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Conditions in the womb can affect cardiovascular health later in life.

Early starts

Although lifestyle is a major contributor to heart disease in adults, many key risk factors exert their effects in early childhood, and even before birth.

By Bianca Nogrady

For preventive cardiologist Michele Mietus-Snyder, the quest to understand and address the early causes of heart disease is like going down the rabbit hole in Lewis Carroll's *Alice's Adventures in Wonderland*.

"When I'm seeing my adolescent patients, I'm not just trying to prevent heart disease for that child, but for that child's children," she says.

Initially, risk factors might seem to be an individual's lifestyle – poor diet or lack of physical activity, for example. But delve deeper and it becomes clear that heart disease can be set in motion long before these lifestyle decisions are made. "The foundations of cardiovascular risk are laid before birth," says Mietus-Snyder, at the Children's National Hospital in Washington DC.

The endpoints of cardiovascular disease are exceptionally well characterized. This is unsurprising, given that ischaemic heart disease is the single biggest cause of mortality worldwide, responsible for 16% of all deaths. But the paths that lead to that endpoint are much less well understood. What is becoming apparent is that many people are born already holding a poor hand of cards when it comes to their cardiovascular health, thanks to genetic and 'epigenetic' factors, parent's and grandparent's lifestyles and exposures, conditions in the womb and growth patterns in the first year of life. That doesn't mean, however, that they are doomed to disease. Understanding these influencing factors means that interventions to reduce risk can be developed and applied early, long before processes have gone past the point of disease prevention.

Genetic foundations

One inherited disorder associated with cardiovascular disease is familial hypercholesterolaemia. This condition can cause high cholesterol and is linked to a 10- to 20-fold increased risk of one manifestation of cardiovascular disease: coronary artery disease – blockages of the arteries that supply blood to the heart.

But familial hypercholesterolaemia might be just the tip of the genetic iceberg. Interest is growing not just in the genes that are inherited, but in the changes that are made to those genes before a child is even conceived.

"It's very well established that a mother's weight or body mass index going into pregnancy is associated with the child having increased risk of obesity and related metabolic phenotypes," says Rae-Chi Huang, a paediatrician and researcher at the Telethon Kids Institute in Perth, Australia. The question facing researchers is what is behind that link.

Huang is interested in epigenetics – changes to genes that aren't caused by modifications to the underlying DNA – and what role the changes have in the later development of obesity and cardiovascular disease. Emerging evidence also suggests that DNA methylation – the addition of a methyl group to the DNA – might be the link between the conditions a fetus is exposed to in the womb and later obesity.

Huang and her colleagues have been studying both the causes and consequences of DNA methylation, using techniques that allow them to scan for the modification across hundreds of thousands of genetic locations. In one paper[1], they looked at DNA methylation patterns in a cohort of nearly one thousand 17-year-olds. Around one-third of the participants had mothers who smoked tobacco while pregnant. Of the 23 DNA sites found to be associated with maternal smoking during pregnancy, many were linked to cardiometabolic performance, including cholesterol levels and blood pressure. The authors argued that the methylation patterns suggested that smoking during pregnancy had a potentially long-lasting effect on the heart health of the child.

Another possible contributor to DNA methylation in offspring is whether their mothers are overweight or obese during pregnancy. Researchers have found different patterns of DNA methylation in the children of women who were either underweight or overweight before pregnancy. Higher levels of DNA

methylation at certain sites in the children of women who were obese were associated with a greater likelihood of obesity in offspring, whereas the opposite was seen in women who were underweight[2].

DNA methylation could be influencing heart disease through the kidneys – which help to control blood pressure – by altering the development of the fetal kidney and its filtering units, called nephrons. These form between 20 and 34 weeks of gestation, Huang says. After around 34 weeks the number of nephrons is fixed. Some research in animals suggests that reduced DNA methylation could affect that process, lowering the kidneys' ability to function as well as they might. This is, in turn, associated with high blood pressure later in life – a risk factor for cardiovascular disease.

Epigenetic changes could affect how and where the body stores excess fat, and this can have an impact on heart-disease risk as an adult. Key players in this process are the cells' mitochrondria, which generate energy from carbohydrate and fat. Mietus-Snyder is studying which epigenetic changes might be altering the function of the mitochondria, and possibly tipping the fat-storage pattern towards unhealthy storage in adipose tissue, particularly around organs.

"Mitochondria are implicated mechanistically in that unhealthy adipose tissue problem," she says. "And some of the epigenetic markers are associated with unhealthy mitochondria and unhealthy fat storage." If an individual's lifestyle choices mean they consume more fat than the body needs for energy, those epigenetic changes might be directing the excess calories to storage around the abdominal organs, which is also implicated in a higher risk of heart disease. "They go into unhealthy places like the liver or the viscera around the intestinal tract, or into heart muscle or into the pancreas or around the kidneys, and they start causing all of these cardiometabolic problems."

Early nutrition

When paediatric nutritionist Atul Singhal began his nutritional research in the late 1990s, babies with a low birth weight – who are at increased risk of heart disease in later life – were encouraged to gain weight in early life to 'catch up', in the hope that this might reduce their risk of disease. Singhal and his colleagues at University College London's Great Ormond Street Institute of Child Health decided to put this idea to the test by feeding smaller babies a high-protein diet, expecting that the children would grow up healthier as a result[3].

Instead they found the opposite. "They ended up being more obese, had higher cholesterol concentration and higher blood pressure," Singhal says. That finding has contributed to a complete rethink of infant nutrition and growth. What he and many others now think is that the higher incidence of cardiovascular disease in babies with a low birth weight was the result not of babies low birth weight, but of the rapid catch-up growth that was encouraged during the babies' first six months.

"This is known as programming: the idea that you can manipulate nutrition in early life, to have a long-term effect on structure and function of an organism," Singhal says. But the challenge for researchers such as Singhal is establishing causality: finding the mechanism by which rapid weight gain in early life causes obesity and cardiovascular disease later in life. He says that although epigenetics is "the big trendy mechanism" right now, he is interested in what effect this early weight gain has on appetite.

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His theory is that children with a higher nutrient intake in those early months have their appetite programmed to expect that level of intake – they can eat more before they feel full. In animals, reduced nutrient intake in infancy is associated with reduced appetite and fat mass in later life, as well as a longer lifespan.

Conducting those experiments in humans is harder, especially because Singhal's work on children with different nutrient intakes in infancy suggests that the effects don't become evident until around the age of four.

"Once these children get to a point where appetite regulation is not so much controlled by their parents, and that they're more free living, will the group that has a lower nutrient intake have a lower set-point of appetite?" he says. He speculates that there are feedback loops in the hypothalamus – a region of the brain that controls appetite through hormonal mechanisms – that are set by early eating habits, but the work to demonstrate that is ongoing.

Young hearts

The link between being overweight or obese as a child and having an increased risk of heart disease as an adult is well established. Less well known is why that might be the case. At the Murdoch Children's Research Institute in Melbourne, Australia, bioengineer Jonathan Mynard is examining the role that high blood pressure might have in connecting risk factors in childhood with adult disease. And he is looking for the physiological 'smoking guns' that form the connection.

"There's really good evidence that high blood pressure in children leads to high blood pressure in adults, and there's very good evidence in adults that high blood pressure leads to cardiovascular events – including stroke and myocardial infarction," Mynard says.

The difficulty, he says, is that there are few studies that directly connect childhood risk factors and the hard adult endpoints of cardiovascular disease – death, for example.

Mynard's interest in the mechanics of the heart have led him to examine something called arterial stiffness – reduced elasticity of blood-vessel walls – which is a precursor to high blood pressure at any age. Although some arterial stiffness in children is associated with congenital heart abnormalities, there's also evidence connecting the condition to obesity – possibly mediated by inflammation. Other theories posit that arterial stiffness in children could result from prematurity, reduced oxygen exposure in the womb or poor kidney function. Mynard says it's a complex picture, but the good news is that it is reversible.

"Blood vessels are living tissues that are always adapting to their environment," he says. "Childhood is the best time to be intervening because the horse hasn't bolted and the changes that are occurring are not at the end stage."

Despite global concerns about the spiralling rates of obesity in children – and the potential consequences for them in adulthood – biology isn't necessarily destiny. Simple lifestyle interventions, such as switching to a diet high in vegetables, fruit and whole grains and low in sugar, salt and processed meat, can make a major difference to cardiovascular risk factors in as little as ten days, despite the genetic odds being stacked against some people.

"I always tell my patients that hereditary roots are like cards we're dealt," Mietus-Snyder says. "It's up to us to play a smart hand."

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1. Rauschert, S. *et al. Front. Genet.* **10**, 770 (2019).
2. Sharp, G. C. *et al. Int. J. Epidemiol.* **44**, 1288–1304 (2015).
3. Singhal, A., Cole, T. J. & Lucas, A. *Lancet* **357**, 413–419 (2001).