Mothers' sleep, late in pregnancy, affects offspring's weight gain as adults

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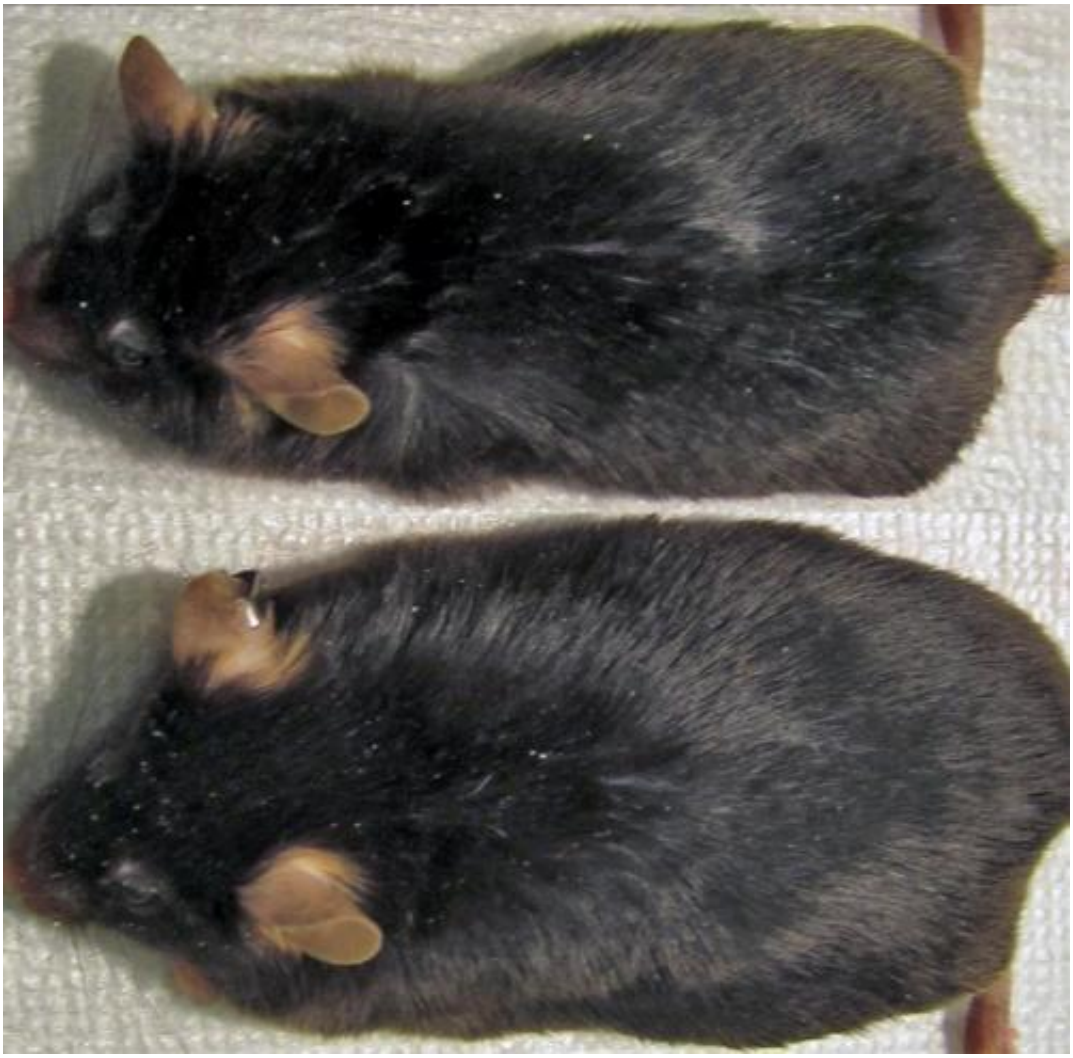

By 24 weeks the sons (below) of sleep-disturbed mothers weighed about 10 percent more than the sons (above) of mice with uninterrupted sleep. Credit: Abdelnaby Kahlyfa

Poor-quality sleep during the third trimester of pregnancy can increase the odds of weight gain and metabolic abnormalities in offspring once they reach adulthood, according to a new study published online May 8, 2014, in the journal *Diabetes*.

The researchers linked the excess weight and changes in metabolism to epigenetic modifications that reduce expression of the gene for adiponectin—a hormone that helps regulate several metabolic processes, including glucose regulation. Lower levels of adiponectin correlate with increased body fat and reduced activity.

"Disrupted sleep is a common problem during the final trimester of a pregnancy," said study director, sleep specialist David Gozal, MD, the Herbert T Abelson professor of pediatrics at the University of Chicago. "For some women, sleep fragmentation, especially sleep apnea, can be profound. We wanted to devise a system that enabled us to measure the potential impact of fragmented sleep on the fetus, which is uniquely susceptible so early in life."

To test this in humans could take 50 years, so Gozal's team devised experiments using pregnant mice. The researchers interrupted sleep for half of the mice during days 15 through 19 of pregnancy, the mouse equivalent of the third trimester. During the day, when mice normally sleep, a motorized brush swept through those cages every two minutes, forcing the mouse mothers-to-be to wake up briefly, step over the brush and go back to sleep. Pregnant mice in the other cages were not disturbed.

Newborns from both groups weighed the same at birth and initially had normal feeding habits and growth trajectories, but diverged in adulthood.

"For several weeks after weaning all the mice seemed fine," Gozal said. "But after 16 to 18 weeks—the mouse equivalent of early middle

age—we noticed that the male mice born to moms with fragmented sleep were eating more. Their weights started creeping up."

The researchers focused on males because their hormone levels are less complex and easier to track. By 24 weeks the sons of sleep-disturbed mothers weighed about 10 percent more than the sons of mice with uninterrupted sleep.

"This is not huge obesity," Gozal said, "just 10 percent, a little extra at this stage. This would amount to 15 extra pounds in a human adult." A few of these mice, however, "became morbidly obese at 18 months of age or so," he said. "They died long before their unexposed counterparts."

Offspring from mothers with fragmented sleep revealed health problems in addition to weight gain. They scored poorly on glucose-tolerance tests. They produced normal amounts of insulin but it was less effective, failing to lower glucose levels as expected. Insulin resistance is a hallmark of metabolic syndrome and type 2 diabetes.

They also had disproportionately high amounts of visceral white adipose tissue, the "bad fat," as well as elevated levels of low-density lipoproteins, the bad cholesterol. Plus, their fat cells produced less adiponectin.

Adiponectin is usually a "beneficial hormone," Gozal said. "It can reduce cholesterol, make you more sensitive to insulin, protect your heart." As adiponectin levels in adults go up, body-fat percentage tends to go down. Expression of the adiponectin gene was reduced in the offspring of sleep-fragmented mothers, especially in their visceral fat cells.

A closer look revealed epigenetic changes, such as methylation and histone modification, which shut down selected genes, often in response

to environmental stresses.

"We found that the offspring of sleep-deprived mothers had largely inactivated AdipoQ, the adiponectin gene," Gozal said. "Such changes may affect other genes as well; we haven't studied all the potential targets yet. Even so, this is the first example of a perturbation during pregnancy that translates into a genetic risk, in midlife, for the next generation."

"This is kind of scary," he added. "Will this generation, the sons of sleep-deprived mice, who are already at increased risk for metabolic syndrome and type 2 diabetes, transmit this inherited risk, perhaps compounded by new stresses, to their offspring?"

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