. While the portion sizes act as a guideline, it was shown that even one small portion of mushrooms a week may still be beneficial to reduce chances of MCI.

"This correlation is surprising and encouraging. It seems that a commonly available single ingredient could have a dramatic effect on cognitive decline," said Assistant Professor Lei Feng, who is from

the NUS Department of Psychological Medicine, and the lead author of this work.

The six-year study, which was conducted from 2011 to 2017, collected data from more than 600 Chinese seniors over the age of 60 living in Singapore. The research was carried out with support from the Life Sciences Institute and the Mind Science Centre at NUS, as well as the Singapore Ministry of Health's National Medical Research Council. The results were published online in the Journal of Alzheimer's Disease on 12 March 2019.

Determining MCI in seniors

MCI is typically viewed as the stage between the cognitive decline of normal ageing and the more serious decline of dementia. Seniors afflicted with MCI often display some form of memory loss or forgetfulness and may also show deficit on other cognitive function such as language, attention and visuospatial abilities. However, the changes can be subtle, as they do not experience disabling cognitive deficits that affect everyday life activities, which is characteristic of Alzheimer's and other forms of dementia.

"People with MCI are still able to carry out their normal daily activities. So, what we had to determine in this study is whether these seniors had poorer performance on standard neuropsychologist tests than other people of the same age and education background," explained Asst Prof Feng. "Neuropsychological tests are specifically designed tasks that can measure various aspects of a person's cognitive abilities. In fact, some of the tests we used in this study are adopted from commonly used IQ test battery, the Wechsler Adult Intelligence Scale (WAIS)."

As such, the researchers conducted extensive interviews and tests with the senior citizens to determine an accurate diagnosis. "The interview takes into account demographic information, medical history, psychological factors, and dietary habits. A nurse will measure blood pressure, weight, height, handgrip, and walking speed. They will also do a simple screen test on cognition, depression, anxiety," said Asst Prof Feng.

After this, a two-hour standard neuropsychological assessment was performed, along with a dementia rating. The overall results of these tests were discussed in depth with expert psychiatrists involved in the study to get a diagnostic consensus.

Mushrooms and cognitive impairment

Six commonly consumed mushrooms in Singapore were referenced in the study. They were golden, oyster, shiitake and white button mushrooms, as well as dried and canned mushrooms. However, it is likely that other mushrooms not referenced would also have beneficial effects.

The researchers believe the reason for the reduced prevalence of MCI in mushroom eaters may be down to a specific compound found in almost all varieties. "We're very interested in a compound called ergothioneine (ET)," said Dr Irwin Cheah, Senior Research Fellow at the NUS Department of Biochemistry. "ET is a unique antioxidant and anti-inflammatory which humans are unable to synthesise on their own. But it can be obtained from dietary sources, one of the main ones being mushrooms."

An earlier study by the team on elderly Singaporeans revealed that plasma levels of ET in participants with MCI were significantly lower than age-matched healthy individuals. The work, which was published in the journal *Biochemical and Biophysical Research Communications* in 2016, led to the belief that a deficiency in ET may be a risk factor for neurodegeneration, and increasing ET intake through mushroom consumption might possibly promote cognitive health.

Other compounds contained within mushrooms may also be advantageous for decreasing the risk of cognitive decline. Certain hericenones, erinacines, scabronines and dictyophorines may promote the synthesis of nerve growth factors. Bioactive compounds

in mushrooms may also protect the brain from neurodegeneration by inhibiting production of beta amyloid and phosphorylated tau, and acetylcholinesterase.

Next steps

The potential next stage of research for the team is to perform a randomised controlled trial with the pure compound of ET and other plant-based ingredients, such as L-theanine and catechins from tea leaves, to determine the efficacy of such phytonutrients in delaying cognitive decline. Such interventional studies will lead to more robust conclusion on causal relationship. In addition, Asst Prof Feng and his team also hope to identify other dietary factors that could be associated with healthy brain ageing and reduced risk of age-related conditions in the future.

http://bit.ly/2EWkeoR

People with dwarfism and cleft palate may have been revered in ancient times

Challenging the common notion that life in the past was nasty, brutish, and short

By Andrew Curry

BERLIN—Researchers have been finding them for decades: bones that are too heavy or too light; too long or too short; twisted, perforated, or studded with protruding growth. They're a sign that someone in the past suffered from a rare disease, often defined today as affecting fewer than one in 2000 people, such as dwarfism or osteopetrosis, a disorder that causes dense, brittle bones.

This medieval Hungarian man who had severe cleft palate received a hero's burial. **Luca Kis**

But few scientists have studied these cases or what they reveal about ancient societies. An unusual workshop here this month, which drew more than 130 paleopathologists, bioarchaeologists, geneticists, and rare disease experts, could change that. "This is really the first time people have been confronted with this subject," says Michael Schultz, a paleopathologist at Georg August University of Göttingen in Germany.

Case after case challenged the common notion that life in the past was nasty, brutish, and short. In a line of research called the bioarchaeology of care, scientists are finding that people with rare diseases often enjoyed the support of their societies, survived well into adulthood, and were buried with their communities, not as marginalized outsiders. The lifelong nature and unusual symptoms of some rare conditions—which were effectively unique in small societies—set them apart from typical diseases of old age such as arthritis. "We want to use the individual as a prism to look at the community," says bioarchaeologist Jane Buikstra of Arizona State University in Tempe.

After excavating a partially preserved mummy buried around 1200 C.E. by the Chachapoya people in northern Peru, physical anthropologist Marla Toyne at the University of Central Florida in Orlando noted the man's collapsed spine and bone loss—signs of late-stage adult T-cell leukemia, which probably killed him. "He had fragile bones, pain in his joints—he wasn't walking a great deal," she says—a tremendous handicap in his mountain homeland.

But he was buried in an elite cliffside tomb and his bones lacked signs of stress, suggesting years of light work. "We begin with the individual, but they never live alone," Toyne says. "The community was aware of his suffering. And they most likely had to make some accommodations for his care and treatment."

In some cases, "disease" may not be the best descriptor, because past cultures may have honored people with conditions considered disabilities today. In ancient Egypt, for example, textual evidence and iconography suggest dwarfism was considered a link to the

divine, and rulers sought out people with dwarfism as companions and courtiers. “They are not considered people with disabilities—they were special,” says bioarchaeologist Anna Pieri, an independent researcher in Livorno, Italy.

Pieri recently identified two 4900-year-old cases of dwarfism in prehistoric Hierakonpolis in Egypt. The burials suggest the Egyptian fascination with dwarfs extended further back than previously known, to before the first pharaohs. The man and woman were buried at the center of two separate royal tombs. In his 30s or even 40s, the man was one of the cemetery’s oldest burials, suggesting a life of ease—further evidence of high status. Recent x-ray analysis of the bones led Pieri to suggest the Hierakonpolis dwarfs both had pseudoachondroplasia, a condition that occurs once in every 30,000 births today. Because the condition is sometimes hereditary, Pieri says the pair might have been related.

Even cleft palate, considered a deformity today, may have been viewed differently in the past. Erika Molnar, a paleopathologist at the University of Szeged in Hungary, described a man born with a severe cleft palate and complete spina bifida around 900 C.E. in central Hungary. Breastfeeding as an infant and eating and drinking later in life would have been extremely difficult for him, but he lived well past his 18th birthday. He was buried with rich grave goods—and a horse that also had a visibly twisted muzzle known as “wry mouth.”

“Was his survival a result of high social rank at birth, or was high rank the result of his deformity?” Molnar asks. “His unique position could have been a consequence of his uncommon physical characteristics.”

Archaeological cases may also offer a new perspective on rare diseases today. Last year, Trinity College Dublin geneticist Dan Bradley published ancient DNA from four ancient Irish people. One was an adult Neolithic woman buried between 3343 and 3020 B.C.E. in a tomb topped with huge stones near Belfast; the other three were men buried in a pit grave on an island off the coast of Northern Ireland between about 2000 and 1500 B.C.E. Although the DNA showed the skeletons were from different populations, thanks to a dramatic genetic turnover, all four people carried the gene that causes hemochromatosis, an uncommon condition that causes excess iron to build up in the blood.

Today, Ireland has the world’s highest rates of that mutation. Bradley suggests the gene may have some advantage, perhaps helping protect against bacterial diseases or boosting iron retention in environments with poor diet. Understanding why rare conditions pop up in certain places “may help researchers today to better understand this genetic burden,” he says.

The conference organizers, bioarchaeologist Emmanuele Petiti and paleopathologist Julia Gresky of the German Archaeological Institute here, are working with colleagues to set up a centralized database to share data on ancient individual cases. “To see patterns, you need comparable data,” Petiti says. “It’s the same problem physicians have today—if you want to work on rare diseases, you need enough patients, otherwise it’s just a case study.”

https://wb.md/2XXK8kJ

Lower BP Linked to Cognitive Decline in Frail Elderly

Systolic blood pressure lower than 130 mmHg is linked to additional cognitive decline

Troy Brown, RN

For older patients undergoing treatment for hypertension, having a systolic blood pressure (SBP) lower than 130 mmHg is linked to additional cognitive decline, especially in those with complex health problems, new data suggest.

"Our present findings suggest the importance of close blood pressure monitoring for patients undergoing antihypertensive treatment, to maintain optimal cognition especially in those with complex health

problems, those for whom we observed the strongest effect," the researchers write.

The study, by Sven Streit, MD, PhD, Institute of Primary Health Care, University of Bern, Switzerland, and colleagues, was published online March 11 in *Annals of Family Medicine*.

The latest guidelines from the American College of Cardiology/American Heart Association recommend keeping SBP lower than 130 mmHg for noninstitutionalized older patients.

"Hypertension trials, however, often exclude older, frail patients and those with complex health problems, and many have questioned the generalizability and applicability of the results of these studies," Streit and colleagues explain.

Therefore, the investigators analyzed data from the Integrated Systematic Care for Older Persons (ISCOPE), a population-based prospective cohort study with follow-up of 1 year, to compare cognitive decline among those undergoing hypertension treatment with SBP lower than 130 mmHg with those with SBP of 130 mmHg or higher. They evaluated changes from baseline to 1-year follow-up using several measures, including the Mini–Mental State Examination (MMSE), which assesses cognitive function; the Groningen Activity Restriction Scale (GARS), which assesses the ability to care for oneself and live independently; and the EQ-5D-3L, a quality-of-life index.

The analysis included 1266 participants whose average age was 82.4 years (standard deviation, 5 years); 874 participants (69%) were women. The researchers adjusted for age, sex, and MMSE/GARS/EQ-5D-3L scores at baseline. The investigators stratified the patients for complex health problems, which served as a proxy for frailty.

Among those receiving antihypertensive therapy (1057; 83.5%) whose SBP was lower than 130 mmHg, the crude cognitive decline on the MMSE was 0.90 points, compared with 0.14 points in participants whose SBP was higher than 150 mmHg (0.76-point less decline; *P* for trend, .013).

When the researchers restricted their analysis to participants with complex health problems (n = 674; 53%), the findings were similar. Compared with those with SBP lower than 130 mmHg, participants with SBP of 130 – 150 mmHg demonstrated less cognitive decline after 1 year by 0.99 points (95% confidence interval, 0.32 – 1.66 points; *P* = .004) on the MMSE and by 1.39 points (95% confidence interval, 0.68 - 2.11 points;P < .001) among those with SBP higher than 150 mmHg (*P* for trend, < .001).

By contrast, the association was not found for participants without complex health problems (*P* for trend, 0.35).

Participants with or without antihypertensive treatment had similar sociodemographic characteristics, but those undergoing antihypertensive treatment were more likely to have an SBP > 150 mmHg (35% vs 23%; *P* = .004), cardiovascular disease (48% vs 4%; *P* < .001), diabetes (23% vs 15%; *P* = .013), higher GARS score (33.3 vs 31.2; *P* = .019), and lower quality of life (EQ-5D-3L, 0.66 vs 0.71; *P* = .031).

The authors note several study strengths, including its large number of participants, inclusion of sicker patients, and extensive cognitive, functional, and quality-of-life measurement. Limitations include its observational design.

The observational design of the study precludes demonstrating causation, the authors state. "However, the strength of the associations we identified, consistency with prior studies, dose-response relation, and temporal relation of SBP measurements and outcome assessments all point toward a causal interpretation."

The authors encourage others to study the long-term safety and effectiveness of deprescribing antihypertensives to raise SBP in frail older individuals, but they say that for now, clinicians must choose the most appropriate treatment for individual patients.

"Our results suggest that SBP thresholds for treatment should be redefined, especially for frail older persons. Because older patients are more likely to be frail and experience accelerated cognitive decline, clinicians are advised to be cautious about lowering SBP too much," the researchers conclude.

The study was supported by grants from the Swiss National Science Foundation and the Gottfried and Julia Bangerter-Rhyner Foundation. The authors have disclosed no relevant financial relationships.

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https://wb.md/2TaUo5s

Statins Up Type 2 Diabetes Risk, Overweight at Greatest Risk

Further evidence that statin use increases the risk for the development of type 2 diabetes

Miriam E. Tucker

Further evidence that statin use increases the risk for the development of type 2 diabetes has been published, with the work showing that the risk is particularly high in people who are overweight, obese, or have prediabetes.

Findings from the prospective, population-based study were published online March 5 in the *British Journal of Clinical Pharmacology* by Fariba Ahmadizar, PhD, of the department of epidemiology at Erasmus University Medical Centre, Rotterdam, the Netherlands, and colleagues.

Several previous observational studies and trials have reported an increased risk of incident type 2 diabetes in people treated with statins, but most of them have been lacking in details about glycemic traits.

The incidence seen in observational studies such as the current one has been much higher than in randomized trials, 44% versus 9% to 13%, Ahmadizar and colleagues note.

In their study of 9535 adults older than 45 years without diabetes at baseline, during follow-up those using statins developed higher concentrations of serum fasting insulin, higher rates of insulin resistance, and were 38% more likely to develop type 2 diabetes. The risk was more significant among those who were overweight or obese.

"This suggests that it is necessary to take statin diabetogenicity into consideration in clinical practice [with] rigorous preventive strategies such as glucose control and weight reduction in patients when initiating statin therapy, which might help in minimizing the risk of diabetes," the authors say.

Asked to comment, cardiologist Robert H. Eckel, MD, professor of medicine and director of the Lipid Clinic at the University of Colorado Hospital, Aurora, stressed to *Medscape Medical News*, "It's important to remember that even if statin-treated patients develop type 2 diabetes, the cardiovascular benefit remains."

Eckel advised that clinicians follow the 2018 American College of Cardiology/American Heart Association cholesterol guidelines.

But he also said that because the risk seen in the current study was somewhat higher than that seen in prior observational studies, "I would recommend that HbA_{1c} in the 6.2% to 6.4% range be monitored more closely in statin-treated patients."

Statin Use, Higher Glycemia Linked

In this longitudinal follow-up study of 9535 people without diabetes at baseline, which took place in 1997-2012, the median follow-up period was 4 years. Participants were a mean age of 64 years at baseline, 58% were women, and 64.5% were overweight or obese.

A total of 968 (10%) participants had taken statins, including simvastatin (57%), atorvastatin (25.5%), and pravastatin (10.3%).

Over the study period, 7.5% (716) of participants developed type 2 diabetes.

In an initial cross-sectional analysis adjusted for age, gender, cohort (by time period), smoking status, alcohol consumption, physical activity, education, body mass index (BMI), and hypertension,

baseline statin use was significantly associated with both increased serum fasting insulin concentrations and HOMA-IR (Homeostatic Model Assessment for Insulin Resistance).

However, serum fasting glucose levels lost significance following the adjustments for BMI and hypertension.

Because of that, Ahmadizar and colleagues say, "our finding suggests that the association between statins and diabetes could be through insulin secretion/resistance."

There was no effect of statin type or dose. In a longitudinal follow-up analysis, ever-use of statins was significantly associated with development of type 2 diabetes, with hazard ratios (HR) of 1.64 before and 1.38 after the adjustments, both of which were significant.

The risk was significant among current but not past statin users, with hazard ratios of 1.52 and 1.18, respectively.

Again, no significant effect of statin type or dose on incident type 2 diabetes risk was seen in this analysis, although longer duration of statin use did raise the risk.

Link Between Statins/Diabetes Only Significant in Men, Higher BMIs?

In further sensitivity analyses stratified for BMI at baseline, the association between statins and type 2 diabetes was only significant among those who were overweight or obese but not among those with normal BMI (HR, 1.42 vs 1.18).

And when stratified by gender at baseline, the finding was significant only in men and not women (HR, 1.52 vs 1.28).

Eckel commented: "It was disappointing to have no HbA_{1c} data, but in general those with higher HbA_{1c} without type 2 diabetes are at higher risk, which is supported by their glucose data."

He also faulted the lack of data on family history of type 2 diabetes and questioned the findings on men and the lack of significance for statin dose, noting "statin dose may still be important despite what they found."

Eckel is a member of advisory boards and/or is a consultant for Sanofi, Regeneron, Kowa, Novo Nordisk, Merck, and Endece.

Br J Clin Pharmacol. Published online March 5, 2019. Abstract

http://bit.ly/2Y3hmiz

Chickens Peck Intruder Fox to Death, Because They're Dinosaurs

One fox learned the hard way that it's unwise to mess with a flock of dinosaurs.

By Laura Geggel, Associate Editor

The young fox, just about 6 months old, probably thought it had struck gold when it snuck into a chicken coop at dusk last week at a farm school in Brittany, in northwestern France.

But chickens, like all birds, are the descendants of dinosaurs. And this particular coop held 3,000 hens. As soon as the sun set and the light-controlled, automatic hatch door closed behind the fox, the birds channeled their inner *Tyrannosaurus rex* and attacked the fox.

"There was a herd instinct, and they attacked him with their beaks," Pascal Daniel, head of farming at the agricultural school Le Gros Chêne ("The Big Oak"), told the AFP news agency. "It had blows to its neck, blows from beaks."

The following day, the school's students found the fox's dead body in a corner of the coop.

It's no secret among chicken farmers that these birds can be vicious. Chicken flocks have a clear hierarchy, sometimes referred to as the pecking order, with the biggest, strongest and most aggressive bird ruling the roost. As the "pecking order" name implies, these top birds bully their way to the top by intimidating and pecking weaker birds into submission, according to Modern Farmer, a news outlet for food producers and consumers.

Birds at the top of the hierarchy get better access to food, water and dust-bathing areas, as well as the best spots in the coop, Modern Farmer reported. But these boss birds also bear a special

responsibility; they have to keep a constant lookout for predators and guide the other birds to safety if danger is near. In this case, the chickens didn't flee, but instead banded together to ambush the fox.

"They can be quite tenacious when they are in a pack," Daniel told the regional newspaper Ouest-France (translated from French).

Genetics may be the reason, in part, that some chickens lord over their fellow fowl (and, in this instance, a juvenile fox). According to a 2016 study in the journal Scientific Reports, Chinese scientists found a number of regions on the chicken genome that were associated with aggressive behavior traits.

However, chickens usually don't win the battle against larger predators. The last time a fox got inside the henhouse, more than a year ago, the encounter didn't end so well for the chickens, Daniel said.

http://bit.ly/2T9cqFp

Found: the missing ingredient to grow blood vessels

Discovery important for conditions ranging from diabetes to stroke

Researchers at the University of Virginia School of Medicine have discovered an ingredient vital for proper blood vessel formation that explains why numerous promising treatments have failed. The discovery offers important direction for efforts to better treat a host of serious conditions ranging from diabetes to heart attacks and strokes.

Until now, scientists seeking to grow blood vessels have focused almost exclusively on growing only the inner layer of blood vessels, which are made up of endothelial cells. The hope was that these endothelial cells would then recruit any other cell types needed to form a complete, functional blood vessel. But researchers led by Gary K. Owens, PhD, director of UVA's Robert M. Berne Cardiovascular Research Center, have determined that those vessels can develop properly only if they're grown in conjunction with another cell type, known as perivascular cells, including smooth muscle cells and pericytes.

The researchers liken these perivascular cells to the outer support layers of a rubber hose or on automobile tires, without which they burst or leak.

"Most of the studies of angiogenesis [blood vessel formation] have focused on the inner lining of the pipes themselves," researcher Daniel L. Hess said. "That's fairly well understood. But it's really not well understood how you get a complete functional blood vessel that can withstand the mechanical force exerted by blood pressure."

UVA's new discovery helps answer that - and, in so doing, saves scientists from the time, effort and cost of pursuing treatment strategies that will ultimately bear no fruit.

Innovation and Collaboration

The discovery was made possible by the fortuitous convergence of research in two different labs at UVA. Hess was working on a model of peripheral artery disease in the labs of Owens and UVA's Brian Annex, MD, in the Robert M. Berne Cardiovascular Research Center, while another researcher, Molly R. Kelly-Goss, was working with a model of blood vessel growth she developed in the lab of Shayn M. Peirce, PhD, of UVA's Department of Biomedical Engineering.

By bringing those two models together, the researchers were able to determine the vital role of the perivascular cells in blood vessel formation and to identify a gene, Oct4, that is required for this process. Previously, Oct4 had been thought to be active only in embryonic stem cells during early development and to be permanently inactivated in adult organisms. This belief persisted until two years ago, when the Owens lab showed it was reactivated within smooth muscle cells during formation of atherosclerotic plaques inside blood vessels and required for formation of a protective fibrous cap on those lesions that prevents them from rupturing and setting off a heart attack or stroke - analogous to a

patch on a tire. Now the lab has shown that Oct4 has an important role in the formation of the vessels themselves - ironically, being required for forming the protective outer wall of blood vessels.

Using Kelly-Goss' model, the researchers were able to examine blood vessel formation in real time. They found that vessels that lacked perivascular cell coverage formed incompletely and leaked blood. "Multiple failed trials assumed the perivascular cells were just passive followers," Owens explained. But without them, he said, "the whole process comes to a halt." Importantly, they found that endothelial cells and perivascular cells communicate with one another via Oct4-dependent processes and, without it, functional non-leaky blood vessels or blood vessel networks cannot form.

Ultimately, that means that scientists must take a more sophisticated approach to growing new vessels, a process important in normal growth and reproduction as well as wound repair.

Findings Published

The researchers have published their findings in the scientific journal Nature Communications. The research team consisted of Hess, Kelly-Goss, Olga A. Cherepanova, Anh T. Nguyen, Richard A. Baylis, Svyatoslav Tkachenko, Annex, Peirce and Owens.

The work was supported by the American Heart Association, including through Innovative Research Grant 17IRG33370017; the National Institutes of Health, grants R01 HL082838, R01 Ey022063, 1R01 HL12635, 1R01 HL116455, 2R01 HL101200, R01 HL057353, R01 HL135018 and T32 HL007284; the Hartwell Foundation; and the Wagner Fellowship.

http://bit.ly/2CoqBAP

Pet Dog with Plague Exposed More Than 100 Veterinary Workers to the Disease

Sick dog in Colorado caused alarm when doctors realized it was infected with a rare and deadly illness

By Rachael Rettner, Senior Writer

A sick dog in Colorado caused alarm at a veterinary hospital when doctors realized the animal was infected with a rare and deadly illness: the plague. What's more, the dog had contact with more than 100 people before its illness was discovered, potentially exposing them to the serious infection, according to a new report about the case.

The 3-year-old dog developed a fever and was acting lethargic in December 2017, prompting its owner to take the animal to the vet, where it was treated with antibiotics. But soon thereafter, the dog began coughing up blood and was referred to the Colorado State University Veterinary Teaching Hospital.

Tests revealed that the dog had a lung infection. Four days before the dog became sick, it was seen sniffing a dead prairie dog — an animal that can carry the plague-causing bacteria *Yersinia pestis*. But the vets considered an infection with plague to be unlikely, in part because of the time of year; plague infections mainly occur from April to October in the Western U.S., according to the report. And since dogs are less susceptible to plague than cats are, the chance that the animal was infected would seem even more remote.

Instead, the vets suspected a much more common cause for the dog's illness: so-called aspiration pneumonia, a lung infection due to an inhaled foreign body, such as food. Indeed, results from a CT scan appeared to match this diagnosis, the report said.

Two days later, however, a sample from the dog's lungs tested positive for plague-like bacteria. But the vets still weren't convinced: Because a plague infection was considered so unlikely, they at first thought the test result might be wrong.

The next day, the researchers used a standard testing protocol for plague from the Centers for Disease Control and Prevention (CDC), which also came back positive. What's more, the dog had pneumonic plague, the most serious form of the disease, which can be spread through the air in infected droplets expelled by an sick animal or person.

Possible exposure

Even before the dog's diagnosis was confirmed, news of the suspected plague case spread through the veterinary hospital and staff became nervous about possible exposure to the disease.

Indeed, during the dog's care, the animal had been transported throughout the hospital and even housed in an oxygen cage that vented into a room. Overall, 116 people were identified as possibly being exposed to the plague through contact with the dog or its samples, or by being within 6 feet away (where they could potentially inhale infectious droplets.)

Plague is perhaps best known for killing millions of people in Europe in the 1300s during a pandemic called the Black Death. But the infection still occurs today, although it is relatively rare in the United States, with an average of seven human plague cases reported yearly – particularly in New Mexico, Arizona and Colorado – according to the CDC. Most U.S. human cases of plague occur in the Southwest.

Among employees at the hospital who were potentially exposed to the disease, about 60 percent took preventative antibiotics.

In addition, 46 animals that were housed in the same room as the dog were also considered exposed and were also given preventative antibiotics. Fortunately, there were no reported cases of plague in either humans or animals in connection with the case.

Unfortunately, the dog's condition worsened and it had to be euthanized on the same day it was diagnosed.

Veterinarians should be aware that cases of plague can show up in dogs year round, not just in the more common months of late spring to early fall, the report said.

In 2014, a dog in Colorado contracted pneumonic plague, which lead to an outbreak of the disease in four people — the largest outbreak of the illness since the 1920s, according to the CDC. In that case, a dog spread the illness to three people (including its owner), and a fourth person contracted the disease from the owner, Live Science previously reported.

The case was published online today (March 13) in journal Emerging Infectious Diseases.

http://bit.ly/2ubOVS8

Leading geneticists call for worldwide moratorium on creation of gene-edited children

Prominent scientists are calling for a global moratorium on germline editing to create genetically modified children.

By Anthony King

Writing in *Nature*, they argue for a five-year pause on all clinical uses of editing of reproductive cells.

They write that this is needed because germline editing is not yet safe or effective for patients, and the risk of introducing unintended mutations is unacceptably high. The opinion piece, with 18 signatories including two of the pioneers of the Crispr gene-editing system, describes any attempt to reshape the species on the basis of current knowledge as 'hubris'. It criticises the editing of human embryos by Chinese scientist He Jiankui, whose actions raised fears of a regulatory backlash.

The authors note that scientists who were apparently aware of this work did not stop it, and also that there has been a growing interest in genetic enhancement of humans. Meanwhile, there is no mechanism to discuss whether or when clinical germline editing might be appropriate.

Governments, they suggest, should declare that they will not permit any clinical use of human germline editing for an initial period of five years. A nation could subsequently allow a particular application, but only after they provide two years of notice and engage in international discussions.

They write that there should be 'broad societal consensus in the nation on whether to proceed with human germline editing at all'.

The framework should be backed by a coordinating body, perhaps organised under the World Health Organization (WHO).

The WHO has already established an expert advisory committee on human genome editing. It aims to make recommendations on appropriate governance mechanisms. The first meeting takes place in Geneva, Switzerland, next week.

This call for a moratorium 'demonstrates progress towards an international consensus that heritable human genome editing is not only an important issue with profound implications for us all, but that it also demands globally coordinated agreement', comments Jackie Leach Scully, a bioethicist at Newcastle University, UK. She says past scientific moratoria have been successful, though it's essential they are agreed by a global majority.

'Even if individual scientists or states don't agree with a moratorium on ethical grounds, they need to have a clear sense that the penalties for not keeping them outweigh any advantages,' Leach Scully adds. She is dubious, however, about the call for a broad societal consensus due to 'the practical difficulties of designing, carrying out and evaluating anything that might be called "societal debate"'.

Ethicist Hille Haker at Loyola University Chicago says it is naïve to think people won't replicate He's work again. She believes the goal of public consensus is unattainable and criticises the article for presupposing 'that gene-editing for therapy is ethically sound and [that] enhancement may be'. This, she says, is the contested question. 'I am for a ban – for ethical reasons – and therefore think it must be done by a treaty.'

'He Jiankui, in carrying out this work, already showed himself willing to bend or break existing national regulations, to ignore numerous ethical statements and to fly in the face of strongly expressed scientific and ethical opinion,' adds Sarah Chan, a bioethicist at the University of Edinburgh, UK. Though the statement from the International Summit on Human Gene Editing in 2015 is described in the article as inadequate, Chan questions whether a moratorium would have been any more effective.

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http://bit.ly/2TIiJF8

"Inactive" ingredients may not be, study finds

Most pills contain compounds with potential to cause allergic reactions or discomfort in some patients.

Anne Trafton | MIT News Office

Watch Video

Most pills and capsules, whether over-the-counter or prescription, include components other than the actual drug. These compounds, known as "inactive ingredients," help to stabilize the drug or aid in its absorption, and they can make up more than half of a pill's mass. While these components are usually considered benign, a new study from MIT and Brigham and Women's Hospital has found that nearly all pills and capsules contain some ingredients that can cause allergic reactions or irritations in certain patients. In most cases, doctors have no idea which of these ingredients will be included in the pills they prescribe to their patients, because there are so many different formulations available for any given medication.

"For most patients, it doesn't matter if there's a little bit of lactose, a little bit of fructose, or some starch in there. However, there is a subpopulation of patients, currently of unknown size, that will be extremely sensitive to those and develop symptoms triggered by the inactive ingredients," says Daniel Reker, a Swiss National Science Foundation postdoc at MIT's Koch Institute for Integrative Cancer Research and one of the lead authors of the study.

The researchers hope that their study, published in the March 13 edition of *Science Translational Medicine*, will raise awareness of this issue among patients and health care providers and help to

stimulate reforms that could protect patients from drugs that they don't tolerate well.

"Right now there is an imbalance in the amount of information and understanding out there with respect to the inactive components of medication," says Giovanni Traverso, an assistant professor in MIT's Department of Mechanical Engineering, a gastroenterologist at Brigham and Women's Hospital, and the senior author of the study. Steven Blum, a clinical fellow at Dana-Farber Cancer Institute, is also a lead author of the paper. Other authors include Christoph Steiger, an MIT postdoc; and Kevin Anger, Jamie Sommer, and John Fanikos of the Investigational Drug Services at Brigham and Women's Hospital.

Unknown effects

Traverso began looking into this issue about five years ago following an experience involving a patient he was helping to look after. The patient, who had celiac disease, reacted poorly to omeprazole, a common acid suppressant used to treat stomach ulcers.

The specific formulation of omeprazole the patient had obtained contained ingredients derived from wheat products (potentially containing gluten). This information was only available from the manufacturer at the time. A week after obtaining the medication the patient had reported feeling sick from taking the medication.

"That really brought it home to me as far as how little we know about tablets and the potential adverse effects they might have," Traverso says. "I think there's a tremendous underappreciation of the potential impact that inactive ingredients may have."

Currently, when doctors write a prescription, they specify the type and dosage of the active pharmaceutical, but nothing about the inactive ingredients. Many medications come in dozens of different formulations, and the one that patients get depends on their insurance, their pharmacy, and the manufacturer that supplies the pharmacy. The information that comes with the medication usually lists inactive ingredients, but not the amounts of each one, and they may be difficult to decipher. For example, ingredients that contain gluten may not be listed as "gluten."

The researchers scoured medical journals and found several studies describing patients who had allergic reactions to inactive ingredients such as lactose and chemical dyes. These studies generally did not include patients with intolerances to a particular ingredient, which are milder and produce symptoms such as bloating or stomach ache. However, the researchers believe these milder reactions may affect many more patients. Potential problems could be especially prevalent among people over the age of 65, 30 percent of whom take at least five pills every day, potentially allowing critical ingredients to accumulate.

Next, the researchers set out to find as much as they could about the inactive ingredients found in prescription and nonprescription medications. Getting much of their information from a database called Pillbox, run by the National Library of Medicine, the researchers were able to determine the composition of nearly all prescription and over-the-counter medications available in the United States.

They found that for most medications, more than half of the pill is made up of inactive ingredients, and for some it is as high as 99 percent. They also found that about 93 percent of medications contain allergens such as peanut oil, lactose, or dyes, and nearly all contain compounds that some patients cannot tolerate, such as gluten and certain kinds of sugars. About 55 percent of medications contain sugars known as FODMAP sugars, which can trigger digestive problems in some people with irritable bowel syndrome.

When medications contain peanut oil, manufacturers print warnings on the labels, but for most other allergens or irritants, no warnings are given, and it is not easy to find out if a compound such as lactose or gluten is in the medicine, the researchers say. Even if patients are

aware of their allergies and sensitivities and correctly decipher medication packages, many different treatments might not be available to them because not a single pill that avoids all these ingredients might exist, the researchers add.

Raising awareness

The researchers hope that their findings will help boost awareness of the potential risks that inactive ingredients pose for some patients. If new regulations could be implemented, requiring pharmaceutical companies to provide more information about the inactive ingredients in their formulations, it could be easier for doctors to specify whether a certain ingredient should not be included. The researchers also hope that pharmaceutical companies will develop more alternative formulations for patients with allergies or sensitivities to certain ingredients.

“I think all of these really need to come together,” Traverso says. “Education, increased awareness, and legislation are all important.”

The researchers are now working on a follow-up study in which they are polling health care providers to determine how widespread this problem may be. They also hope to perform clinical trials to study how much lactose or other common inactive ingredients manifest in symptoms in people who have intolerances to those ingredients.

“There need to be more clinical trials and more data out there so that we can really dive deep into how many patients are affected and how we can help them,” Reker says.

The research was funded by the Swiss National Science Foundation, the Brigham and Women’s Department of Medicine Residency Program and Division of Gastroenterology, the Alexander von Humboldt Foundation Feodor Lynen Fellowship, the National Institutes of Health, and the MIT-IBM Watson AI Lab.

https://wb.md/2TV8NqQ

Genetic Shifts in *Bordetella* May Explain Surge in Pertussis

Genetic changes in circulating* Bordetella *may help explain the resurgence of whooping cough and reduced vaccine effectiveness

Nicola M. Parry, DVM

Genetic changes in circulating *Bordetella pertussis* may help explain the resurgence of whooping cough and reduced vaccine effectiveness in recent decades, a study published online today in *Emerging Infectious Diseases* suggests.

"We have developed a representative dataset of complete genome sequence assemblies derived from *B. pertussis* clinical isolates recovered in the United States that captures shifting population genetics concurrent with disease resurgence," write Michael R. Weigand, PhD, from the US Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, and colleagues.

In the United States, cases of whooping cough have been on the rise since the late 1980s."This resurgence has included >48,000 cases reported in 2012 and notable recent statewide epidemics," the authors say.

Among the potential causes of this increase is the possibility that circulating *B. pertussis* undergoes genetic variation, resulting in divergence between vaccine and clinical strains of the bacterium. However, until recently, detailed genetic information was available only for vaccine and laboratory reference strains of the bacterium.

Therefore, Weigand and colleagues analzyed genotypes of 170 circulating *B. pertussis* isolates. The samples had been collected by state public health laboratories from ill patients between 2000 and 2013 and forwarded to CDC.

The completed genome assemblies from the isolates show that the genetic composition of clinical *B. pertussis* isolates has shifted away from that of vaccine strains during the current whooping cough surge. This shift included a circulating mixture of gene sequence (single-nucleotide polymorphisms) and chromosome structure variants, as well as increased pertactin deficiency. Pertactin (Prn), a *B. pertussis* virulence factor, is a key component of the pertussis vaccine.

Weigand and colleagues found 10 Prn-deficient alleles among 57 of the clinical isolates in their study, with the proportion of these alleles rising rapidly from 2010. Mutations associated with Prn deficiency included missense substitutions, deletions, promoter disruption, and IS*481* insertions.

Although the current pertussis vaccines remain effective, these findings "provide a foundation for needed research to direct future public health control strategies," the authors conclude.

This study was supported by the Advanced Molecular Detection program at the US Centers for Disease Control and Prevention. The authors have disclosed no relevant financial relationships.

Emerg Infect Dis. Published online March 13, 2019. Full text

http://bit.ly/2W9n2pP

When is best time to get flu shot? Analysis compares scenarios

Tens of thousands of influenza cases and hundreds of deaths can likely be avoided if older adults wait until October to get their flu immunization

PITTSBURGH, March 14, 2019 - When flu season peaks after mid-winter, tens of thousands of influenza cases and hundreds of deaths can likely be avoided if older adults wait until October to get their flu immunization, a University of Pittsburgh School of Medicine analysis reveals in the April issue of the American Journal of Preventive Medicine.

The protection offered by the flu vaccine wanes as the season progresses, a previous study has shown, which indicates that waiting until closer to the start of flu season ensures greater immunity. However, if flu season arrives early or if delayed vaccination prompts more than one in 20 people who would otherwise be vaccinated to skip their flu shot, then the gains are negated, according to the new study, which is online now.

"There's controversy in the public health community over whether influenza vaccination should happen as soon as the vaccine becomes available in August, or if it's better to wait until later in the fall," said lead author Kenneth J. Smith, M.D., M.S., professor of medicine and clinical and translational science in Pitt's Division of General Internal Medicine. "What we've found is that it's a balancing act, but if a clinician believes a patient will return for vaccination in the fall, then our analysis shows that it is best if they advise that patient to wait."

Smith and his co-authors ran computer models to compare a "compressed" vaccination period that begins in October to the status quo, which typically begins in August, for people aged 65 or older. They focused on older adults because waning vaccine effectiveness is more of a threat to the elderly whose immune systems don't typically mount as strong of a defense to infections as younger people. Older adults also have higher early vaccination rates than younger adults.

Using data from the 2013-2014 and 2014-2015 flu seasons, the researchers forecast the number of cases, hospitalizations and deaths for compressed and status quo vaccination scenarios if the flu season had peaked in December, February or April - early, normal or late, respectively. "Peak" refers to the period when the greatest number of people are sick that season.

In the projections for the normal and late flu seasons, compressed vaccination saved as many as 258 lives and prevented up to 22,062 cases of flu, compared to status quo vaccination timing.

But if flu season peaked early, as it does in about one of every four seasons, the model projected that dozens to hundreds of older adults would die because they wouldn't have been vaccinated in time.

In addition, the team found that if more than 5.5 percent of older adults who defer vaccination ultimately don't get the flu shot, then compressed vaccination will be a failure and will prevent fewer influenza cases than status quo vaccination.

Smith says these findings can help clinicians determine when to offer their patients flu immunizations - if the patients have multiple

appointments each year and will be in the office in the fall or if they are in a senior community where flu immunization is offered through a scheduled clinic, then waiting is likely advisable. But if a patient comes in only for an annual check-up and is unlikely to seek out the flu vaccine in the fall, or if offering vaccinations during a compressed window will put overwhelming strain on the clinic, then getting vaccinated when convenient - even if that's in August - is best.

"In all scenarios, simply getting vaccinated is the best way to avoid the flu," said Smith. "If the choice is between getting the influenza immunization early or not getting it at all, getting it early is definitely better."

Additional authors on this research are Glenson France, M.A., Mary Patricia Nowalk, Ph.D., Jonathan M. Raviotta, M.P.H., Angela Wateska, M.P.H., and Richard K. Zimmerman, M.D., M.P.H., all of Pitt; Jay DePasse, B.S., of Carnegie Mellon University; and Eunha Shim, Ph.D., of Soongsil University in South Korea.

This research was funded by National Institute of General Medical Sciences grant no. R01 GM111121.

http://bit.ly/2u9otIz

Cholesterol-lowering drugs guard against brain haemorrhages

The drugs statins, which are used to prevent cardiovascular diseases, also guard against brain haemorrhages; this is the conclusion from a new Danish study, the most extensive ever, which thus also rebuffs suspicions of the opposite being true

The drugs statins, which are used to prevent cardiovascular diseases, also guard against brain haemorrhages. This is the conclusion of most extensive study ever carried out, which thus also rebuffs suspicions of the opposite being true.

As well as lowering blood cholesterol, the medication statin also acts to guard against haemorrhages. This is shown by the results of the largest study in the world so far, which followed more than half-a-million people being treated with statin over a decade.

"With this study we refute a concern raised by earlier studies that treatment with statins is associated with increased risk of brain haemorrhages. On the contrary, in a cohort of persons with no history of blood clots or haemorrhages in the brain, we demonstrate that statin users compared to non-users are in fact less affected by brain haemorrhages," says postdoc and medical doctor Anette Riisgaard Ribe from the Danish Research Unit for General Practice. She heads this major Danish study which has been carried out in collaboration with Aarhus University, Denmark.

In the study, which has just been published in the scientific journal EClinicalMedicine, 519,800 people were followed from the time that they began to take statins during the period 2004-2014.

The researchers followed both this group of statin users and a control group of people who did not take the medicine, and they investigated how many people subsequently suffered a brain haemorrhage in each of the two groups.

In general terms, the study shows that the risk of suffering a brain haemorrhage is between 22-35 per cent lower for people using statins when compared with non-users after the first six months of treatment.

All participants in the study have in common that they had not previously suffered a blood clot or haemorrhage in the brain.

The use of statins has been an oft discussed topic in medical circles, particularly following a clinical trial in 2006 which showed that treatment with statins was associated with a not insignificant increased risk of brain haemorrhages. However, this applied to people who had previously suffered blood clots or haemorrhages in the brain. Despite not being able to mirror these findings in a number of meta-analyses, this concern has still remained firmly in place, as Ribe explains.

"Current clinical treatment guidelines recommend being particularly careful when prescribing statins to patients who have had brain haemorrhages, while the question of whether statins should also be

avoided for patients with a high risk of brain haemorrhages is debated. So there could be medical doctors who are reluctant to treat patients with statins due to a fear of side effects for particularly frail patients. However, this study makes clear that the risk of brain haemorrhages is significantly reduced after six months of treatment among people who receive statins on the basis of other indications than blood clots in the brain. With our study we can conclude that any concerns are unfounded among this group of patients and that such concerns could even be potentially harmful if they lead to doctors having second thoughts about prescribing medicine so that the patient does not receive the correct treatment," she says.

Due to the large scope of the study with more than half a million statin users, Anette Riisgaard Ribe and her research colleagues have had excellent opportunities to test the study's results. For example, it was possible to compare each individual being treated with statins to five non-users on the basis of age, gender and probability of being treated. This says something about the strength of the study and the level of certainty with which the researchers can speak. Anette Riisgaard Ribe explains:

"In our study, those using statins and the non-users are relatively similar. This means that a reduced risk of brain haemorrhages cannot be explained by statin users being a 'healthier' group which the doctor is not worried about treating with statins."

The many statin users in the study have furthermore made it possible to study the association between treatment with statins and brain haemorrhages at different times following the start of treatment.

"Our study is the first that is large enough to carry out these time analyses. This possibility is particularly important when we want to rule out that statins can actually be harmful - because it would be very troubling if our study had shown that the risk of brain haemorrhages was the same for users and non-users of statins just after the start of the treatment, but subsequently increased significantly among the statin users."

Neither do the researchers see any sign of the reduced risk of brain haemorrhages being linked to the concurrent use of other types of medicine for the prevention of cardiovascular diseases in the statin group. As this is a group of patients who are often treated with several forms of medicine at the same time, it was important for the researchers to clarify whether the protective effect of the statins in reality resulted from the effect of e.g. blood-pressure lowering medications.

"However, we found the same result regardless of whether we only studied the effect of statins among the group of patients receiving concurrent treatment with blood-pressure lowering medications or among those who were not receiving this treatment. We're able to reach these conclusions with great precision precisely because the study is so extensive," says Anette Riisgaard Ribe.

http://bit.ly/2Hp4Jtc

Wolves lead, dogs follow -- and both cooperate with humans

Ability to work with people lies not so much within dogs themselves but in the "wolf within the dog"

Human social life would be unthinkable without cooperation. The frequency and complexity with which humans cooperate with each other are extraordinary, if not unique. To better understand the evolution of this outstanding human skill, researchers have proposed dogs (*Canis familiaris*) as a good model of human cooperation.

The wolf inside dogs makes the difference

A recent study by Vetmeduni Vienna, published in the journal *Scientific Reports*, shows that the ability to work with people lies not so much within dogs themselves but in the "wolf within the dog" - that is to say, in very specific behavioural characteristics that dogs share with wolves. The study tested the extent to which dogs and

grey wolves collaborate with humans in order to solve certain tasks. The findings show that both dogs and wolves cooperate intensively with humans and are equally successful, although the animals attain their goals in different ways.

Wolves show more initiative

Especially in one point the two closely related animals show significantly different forms of behaviour. In their cooperation with human partners, dogs follow the behaviour of the humans while wolves lead the interaction: they are more independent. Study director Friederike Range from the Konrad Lorenz Institute at Vetmeduni Vienna says, "The detailed analysis of the cooperative interactions revealed interesting differences between wolves and dogs. It shows that, while wolves tend to initiate behaviour and take the lead, dogs are more likely to wait and see what the human partner does and follow that behaviour."

Differences in behaviour due to domestication

Based on the results of the study, the researchers propose that in the course of domestication dogs were selected for breeding because of their higher submissive tendencies (deferential behaviour hypothesis). According to this hypothesis, this helped minimize conflicts over resources and ensured the safe coexistence and cooperation in which humans lead and dogs follow.

Teamwork counts for wolves

Forming the background to the study are certain fundamental considerations in the field of behavioural science. As humans and dogs have been exposed to similar environmental pressures, this could conceivably represent a case of convergent evolution. Some research suggests that dogs acquired specific predispositions for cooperative interactions during the domestication process due to reduced aggression and increased tolerance. Against this background, better cooperation with humans would be expected in dogs than in wolves. However, wolves are a highly cooperative species, working together to raise the young, hunt and defend their territory.

Early socialization with humans is crucial

The research team led by Friederike Range therefore hypothesized that dogs did not develop any new traits during domestication, but rather that the collaborative skills of their common ancestors - wolves - form the basis for the evolution of dog-human cooperation (canine cooperation hypothesis).

In contrast to the hypotheses of other scientists, the researchers from Vetmeduni Vienna therefore did not assume that dogs will outperform wolves when cooperating with humans. As Friederike Range says, "Based on the canine cooperation hypothesis, we expected that wolves would cooperate with humans as well as dogs if early and intensive socialization is given." The present study fully confirms this assumption.

For the experiment portion of the study, 15 grey wolves (11 males, 4 females, age: 2 to 8 years) and 12 mixed-breed dogs (7 males, 5 females, age: 2 to 7 years) were tested at the Wolf Science Center in Ernstbrunn, Austria, where animals are socialized with people very early on and have close ties to them. The results of the experiment show that dogs and wolves, when socialized with humans and kept under similar conditions, work similarly successfully with humans, albeit in very different ways, which explains why dogs make the better pet.

Service: *The article "Wolves lead and dogs follow, but they both cooperate with humans" by Friederike Range, Sarah Marshall-Pescini, Corinna Kratz and Zsófia Virányi was published in* Scientific Reports. *https://www.nature.com/articles/s41598-019-40468-y*

http://bit.ly/2O9PSmS

Ancient switch to soft food gave us an overbite—and the ability to pronounce ‘f’s and ‘v’s

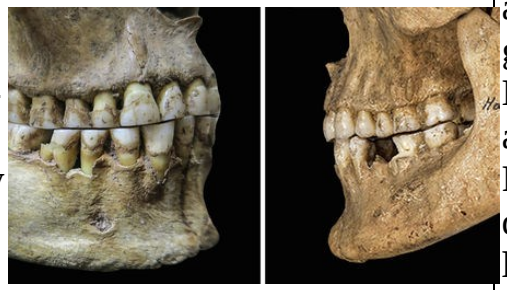
Don't like the F-word? Blame farmers and soft food.

By Ann Gibbons

When humans switched to processed foods after the spread of agriculture, they put less wear and tear on their teeth. That changed the growth of their jaws, giving adults the overbites normal in children. Within a few thousand years, those slight overbites made it easy for people in farming cultures to fire off sounds like "f" and "v," opening a world of new words.

The newly favored consonants, known as labiodentals, helped spur the diversification of languages in Europe and Asia at least 4000 years ago; they led to such changes as the replacement of the Proto-Indo-European *patēr* to Old English *faeder* about 1500 years ago, according to linguist and senior author Balthasar Bickel at the University of Zurich in Switzerland.

The paper shows "that a cultural shift can change our biology in such a way that it affects our language," says evolutionary morphologist Noreen Von Cramon-Taubadel of the University at Buffalo, part of the State University of New York system, who was not part of the study.



An ancient woman from Romania shows an edge to-edge bite (left). A Bronze Age man from Austria had a slight overbite (right). **D. E. BLASI *ET AL.*, *SCIENCE*, 363, 1192 (2019)**

Postdocs Damián Blasi and Steven Moran in Bickel's lab set out to test an idea proposed by the late American linguist Charles Hockett. He noted in 1985 that the languages of hunter-gatherers lacked labiodentals, and conjectured that their diet was partly responsible: Chewing gritty, fibrous foods puts force on the growing jaw bone and wears down molars.

In response, the lower jaw grows larger, and the molars erupt farther and drift forward on the protruding lower jaw, so that the upper and lower teeth align.

That edge-to-edge bite makes it harder to push the upper jaw forward to touch the lower lip, which is required to pronounce labiodentals. But other linguists rejected the idea, and Blasi says he, Moran, and their colleagues "expected to prove Hockett wrong."

First, the six researchers used computer modeling to show that with an overbite, producing labiodentals takes 29% less effort than with an edge-to-edge bite.

Then, they scrutinized the world's languages and found that hunter-gatherer languages have only about one-fourth as many labiodentals as languages from farming societies.

Finally, they looked at the relationships among languages, and found that labiodentals can spread quickly, so that the sounds could go from being rare to common in the 8000 years since the widespread adoption of agriculture and new food processing methods such as grinding grain into flour.

Bickel suggests that as more adults developed overbites, they accidentally began to use "f" and "v" more. In ancient India and Rome, labiodentals may have been a mark of status, signaling a softer diet and wealth, he says. Those consonants also spread through other language groups; today, they appear in 76% of Indo-European languages.

Linguist Nicholas Evans of Australian National University in Canberra finds the study's "multimethod approach to the problem" convincing.

Ian Maddieson, an emeritus linguist at the University of New Mexico in Albuquerque, isn't sure researchers tallied the labiodentals correctly but agrees that the study shows external factors like diet can alter the sounds of speech.

The findings also suggest our facility with f-words comes at a cost. As we lost our ancestral edge-to-edge bite, "we got new sounds but maybe it wasn't so great for us," Moran says. "Our lower jaws are

shorter, we have impacted wisdom teeth, more crowding—and cavities."

***Correction, 15 March, 11:10 a.m.:** This story erroneously stated that the newly favored consonants led to the replacement of the Latin* patēr *to Old English* faeder *about 1500 years ago.* Patēr *came not from Latin, but from the Proto-Indo-European language that gave rise to Latin and other languages in Europe and Asia.*

http://bit.ly/2CjSXw4

The sweet spot: Scientists discover taste center of human brain

Precisely where the "gustatory" cortex is and how it works has been a mystery

ITHACA, N.Y. - Researchers long ago mapped sight, hearing and other human sensory systems in the brain. But for taste, which could be considered our most pleasurable sense, precisely where the "gustatory" cortex is and how it works has been a mystery.

Using functional magnetic resonance imaging (fMRI) and a new method of statistical analysis, researchers have discovered the taste center in the human brain by uncovering which parts of the brain distinguish different types of tastes.

"We have known that tastes activate the human brain for some time, but not where primary taste types such as sweet, sour, salty and bitter are distinguished," said Adam Anderson, professor of human development at Cornell University and senior author of the study, published in *Nature Communications*.

"By using some new techniques that analyze fine-grained activity patterns, we found a specific portion of the insular cortex - an older cortex in the brain hidden behind the neocortex - represents distinct tastes," Anderson said.

The insular cortex, which separates the frontal and temporal lobes, has long been thought to be the primary sensory area for taste. It also plays a role in other important functions, including visceral and emotional experience. "The insular cortex represents experiences from inside our bodies," Anderson said. "So taste is a bit like perceiving our own bodies, which is very different from other external senses such as sight, touch, hearing or smell."

Previous work has shown a nearby insular region processes information originating from inside the body - from the heart and lungs, for example. In this way, distinct tastes and their associated pleasures may reflect the needs of our body. Taste not only reflects what is on our tongue but also our body's need for specific nutrients, Anderson said.

The researchers found evidence that could be considered the "sweet" spot in the insula - a specific area where a large ensemble of neurons respond to sweetness stimulation on the tongue.

"While we identified a potential 'sweet' spot, its precise location differed across people and this same spot responded to other tastes, but with distinct patterns of activity," Anderson said. "To know what people are tasting, we have to take into account not only where in the insula is stimulated, but also how."

Compared with previous animal studies that show distinct activation clusters of basic tastes in the brain, the new study's results reveal a more complex taste map in the human brain, Anderson said, where the same insular region represents multiple tastes.

First author of the study is Junichi Chikazoe, former postdoctoral researcher in Anderson's Affect and Cognition Lab. Also contributing to the study were researchers from Columbia University and the University of Colorado. Funding was provided by the Canadian Institutes of Health Research, the Japan Society for the Promotion of Science and the Takeda Science Foundation.

https://ind.pn/2TMAv9v

Actors shut down parts of their brains to take on roles, scans reveal

'I got the idea that maybe acting was a bit similar to possession... when you're acting you're kind of being taken over by character,' says scientist

Josh Gabbatiss Science Correspondent

To truly inhabit a role, actors must effectively turn off part of their brain, according to a new study based on brain scans of thespians.

In a series of experiments, actors were placed in MRI machines and asked to respond to questions as if they were Romeo or Juliet during the "balcony scene" from William Shakespeare's play.

Scientists were surprised to see that as the participants mused on concepts ranging from romance to religion, their brains were truly taken over by those of the famous star-crossed lovers. They watched as brain activity dropped off, with a notable deactivation in a part of the frontal lobe. This result suggested the portrayal of a fictional character goes far deeper than simply learning a script.

The research was led by Dr Steven Brown, a neuroscientist at Canada's McMaster University, who specialises in how the brain behaves while people are participating in music, dance and other art forms. As no one had ever attempted to measure the brain activity underpinning drama, Dr Brown recruited a group of willing, university-trained actors to participate in his new study.

Inspired by a visit to Brazil in which he witnessed an indigenous possession ceremony, he thought there may be parallels to be drawn with actors. "I got the idea that maybe acting was a bit similar to possession – that when you're acting you're kind of being taken over by character," said Dr Brown.

This, he said, influenced his interpretation of the experiments, which he had originally assumed would reveal something quite different.

Normally his team looks for increases in brain activity that may underlie artistic pursuits, but in this study they were surprised to find activity was actually decreasing in certain key areas.

"There wasn't a literature to go by to make predictions, because this was the first study of its kind," he said. "We thought there might be activation increases relating to pretending to be some kind of character – but instead we saw this activation decrease. That was very surprising to us."

Over the course of four sessions in the MRI machines, the participants had to respond in four different ways – as themselves, as themselves with a British accent, answering for a friend and finally as if they were either Romeo or Juliet.

Only while undertaking their Shakespearean role did the people show deactivations in regions across their brains.

Like the people in the ceremony he had witnessed, Dr Brown suggested these people were actually losing their "sense of self" as they inhabited the characters' minds.

Though this new area of research is still in its early days, publishing their findings in the journal *Royal Society Open Science*, the scientists said their study provided the first step towards understanding how people's brains change when they take on different roles – whether in their daily lives or on stage.

http://bit.ly/2Taolmh

Since 1990s, heart attacks have become less deadly, frequent for Americans

Americans today are less likely to have heart attacks and also less likely to die from them than two decades ago

New Haven, Conn. - Heart attack prevention and outcomes have dramatically improved for American adults in the past two decades, according to a Yale study in JAMA Network Open. Compared to the mid-1990s, Americans today are less likely to have heart attacks and also less likely to die from them, said the researchers.

Tracking more than four million Medicare patients between 1995 and 2014, this is the largest and most comprehensive study of heart attacks in the United States to date. Its two key findings are that hospitalizations for heart attacks have declined by 38%, and the 30-day mortality rate for heart attacks is at an all-time low of 12%, down by more than a third since 1995. In the words of Dr. Harlan Krumholz, lead author and Yale cardiologist, these gains are "remarkable."

The Yale cardiologist also believes these gains are no accident. Krumholz explained that the last 20 years have been marked by national efforts to prevent heart attacks and improve care for those who suffer them. The Centers for Medicare and Medicaid Services, the American College of Cardiology, and the American Heart Association -- along with other organizations and "legions of researchers and clinicians and public health experts" -- have focused on reducing risk by promoting healthy lifestyles, addressing risk factors, and improving the quality of care, the researchers noted.

While the study tallies the impressive overall gains, it also sheds light on the health outcome disparities in America on a county by county basis. "Priority health areas," which were previously identified by Yale research as lagging areas, saw little or no change in their 30-day mortality rates in the past two decades -- indicating that they should receive particular attention in future healthcare improvement activities, the researchers concluded.

"We are now at historic lows in the rates of heart attacks and deaths associated with heart attacks," said Krumholz. "However, this is no time to be complacent. We document extraordinary gains -- but the effort is far from finished. The goal is to one day relegate heart attacks to the history of medicine."

Other authors include Sharon-Lise T. Normand of Harvard and Yun Wang of Harvard and Yale.

Disclosures for all potential conflicts of interest can be found in the study.

http://bit.ly/2ClW1ry

Ablation better than drugs for reducing Afib, improving QOL, but not for reducing death

Heart procedure for AFib better than drug therapy for reducing episodes, improving quality of life and symptoms, but not for reducing death or stroke

ROCHESTER, Minn. -- Atrial fibrillation is a common arrhythmia that affects an estimated 30 million people worldwide. New research shows that catheter ablation, a common cardiovascular procedure, appears no more effective than drug therapy to prevent strokes, deaths and other complications in patients with atrial fibrillation. But patients who receive catheter ablation experience much greater symptom relief and long-term improvements in quality of life. And they have fewer recurrences of their atrial fibrillation and fewer hospitalizations than those who receive only drugs. You can learn more about this new research in the March 15 issue of *JAMA*.

This research, funded by the National Heart, Lung, and Blood Institute (NHLBI), part of the National Institutes of Health and industry collaborators, is the result of the Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation trial (CABANA), the largest international randomized clinical trial comparing left atrial catheter ablation -- which involves inserting long, narrow tubes to reach and apply energy (hot or cold) to destroy abnormal heart tissue -- with current state-of-the-art drug therapy to reduce the consequences of atrial fibrillation. A related observational study using big data to support clinical trial evidence is published in the European Heart Journal. Read the news release.

Most individuals with atrial fibrillation have identifiable risk factors, such as high blood pressure or structural heart disease, and tend to be elderly. Some patients with atrial fibrillation are symptomatic, while others remain asymptomatic. Atrial fibrillation also increases a person's risk of stroke, heart failure and other serious health conditions. Treating atrial fibrillation with antiarrhythmic drugs has been challenging due to limited effectiveness and potential adverse effects. Thus, catheter ablation therapy has become a generally adopted alternative technique to treat atrial fibrillation. Modestly sized randomized controlled trials have compared the therapies, but much uncertainty still exists about the long-term benefits of ablation relative to drug therapy.

"We have long known that physicians and patients are dissatisfied with drug therapy for atrial fibrillation, so we pursued this study to find out if catheter ablation would provide more effective treatment for these patients," says Douglas Packer, M.D., a Mayo Clinic cardiologist and the study's principal investigator. "While data from the trial was inconclusive in showing that catheter ablation was better than drug therapy in reducing rates of deaths and strokes, it showed strong evidence of reduced recurrence of atrial fibrillation, as well as reductions in mortality or cardiovascular hospitalizations."

CABANA enrolled 2,204 patients at 126 centers in 10 countries from 2009 to 2016. Each patient had new-onset or undertreated atrial fibrillation. In the study population, the median patient age was 68, and 37 percent were women. There were significant co-morbidities, such as high blood pressure, and a history of stroke and diabetes. Patients were randomly assigned to two groups of equal proportions to catheter ablation or drug therapy.

The primary comparison between catheter ablation and drug therapy showed a 14 percent lower risk of major complications such as death, stroke, severe bleeding and cardiac arrest, but the difference was not statistically significant. Ablation significantly reduced mortality or cardiovascular hospitalization by 17 percent when compared with drug therapy and reduced atrial fibrillation recurrence by 48 percent. When compared to drug therapy, ablation produced clinically important improvements in quality of life and in symptoms related to atrial fibrillation. These improvements were sustained over five years.

In large trials with longer follow-up, such as CABANA, patients don't always follow the assigned therapy. About nine percent of the ablation patients did not get their procedure and almost 30 percent of the drug therapy group got an ablation procedure, researchers reported. These "crossovers" who did not receive their assigned therapy may have affected the results of the study, Dr. Packer says. "You can't benefit from a therapy if you don't receive the therapy," he says.

However, when investigators examined the data according to the treatment received, the ablation group had significantly lower rates of death (40 percent), as well as the combination of death, disabling stroke, serious bleeding, or cardiac arrest (33 percent), compared with patients who only received drug therapy, he says.

One year after the start of treatment, patients in both groups showed substantial improvements in quality of life measures and measures related to atrial fibrillation, such as fatigue and shortness of breath. When compared to drug therapy, however, ablation produced additional improvements in quality of life and symptoms that were sustained over the five-year period, says Daniel Mark, M.D., of Duke Clinical Research Institute who led the quality of life analysis.

For example, at the beginning of the study, 86 percent of patients in the ablation group and 84 percent of patients on drug therapy reported atrial fibrillation symptoms during the previous month. By the end of the study, only 25 percent in the ablation group reported symptoms, compared with 35 percent in the drug therapy group, Dr. Mark says.

Mayo Clinic and Dr. Packer have a financial interest in the Analyze-AVW mapping technology that may or may not have been used in this research. In accordance with the Bayh-Dole Act, this technology has been licensed to St. Jude Medical (Abbott) and Mayo Clinic, and Dr. Packer has received annual royalties greater than $10,000, the federal threshold for significant financial interest. In addition, Mayo Clinic holds an equity position in the company to which the AVW technology has been licensed.

http://bit.ly/2HIQFKF

Bad news for egg lovers

Higher egg and cholesterol consumption hikes heart disease and death risk

CHICAGO --- Cancel the cheese omelet. There is sobering news for egg lovers who have been happily gobbling up their favorite breakfast since the 2015-2020 Dietary Guidelines for Americans no longer

limited how much dietary cholesterol or how many eggs they could eat. A large, new Northwestern Medicine study reports adults who ate more eggs and dietary cholesterol had a significantly higher risk of cardiovascular disease and death from any cause.

"The take-home message is really about cholesterol, which happens to be high in eggs and specifically yolks," said co-corresponding study author Norrina Allen, associate professor of preventive medicine at Northwestern University Feinberg School of Medicine. "As part of a healthy diet, people need to consume lower amounts of cholesterol. People who consume less cholesterol have a lower risk of heart disease."

Egg yolks are one of the richest sources of dietary cholesterol among all commonly consumed foods. One large egg has 186 milligrams of dietary cholesterol in the yolk.

Other animal products such as red meat, processed meat and high-fat dairy products (butter or whipped cream) also have high cholesterol content, said lead author Wenze Zhong, a postdoctoral fellow in preventive medicine at Northwestern.

The study will be published March 15 in *JAMA*.

The great debate

Whether eating dietary cholesterol or eggs is linked to cardiovascular disease and death has been debated for decades. Eating less than 300 milligrams of dietary cholesterol per day was the guideline recommendation before 2015. However, the most recent dietary guidelines omitted a daily limit for dietary cholesterol. The guidelines also include weekly egg consumption as part of a healthy diet.

An adult in the U.S. gets an average of 300 milligrams per day of cholesterol and eats about three or four eggs per week.

The study findings mean the current U.S. dietary guideline recommendations for dietary cholesterol and eggs may need to be re-evaluated, the authors said.

The evidence for eggs has been mixed. Previous studies found eating eggs did not raise the risk of cardiovascular disease. But those studies generally had a less diverse sample, shorter follow-up time and limited ability to adjust for other parts of the diet, Allen said.

"Our study showed if two people had exact same diet and the only difference in diet was eggs, then you could directly measure the effect of the egg consumption on heart disease," Allen said. "We found cholesterol, regardless of the source, was associated with an increased risk of heart disease."

Exercise, overall diet quality and the amount and type of fat in the diet didn't change the association between the dietary cholesterol and cardiovascular disease and death risk.

The new study looked at pooled data on 29,615 U.S. racially and ethnically diverse adults from six prospective cohort studies for up to 31 years of follow up.

It found:

- ***Eating 300 mg of dietary cholesterol per day was associated with 17 percent higher risk of incident cardiovascular disease and 18 percent higher risk of all-cause deaths. The cholesterol was the driving factor independent of saturated fat consumption and other dietary fat.***
- ***Eating three to four eggs per week was associated with 6 percent higher risk of cardiovascular disease and 8 percent higher risk of any cause of death.***

Should I stop eating eggs?

Based on the study, people should keep dietary cholesterol intake low by reducing cholesterol-rich foods such as eggs and red meat in their diet.

But don't completely banish eggs and other cholesterol-rich foods from meals, Zhong said, because eggs and red meat are good sources of important nutrients such as essential amino acids, iron and choline. Instead, choose egg whites instead of whole eggs or eat whole eggs in moderation.

"We want to remind people there is cholesterol in eggs, specifically yolks, and this has a harmful effect," said Allen, who cooked scrambled eggs for her children that morning. "Eat them in moderation."

How the study was conducted

Diet data were collected using food frequency questionnaires or by taking a diet history. Each participant was asked a long list of what they'd eaten for the previous year or month. The data were collected during a single visit. The study had up to 31 years of follow up (median: 17.5 years), during which 5,400 cardiovascular events and 6,132 all-cause deaths were diagnosed.

A major limitation of the study is participants' long-term eating patterns weren't assessed. "We have one snapshot of what their eating pattern looked like," Allen said. "But we think they represent an estimate of a person's dietary intake. Still, people may have changed their diet, and we can't account for that."

Other Northwestern authors include: Linda Van Horn, Marilyn Cornelis, Dr. John Wilkins, Dr. Hongyan Ning, Mercedes Carnethon, Dr. Philip Greenland, Lihui Zhao and Dr. Donald Lloyd-Jones.

The study was supported in part by the American Heart Association and by the National Heart, Lung and Blood Institute grants R21 HL085375, HHSN268201300046C, HHSN268201300047C, HHSN268201300049C, HHSN268201300050C, HHSN268201300048C of the National Institutes of Health.

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Does a new genetic analysis finally reveal the identity of Jack the Ripper?

By David Adam

Forensic scientists say they have finally fingered the identity of Jack the Ripper, the notorious serial killer who terrorized the streets of London more than a century ago.

Genetic tests published this week point to Aaron Kosminski, a 23-year-old Polish barber and a prime police suspect at the time. But critics say the evidence isn't strong enough to declare this case closed.

A historical image of police discovering a Jack the Ripper murder victim
Chronicle/Alamy Stock Photo

The results come from a forensic examination of a stained silk shawl that investigators said was found next to the mutilated body of Catherine Eddowes, the killer's fourth victim, in 1888.

The shawl is speckled with what is claimed to be blood and semen, the latter believed to be from the killer. Four other women in London were also murdered in a 3-month spree and the culprit has never been confirmed.

This isn't the first time Kosminski has been linked to the crimes. But it is the first time the supporting DNA evidence has been published in a peer-reviewed journal. The first genetic tests on shawl samples were conducted several years ago by Jari Louhelainen, a biochemist at Liverpool John Moores University in the United Kingdom, but he said he wanted to wait for the fuss to die down before he submitted the results. Author Russell Edwards, who bought the shawl in 2007 and gave it to Louhelainen, used the unpublished results of the tests to identify Kosminski as the murderer in a 2014 book called *Naming Jack the Ripper*. But geneticists complained at the time that it was impossible to assess the claims because few technical details about the analysis of genetic samples from the shawl were available.

The new paper lays those out, up to a point. In what Louhelainen and his colleague David Miller, a reproduction and sperm expert at the University of Leeds in the United Kingdom, claim is "the most systematic and most advanced genetic analysis to date regarding the Jack the Ripper murders," they describe extracting and amplifying the DNA from the shawl. The tests compared fragments of

mitochondrial DNA—the portion of DNA inherited only from one's mother—retrieved from the shawl with samples taken from living descendants of Eddowes and Kosminski. The DNA matches that of a living relative of Kosminki, they conclude in the *Journal of Forensic Sciences*.

The analysis also suggests the killer had brown hair and brown eyes, which agrees with the evidence from an eyewitness. "These characteristics are surely not unique," the authors admit in their paper. But blue eyes are now more common than brown in England, the researchers note.

The results are unlikely to satisfy critics. Key details on the specific genetic variants identified and compared between DNA samples are not included in the paper. Instead, the authors represent them in a graphic with a series of colored boxes. Where the boxes overlap, they say, the shawl and modern DNA sequences matched.

The authors say in their paper that the Data Protection Act, a U.K. law designed to protect the privacy of individuals, stops them from publishing the genetic sequences of the living relatives of Eddowes and Kosminski. The graphic in the paper, they say, is easier for nonscientists to understand, especially "those interested in true crime."

Walther Parson, a forensic scientist at the Institute of Legal Medicine at Innsbruck Medical University in Austria, says mitochondrial DNA sequences pose no risk to privacy and the authors should have included them in the paper. "Otherwise the reader cannot judge the result. I wonder where science and research are going when we start to avoid showing results but instead present colored boxes."

Hansi Weissensteiner, an expert in mitochondrial DNA also at Innsbruck, also takes issue with the mitochondrial DNA analysis, which he says can only reliably show that people—or two DNA samples—are not related. "Based on mitochondrial DNA one can only exclude a suspect." In other words, the mitochondrial DNA from the shawl could be from Kosminski, but it could probably also have come from thousands who lived in London at the time.

Other critics of the Kosminsky theory have pointed out that there's no evidence the shawl was ever at the crime scene. It also could have become contaminated over the years, they say.

The new tests are not the first attempt to identify Jack the Ripper from DNA. Several years ago, U.S. crime author Patricia Cornwell asked other scientists to analyze any DNA in samples taken from letters supposedly sent by the serial killer to police. Based on that DNA analysis and other clues she said the killer was the painter Walter Sickert, though many experts believe those letters to be fake. Another genetic analysis of the letters claimed the murderer could have been a woman.

doi:10.1126/science.aax3500

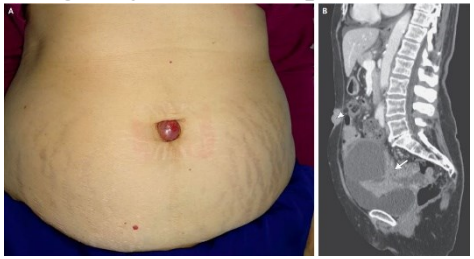
http://bit.ly/2Fjapmh

A Lump Grew Out of a Woman's Belly Button. It Was Cancer.

A strange lump growing out of a woman's belly button turned out to be metastatic cancer, according to a new report of her case.

By Rachael Rettner, Senior Writer | March 15, 2019 07:01am ET

The 73-year-old woman went to an emergency room in Spain, where she told doctors that the painful lump in her belly button had been enlarging over the past four months. Two days earlier, she had noticed blood coming out of the lump.



A woman in Spain had a lump protruding out of her belly button that turned out to be cancer. Above, an image of the lump (left) and a CT scan showing masses in the pelvis and near the belly button area (right, arrows). **The New England Journal of Medicine ©2019**

The mass was firm and measured 2 centimeters (0.8 inches) in diameter, the report said. Doctors could also feel a mass in her pelvis.

Imaging tests showed that the woman had a relatively large mass in her pelvic area, measuring 11 cm by 11 cm by 9.5 cm (4.3 by 4.3 by 3.7 inches).

Biopsies of both masses revealed that the woman had an advanced stage of ovarian cancer. Indeed, the mass protruding from her belly button was the result of the cancer spreading, or metastasizing.

This type of metastasis to the belly button, or umbilicus, is known as a "Sister Mary Joseph's nodule," according to the report, published online yesterday (March 13) in The New England Journal of Medicine.

A Sister Mary Joseph's nodule is sometimes seen in patients who have gynecologic or gastrointestinal cancers. But it's "relatively rare," said case report co-author Dr. Javier Barambio, a general surgery and digestive system physician at the University Hospital Foundation Jiménez Díaz in Madrid, Spain, who treated the woman. Only about 1 to 3 percent of abdominal and pelvic cancers spread to the umbilicus, according to a 2013 report.

It's unclear exactly how cancer spreads to the belly button area, said Dr. Wasif Saif, deputy physician in chief of medical oncology at Northwell Health Cancer Institute in Lake Success, New York, who wasn't involved in the case. But it may spread through the blood or lymphatic system, or may travel along ligaments or remnants of embryological structures that were needed during development but no longer have a purpose after birth, he said.

The appearance of a lump in the umbilicus alerts doctors to the possible presence of a tumor in the abdomen or pelvis, Saif said. But it doesn't definitely mean that a person has cancer — for example, the lump could be caused by something else, such as a hernia — so additional testing is needed, Saif told Live Science.

The woman had surgery to reduce the size of her tumor, along with chemotherapy to treat the remaining cancer, the report said.

Patients with a Sister Mary Joseph's nodule generally have a poor prognosis, since it is a sign of advanced cancer, according to 2009 report.

But in this case, the patient may have beaten the odds. She is in "good general condition" and free of disease after her treatment, Barambio told Live Science.

https://wb.md/2UGqqin

AAP Now Endorses Influenza Vaccine Shot and Nasal Spray

Injectable vaccine and the nasal spray vaccine are acceptable for the 2019-2020 season

Troy Brown, RN

The American Academy of Pediatrics (AAP) has updated its influenza vaccination recommendations, saying both the injectable vaccine (inactivated vaccine; IIV) and the nasal spray vaccine (quadrivalent live attenuated influenza vaccine; LAIV4) are acceptable for the 2019-2020 season.

The decision is being announced now to allow healthcare providers time to place vaccine orders, AAP says.

"The current year data regarding LAIV vaccine effectiveness against all influenza strains was used to make the decision," Bonnie Maldonado, MD, FAAP, chair of the AAP Committee on Infectious Diseases, told *Medscape Medical News.*

Last season, the AAP recommended children receive the injectable vaccine and only get the nasal spray in situations when they might not otherwise get vaccinated — for example, during vaccine shortages or when a child refuses the shot.

"This year the AAP is comfortable with recommending the use of either LAIV or IIV, with no preference, based on the data available at this time. It is important for all individuals 6 months of age and older to receive an influenza vaccine every year in order to prevent infection and possible complications," Maldonado explained.

The US Centers for Disease Control and Prevention (CDC) recommended either the injectable or nasal spray vaccines during the 2018-2019 season. The AAP's updated influenza vaccine recommendation is now consistent with CDC's.

“Every year we are never sure if the vaccine strains are going to be perfectly matched up with incoming flu strains, but based on the information that we have now, we believe the nasal spray is an acceptable option," Maldonado said in an AAP news release.

The AAP Board of Directors reviewed the latest data on the IIV and LAIV4 vaccines and approved both on March 14, 2019. The nasal spray is indicated for healthy individuals aged 2 through 49 years, the AAP explained in the news release.

The AAP will release a formal policy statement on prevention and treatment of influenza later in the year.

In the 2013-2014 and 2015-2016 influenza seasons, the LAIV4 formulation was not as effective against the A/H1N1 strain as the IIV formulation; therefore, the AAP did not recommend it during the 2016-2017 and 2017-2018 seasons.

The manufacturer of the LAIV4 changed the formulation to include a new A/H1N1 strain in 2017, and new data from Great Britain, based "on a limited number of cases in other countries," support the effectiveness of the nasal spray vaccine against some influenza strains, according to the news release.

"There may not be sufficient data regarding LAIV from this year's US influenza season because of low usage to determine its effectiveness. There may be data from other countries but if so not until later this year," Maldonado told *Medscape Medical News*.

More children were vaccinated against influenza during the fall of 2018 than the year before; however, there is still room for improvement. By November 2018, approximately 45% had been vaccinated, up from 38% in November 2017, the AAP noted in the news release.

Parents should talk with their child's pediatrician if they have questions about immunizations.

"The flu virus is unpredictable and can cause serious complications even in healthy children," Flor M. Munoz, MD, FAAP, a member of the AAP Committee on Infectious Diseases, said in the news release. "Children who have been immunized are less likely be hospitalized due to flu."

Maldonado has disclosed no relevant financial relationships.

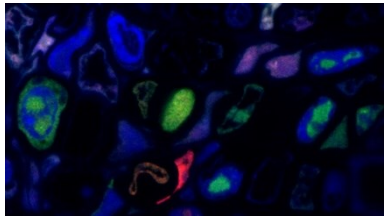
http://bit.ly/2Jhfn74

A New Discovery Upends What We Know About Viruses

A plant virus distributes its genes into eight separate segments that can all reproduce, even if they infect different cells.

Ed Yong

It is a truth universally acknowledged among virologists that a single virus, carrying a full set of genes, must be in want of a cell. A virus is just a collection of genes packaged into a capsule. It infiltrates and hijacks a living cell to make extra copies of itself. Those daughter viruses then bust out of their ailing host, and each finds a new cell to infect. Rinse, and repeat. This is how all viruses, from Ebola to influenza, are meant to work.



Plant cells (blue) infected by different virus segments (red and green)
Stephane Blanc

But Stéphane Blanc and his colleagues at the University of Montpellier have shown that one virus breaks all the rules.

Faba bean necrotic stunt virus, or FBNSV for short, infects legumes, and is spread through the bites of aphids. Its genes are split among eight segments, each of which is packaged into its own capsule. And, as Blanc’s team has now shown, these eight segments can reproduce themselves, *even if they infect different cells*. FBNSV needs all of its

components, but it doesn't need them in the same place. Indeed, this virus never seems to fully come together. It is always distributed, its existence spread between capsules and split among different host cells.

"This is truly a revolutionary result in virology," says Siobain Duffy of Rutgers University, who wasn't involved in the study. "Once again, viruses prove that they've had the evolutionary time to try just about every reproductive strategy, even ones that are hard for scientists to imagine."

FBNSV is one of several "multipartite viruses" that split their genes among different capsules. These oddballs were first discovered in the 1940s, and though they account for about 20 percent of known viral species, they're still rather obscure. Blanc thinks that's because they almost always infect plants and fungi, and only two have been found in animals—one in a moth and one in a mosquito. "I lecture on several virology courses, and even people in Ph.D. programs haven't heard of them," he laments. "They're everywhere, but because they're mainly on plants, no one cares."

These viruses have always been baffling, even to virologists who knew about them. Everyone assumed that they could only reproduce if all the segments infected the same host cell. But the risk of losing a piece, and so dooming the others, skyrockets as the number of pieces goes up. In 2012, two researchers calculated that the odds of successfully getting every segment in the same cell become too low with anything more than three or four segments. FBNSV, with its *eight* segments, "should never have evolved," Blanc says. Its mere existence suggests "that something must be wrong in the conceptual framework of virology."

Perhaps, he realized, these viruses don't actually need to unite their segments in the same host cell. "If theory was saying that this is impossible, maybe the viruses just don't do it," he says. "And once we had this stupid idea, testing it was very easy."

His colleagues Anne Sicard and Elodie Pirolles labeled pairs of FBNSV's genes with molecules that glowed in different colors—red for one segment, for example, and green for another. Then, they simply looked down a microscope to see whether the colors overlapped in the same cells. They almost never did. When the team first saw that, "we were jumping and running around the lab," Blanc says. "But we were also scared about it being a [mistake]. We took six years to verify it."

For example, they showed that the levels of one segment aren't tied to the levels of another, as you would expect if they were replicating in the same host cell. Instead, in any one infected plant, the different segments seem to accumulate at different rates.

But that discovery raised another problem. Each of the eight segments carries a gene with its own vital role. One makes the proteins that copy the virus's DNA once it gets inside its hosts. Another creates the proteins that form the virus's capsules. See the problem? If these segments end up in *different cells*, the DNA-copying one shouldn't be able to make capsules, the capsule-making gene shouldn't be able to copy itself, and both of them would be stuck.

That doesn't happen, the team discovered, because the virus's genes might be stuck in neighboring cells, but the proteins created by those genes can move. The capsule-making *protein* can get into a cell with the DNA-copying gene, and cover it. The DNA-making *protein* can get into a cell with the capsule-making gene, and copy it. Think of the eight segments as factories in different cities, shipping assembly robots to one another so that each site can manufacture its own separate product. It is within this expansive trade network that the distributed virus truly exists.

It's not clear *how* this network operates, but many scientists have found that plant proteins can voyage between cells, even over long distances from root to shoot. Some researchers who study multipartite viruses have even suggested that they could make use of

these botanical highways. But Blanc's team has now found clear and unambiguous evidence that they do. Perhaps, he says, "this is why multipartite viruses don't exist so much in animals. Maybe it's harder for our proteins to travel between cells."

"The work is very important … and very carefully done," says Marilyn Roossinck of Pennsylvania State University. For decades, she has been studying a different multipartite virus that affects cucumbers, and though she has seen some of the patterns that Blanc's team did, "these were never published, as their significance wasn't clear," she says.

"This report challenges a fundamental assumption of virology," adds Rodrigo Almeida of the University of California at Berkeley, who studies plant diseases. "I am not aware of any similar example in biology, where genetic information appears to be split among host cells."

The closest example I can think of exists in cicadas. These noisy insects rely on a bacterium called *Hodgkinia*, which lives inside their cells and provides them with nutrients. But this one bacterium has fractured into several daughter species, each of which contains just a few of *Hodgkinia*'s full set of genes. None of these partial microbes can survive on its own; they only function as a set. But these daughter species are all still locked within the same cell, so they're not truly distributed as the virus is. They are also problematic: If any of them were to disappear, the rest would also die out, as would their cicada host. *Hodgkinia*'s fragmented existence is a looming disaster—"a slow-motion extinction event," according to John McCutcheon, who described it.

By contrast, multipartite viruses are clearly very successful, so their bizarre distributed existence must have some benefit. And Blanc thinks he knows what that might be.

His team has shown that when FBNSV infects a plant, the frequency of each segment is very predictable. Some of them are common and others are rare, but their relative proportions are constant, at least within a given species of plant. If the virus infects a different plant species, those proportions change—to a different, but still predictable, pattern. Blanc calls these "genome formulas"—ratios of genes that FBNSV uses for different hosts.

The virus's use of these formulas reminds Blanc of the ways in which animals and other complex organisms adapt to different environments by tweaking the numbers of important genes. In very rough terms, the more copies you have, the more effectively that gene can do its thing. But viruses are tiny entities, whose capsules only have room for small genomes. There's not enough space for them to just wantonly double their gene counts.

Multipartite viruses don't have to. If they want to emphasize the use of a certain gene, they just need to get the segment carrying it into more host cells. "This lifestyle allows the virus to adjust its gene copy number without mutating," Blanc says. It's as if FBNSV has found a way to have the flexibility of a much larger and more complex genome, while still keeping the unflinching efficiency of a virus.

These discoveries could also change our understanding of other more traditional viruses. Influenza's genome is split into eight segments, and unlike FBNSV, all of these are packaged into the same capsule. Researchers typically assume that every capsule contains the full octet, but in 2013, Christopher Brooke of the University of Illinois showed that 90 percent of them are missing at least one segment. Influenza virus "exists primarily as a swarm of complementation-dependent, semi-infectious virions," Brooke wrote.

Three years later, a different team showed that the same is true for the virus behind Rift Valley fever: Only a minority contain all three of the virus's gene segments, and most are missing one. "Perhaps the boundary between these viruses and the multipartite ones isn't so clear," Blanc says.

Many viruses also produce capsules called "defective interfering particles," which … well, the clue's in the name. They're defective because, for some reason, they've lost part of their full genome. They're interfering because, though they're defective, their parent viruses will still make copies of them, flooding the total pool of capsules with noninfective deadbeats. "These things have been known for a century, and they've long been considered as junk," Blanc says. "But they are very efficiently maintained in any viral infection. Maybe they can profit from the system we have identified."

http://bit.ly/2FkZVTv

Calcium in arteries is shown to increase patients' imminent risk of a heart attack

New research study shows that identifying the presence or absence of coronary artery calcium (CAC) in a patients' arteries can help determine their future risk of a heart attack.

About six million people come into an emergency department every year with chest pain, but not all of them are having a heart attack -- and many are not even at risk or are at very low risk for having one.

Now, a new research study presented at the American College Cardiology Scientific Sessions from the Intermountain Healthcare Heart Institute in Salt Lake City shows that identifying the presence or absence of coronary artery calcium (CAC) in a patients' arteries can help determine their future risk.

"Through these results, we're seeing more clearly that the presence of coronary artery calcium can help us to predict who is more likely to have a cardiac event, not only later in life, but when symptoms are present, in the near future and hopefully, medically intervene in time to stop it," said Viet T. Le, PA-C, principal investigator and researcher at the Intermountain Healthcare Heart Institute in Salt Lake City.

Results of the study were presented at the American College of Cardiology Scientific Sessions in Atlanta on March 16, 2019.

For the study, researchers identified 5,547 patients without a history of coronary artery disease who came to Intermountain Medical Center with chest pain between April 2013 and June 2016.

These patients had undergone PET/CT scans to assess for ischemia, a disruption of normal blood flow through the heart arteries to the muscle tissues of the heart. This scan also looks for the presence of CAC, which are calcium deposits on the walls of the heart's arteries, indicating atherosclerosis, or plaque, the hallmark of heart disease. The researchers then examined patients' medical outcomes for up to the next four years.

Researchers found that patients whose scans revealed CAC were at higher risk of having a heart event within 90 days compared with patients whose PET/CT showed they had no CAC. Researchers also found that patients with CAC were also more likely over the following years to have high-grade obstructive coronary artery disease, revascularization surgery, and/or other major adverse cardiac events than patients who had no coronary artery calcium.

The findings can be used in two different ways, said Le.

First, testing for CAC can help emergency departments quickly identify those patients with chest pain, but are not in acute distress as being at risk for a future heart event from those who may have non-heart related symptoms and should follow up with their primary care physician to identify the true source of the chest pain, which may be as simple as a pulled muscle. These CAC scans are non-invasive, use only as much radiation as a mammogram, and are relatively cheap, especially compared to PET/CT stress tests, Le said.

Second, CAC isn't easily visually identifiable at low or moderate levels in the arteries without a formal scan. Checking patients who are not actively found to be experiencing a heart event but who have suspicious symptoms when they come to the ED can help physicians identify who is at risk for a future event. This allows for early

initiation of risk reducing lifestyle changes in those found to have CAC to avoid future events.

"We can have that discussion about improving their lifestyle a little sooner this way because they may not be having an acute event but they're looking down the barrel of one, so let's see if we can move that barrel away," said Le.

Future studies are needed to demonstrate whether a CAC first strategy in these symptomatic patients will better identify those who should have further stress testing as well as improve patient education and early implementation of risk reducing strategies.

This research was funded by the Intermountain Foundation.

https://nyti.ms/2CpnyIS

Tens of Thousands of Heart Patients May Not Need Open-Heart Surgery

Replacement of the aortic valve with a minimally invasive procedure called TAVR proved effective in younger, healthier patients.

By Gina Kolata

The operation is a daring one: To replace a failing heart valve, cardiologists insert a replacement through a patient's groin and thread it all the way to the heart, maneuvering it into the site of the old valve.

The procedure, called transcatheter aortic valve replacement (TAVR), has been reserved mostly for patients so old and sick they might not survive open-heart surgery. Now, two large clinical trials show that TAVR is just as useful in younger, healthier patients.

It might even be better, offering lower risks of disabling strokes and death, compared to open-heart surgery. Cardiologists say it will likely change the standard of care for most patients with failing aortic valves.

"Is it important? Heck, yes," said Dr. Robert Lederman, who directs the interventional cardiology research program at the National Heart, Lung and Blood Institute. The findings "were remarkable," he added. Dr. Lederman was not involved with the studies and does not consult for the two device companies that sponsored them.

In open-heart surgery, a patient's ribs are cracked apart and the heart is stopped to insert the new aortic valve.

With TAVR, the only incision is a small hole in the groin where the catheter is inserted. Most patients are sedated, but awake through the procedure, and recovery takes just days, not months, as is often the case following the usual surgery.

The results "shift our thinking from asking who should get TAVR to why should anyone get surgery," said Dr. Howard Herrmann, director of interventional cardiology at the University of Pennsylvania.

"If I were a patient, I would choose TAVR," said Dr. Gilbert Tang, a heart surgeon at the Icahn School of Medicine at Mount Sinai in New York, who was not involved in the new research.

The studies are to be published in the New England Journal of Medicine and presented on Sunday at the American College of Cardiology's annual meeting.

The Food and Drug Administration is expected to approve the procedure for lower-risk patients. As many as 20,000 patients a year would be eligible for TAVR, in addition to the nearly 60,000 intermediate- and high-risk patients who get the operation now.

"This is a clear win for TAVR," said Dr. Michael J. Mack, a heart surgeon at Baylor Scott and White The Heart Hospital-Plano, in Texas. From now on, "we will be very selective" about who gets open-heart surgery, said Dr. Mack, a principal investigator in one of the trials.

Some healthier patients will still need the traditional surgery — for example, those born with two flaps to the aortic valve instead of the usual three. Having two flaps can lead to early aortic valve failure.

TAVR was not tested in these patients, and the condition occurs more often in younger patients who are low surgical risks.

Aortic valve failure stems from a stiffening of the valve controlling flow from the large vessel in the heart that supplies blood to the rest of the body. Patients often are tired and short of breath.

There is no way to prevent the condition, and no treatment other than replacing the valve. The main risk factor is advancing age.

Although both studies enrolled over 1,000 patients, the trials differed slightly in design, making direct comparisons difficult.

The study led by Dr. Mack and Dr. Martin Leon, an interventional cardiologist at Columbia University in New York, tracked deaths, disabling strokes and hospitalizations at one year following the procedures. The rates were 15 percent with surgery versus 8.5 percent with TAVR.

The rates of deaths and disabling strokes — the factors most important to patients — were 2.9 percent with surgery versus 1 percent with TAVR.

The second study estimated deaths or disabling strokes at two years, finding rates of 6.7 percent with surgery versus 5.3 percent with TAVR.

The trials were sponsored by makers of TAVR valves, Edwards Lifesciences of Irvine, Calif., and Medtronic, headquartered in Dublin. The two companies make slightly different valves.

The Edwards valve is compressed onto a balloon catheter that is pushed through a blood vessel from the groin to the aorta. Once it reaches the aorta, a cardiologist inflates the balloon and expands the valve, which pushes aside the failing valve.

The Medtronic valve is made of nitinol, a metal that shrinks when it is cold and expands when warm. The valve is chilled and put onto a catheter. When it reaches the aorta, the cardiologist pulls back a sheath, freeing the new valve. Warmed by the body, it expands to fill the narrowed opening and remains there.

With traditional surgery, by contrast, a doctor cuts out the old valve and sews in a new one, removing the old valve instead of leaving it in the heart.

Dr. Jeffrey J. Popma, an interventional cardiologist at Beth Israel Deaconess in Boston, led the second trial and is a consultant for both manufacturers. He uses both devices in surgery, and said the important finding is that both were preferable to surgery.

The studies involved leading surgeons and cardiologists at academic medical centers, many enlisted as consultants. Independent data and safety monitoring committees oversaw the trials, and independent statisticians confirmed the results.

Aortic valve replacements have been performed for decades, and surgeons know the valves placed during surgery last at least 10 to 15 years. It remains to be seen if TAVR valves will fare as well.

The question is especially important for younger patients. The average age of subjects in the current studies was the low to mid 70s, younger by a decade or more than most patients getting TAVR now.

Hospitals offering TAVR will take a financial hit when lower-risk patients start opting for it, Dr. Herrmann said. The TAVR valves cost far more than valves placed surgically, but insurers usually pay equally for either procedure.

“Open-heart surgery, particularly in low-risk patients, is very profitable,” Dr. Herrmann said.

More than half a dozen companies make surgical valves, but only two market TAVR valves. Perhaps with more competition, Dr. Herrmann said, prices for TAVR valves will come down.

At the moment, it will be up to most patients which procedure they choose, Dr. Popma said — TAVR or surgery.

For Robert Pettinato, 79-year-old retiree in Scranton, Pa., there was no question. He had been feeling mild chest pain, and he was finding it difficult to finish a round of golf.

But last year, when his cardiologist told Mr. Pettinato that he needed a new valve, the only way he could get TAVR was to enter a clinical trial. He enrolled in the Edwards trial at the University of Pennsylvania.

He had TAVR in November, stayed in the hospital for 24 hours and went home. A few days later, he went to the football game at Lehigh University against its archrival, Lafayette. (He's a Lehigh alumnus and never misses that game.)

Shortly afterward, his younger brother Jim, who lives in Florida, had to have aortic valve replacement. He wanted TAVR, but the clinical trials were closed. He had surgery instead.

It took his brother four months to recover enough to play a round of golf, Mr. Pettinato said.

Mr. Pettinato is back to playing golf himself. "I am the luckiest guy in the world," he said.

http://bit.ly/2F8DQGq

World's oldest semen still viable

Ram sperm frozen for 50 years successfully used to impregnate 34 ewes

Semen stored since 1968 in a laboratory in Sydney has been defrosted and successfully used to impregnate 34 Merino ewes, with the resulting live birth rate as high sperm frozen for just 12 months.

"This demonstrates the clear viability of long-term frozen storage of semen. The results show that fertility is maintained despite 50 years of frozen storage in liquid nitrogen," said Associate Professor Simon de Graaf from the Sydney Institute of Agriculture and School of Life and Environmental Sciences at the University of Sydney.

"The lambs appear to display the body wrinkle that was common in Merinos in the middle of last century, a feature originally selected to maximise skin surface area and wool yields. That style of Merino has since largely fallen from favour as the folds led to difficulties in shearing and increased risk of fly strike," Associate Professor de Graaf said.

His colleague on this project, Dr Jessica Rickard, said: "We believe this is the oldest viable stored semen of any species in the world and definitely the oldest sperm used to produce offspring."

Associate Professor de Graaf said that it was the reproductive biology and genetic aspects of these as-yet unpublished findings that were of most interest to him.

"We can now look at the genetic progress made by the wool industry over past 50 years of selective breeding. In that time, we've been trying to make better, more productive sheep," he said. "This gives us a resource to benchmark and compare."

Dr Rickard is a post-doctoral McCaughey Research Fellow in the Sydney Institute of Agriculture. She is continuing the strong animal reproduction research tradition in veterinary and biological sciences at the University of Sydney through her work in the Animal Reproduction Group.

Dr Rickard did the original work to determine if the stored semen was viable for artificial insemination. This involved thawing the semen, which is stored as small pellets in large vats of liquid nitrogen at -196 degrees. She and her colleagues then undertook in vitro tests on the sperm quality to determine the motility, velocity, viability and DNA integrity of the 50-year-old sperm.

"What is amazing about this result is we found no difference between sperm frozen for 50 years and sperm frozen for a year," Dr Rickard said.

Out of 56 ewes inseminated, 34 were successfully impregnated. This compares to recently frozen semen from 19 sires used to inseminate 1048 ewes, of which 618 were successfully impregnated. This gives

a pregnancy rate of 61 percent for the 50-year-old semen against 59 percent for recently frozen sperm, a statistically equivalent rate.

The original semen samples were donated in the 1960s from sires owned by the Walker family. Those samples, frozen in 1968 by Dr Steven Salamon, came from four rams, including 'Sir Freddie' born in 1963, owned by the Walkers on their then property at Ledgworth. The Walkers now run 8000 sheep at 'Woolaroo', at Yass Plains, and maintain a close and proud relationship with the animal breeding program at the University of Sydney.

The research was undertaken in part courtesy of a grant from Australian Wool Innovation.