Exercise for older mouse mothers lowers risk of heart defects in babies

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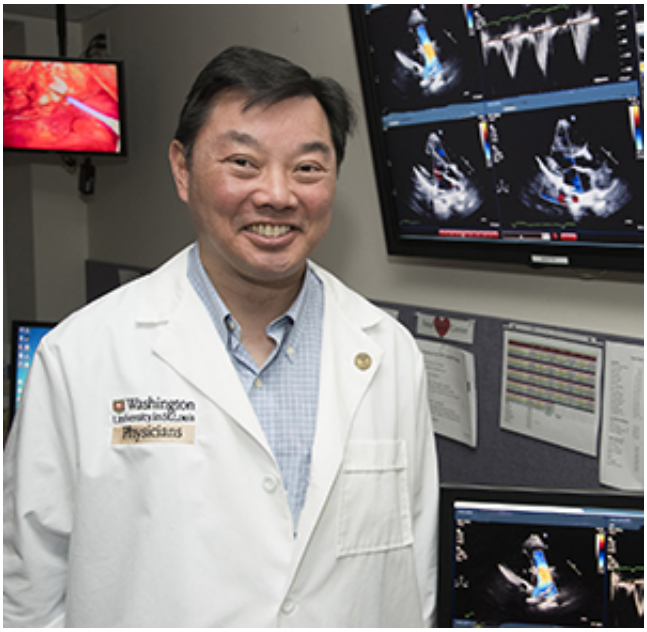

In people, a baby's risk of congenital heart defects is associated with the age of the mother. Risk goes up with increasing age. Newborn mice predisposed to heart defects because of genetic mutations show the same age association.A new study demonstrates that older mouse mothers reduce this risk for their offspring to that of younger mouse mothers through exercise alone, according to researchers led by Patrick Y. Jay, MD, PhD, at Washington University School of Medicine in St. Louis. The study also suggests that the increased risk of congenital heart defects is tied to the age of the mother and not the age of her eggs. The study appears April 1 in *Nature*. Credit: Robert Boston

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The risk that an infant human or mouse may develop a congenital heart defect results from a complex interplay of genes inherited from both parents and environmental effects experienced by the embryo. Genetic mutations are known to increase a child's risk of developing a heart that has abnormally formed valves, vessels or chambers, or holes between the chambers. However, many people who have family histories of congenital heart disease or known mutations have normal hearts, and older mothers usually have healthy children.

"In my lab, we are interested in understanding why certain individuals who are exposed to a known cause of congenital heart disease—whether genetic or environmental—escape the condition, and others don't," said senior author Patrick Y. Jay, MD, PhD, associate professor of pediatrics. "We study mice with a mutation that increases the risk of heart defects. The mutation first was found in people. But not every mouse with the mutation gets a heart defect, just as in humans. For the past 10 years, we have been trying to figure out the genetic and environmental factors that might influence risk. Understanding them could help us develop a way to prevent heart defects despite exposure to a known cause."

Mirroring observations in people, past work from Jay's lab has shown

that older mouse mothers tended to bear pups with higher rates of congenital heart defects when compared with younger mothers. Other variables in the laboratory mice, such as age of the father or litter size, were not associated with any difference in risk.

"Conventional wisdom says this increased risk seen for older mothers results from aging eggs," Jay said. "Since all of a woman's eggs were produced when she was an embryo, there's this notion that over decades the eggs just go bad. But the evidence for this is pretty circumstantial. In humans, you can only show associations. You can't establish causality."

To look at the question of aging eggs more carefully, Jay and his colleagues performed a relatively simple experiment, yet one that, to his knowledge, has not been reported previously.

Working in mice genetically prone to relatively high rates of congenital heart defects, the researchers took ovaries from older mothers and transplanted them into younger mothers. Likewise, they took the ovaries of younger mothers and transplanted them into older mothers. They examined the offspring to determine if higher rates of heart defects tracked with the age of the mothers or the age of the ovaries.

"We discovered that the rates track exactly with the age of the mother," said Jay, also a pediatric cardiologist at St. Louis Children's Hospital.

In other words, young mice with old ovaries bore offspring with low rates of heart defects, similar to young mice with young ovaries. And older mice, even with young ovaries, bore offspring with higher rates of heart defects, similar to older mice with older ovaries.

"This is exciting from a prevention standpoint," Jay said. "If there is something about the mother that is contributing to the risk, independent of the ovary, then we have a much better chance of altering that risk than

we would if the problem were solely with aging eggs—simply because adults are easier to treat than eggs or embryos."

In an effort to identify possible drivers of age-associated risk of congenital heart disease, Jay and his team looked at diet.

"We knew that obesity and diabetes contribute to congenital heart disease in people and that the risk of these metabolic conditions goes up as you age," he said. "So we put the mice on a high-fat diet."

Despite becoming obese and diabetic, these mouse mothers did not have a greater risk of bearing offspring with increased heart defects. Still thinking that healthy metabolism was likely important for healthy developing embryos, Jay and his colleagues next looked at exercise.

"We gave the mice access to running wheels, like you would find at a pet store," he said. "And we just let the mothers run."

This time, the researchers found that risk of heart defects in offspring of older mothers dropped from about 20 percent for sedentary mothers to 10 percent for exercising mothers. They didn't see a significant effect of exercise in the younger mothers, with rates staying at about 10 percent for them regardless of physical activity.

"In the babies of the old mothers who exercised, the incidence of heart defects goes down, but it does not go below the incidence of the young mothers," Jay said. "There's still a baseline level that we didn't get past."

Even so, Jay said, cutting rates in half would be significant.

"If you can prevent even one heart defect, that can have a huge emotional and economic impact on a family," Jay said. "While we've gotten very good at treating congenital heart defects, the surgeries don't

cure the patients. Now that so many have reached adulthood, we know they are coming back with heart failure, arrhythmias and other difficult heart problems."

While Jay said they don't know how such data might translate into people, they showed that exercise did not have to be life-long to produce a measurable benefit. Older mouse mothers who exercised for at least three months prior to birth saw an effect similar to that seen in older mothers who had exercised since they were the equivalent of teenagers. Jay explained that the benefit was observed with high-intensity physical activity by human standards. Mice like to run and, if given the opportunity, will do so for most of their waking hours.

Still, Jay said, they are pleased to have demonstrated the concept that a treatment or intervention focused on the mother can prevent disease in the offspring that carries the causal mutation.

"I hope this study will change the way investigators think about congenital heart disease," he said. "Right now, the field is very focused on the embryo—finding genetic mutations and figuring out the biology to see how they affect cardiac development. That research is important and necessary, but this opens up a whole new conversation."

More information: Schulkey CE, Regmi SD, Magnan RA, Danzo MT, Luther H, Hutchinson AK, Panzer AA, Grady MM, Wilson DB, Jay PY. The maternal age-associated risk of congenital heart disease is modifiable. *Nature*. April 1, 2015. DOI: 10.1038/nature14361

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