who spoke to The Scientist agree that it remains unresolved what might underlie these associations in people.

A working theory

Richard Pilsner started pondering sperm epigenetics around the time he and his wife started planning a family a little over a decade ago. Having trained in environmental health sciences, Pilsner recalls warning his wife about the risks of smoking and other behaviors that might affect conception or fetal development. That made them wonder whether he, too, might inadvertently affect his future child through his own lifestyle. After joining the faculty at the University of Massachusetts Amherst, Pilsner decided to dig into this potential link between parental exposure and child development. In 2014, he and colleagues launched the Sperm Environmental Epigenetics and Development Study (SEEDS), a cohort that uses leftover samples from IVF clinics, with participants’ consent, to look at the relationship between a father’s environment and his sperm epigenome—plus perhaps one day, his child’s epigenome and health outcomes.

Focusing on sperm has advantages from the perspective of studying how parental environments influence future generations. For starters, because fathers and their babies are physically separated, it bypasses some of the confounding effects of in utero exposure that lead to a common criticism of studies in the field—that they confound prenatal with inter- and transgenerational effects. Additionally, it could help researchers home in on what’s physically transmitted across generations, rather than trying to infer it from parent-lifestyle and child-health associations. The sperm-centric approach has taken off in the animal literature, too—investigations of sperm epigenetics in rodent models have found that both negative experiences (exposure to harmful chemicals, for example) and purportedly positive ones (exercise) are associated with differing levels of DNA methylation and of RNA modification in sperm, and with measurable changes in offspring phenotype.

Pilsner’s group, now at Wayne State University in Michigan, has completed several studies with the SEEDS data set. In a small-scale study a few years ago, the team followed up on other groups’ reports that exposure to chemicals found in everyday plastic and altered DNA methylation in rodent sperm. Using urine samples to measure nearly 50 men’s exposure to phthalates, Pilsner and colleagues identified more than 130 regions of the genome that were differentially methylated in the sperm of people who were exposed to the chemicals. Many of these regions were found around genes involved in growth and development.

More recently, the researchers explored another proposed risk factor for certain health conditions in children: advanced paternal age. While scientists have proposed multiple mechanisms, including accumulated mutations and the decreased structural integrity of DNA in sperm, to explain reported connections between advanced paternal age and risk of certain cancers and neurodevelopmental disorders, Pilsner’s group published data suggesting that sperm methylation may also play a role. Specifically, the researchers found that male age was associated with particular epigenetic patterns at genes involved in embryogenesis and neurodevelopment.

Whether epigenetic changes seen in sperm persist past fertilization or have biological effects in offspring is harder to gauge from these studies. Indeed, some of the rodent research that inspired the SEEDS phthalate study suggested the DNA methylation alterations in exposed males’ sperm were completely reversed in the next generation. But a recent mouse study by Pilsner and colleagues reported that while DNA methylation patterns did differ between sperm and the embryonic cells of newly conceived offspring, the latter varied consistently in relation to the former. “We see what we call an amplified effect—we see many more changes in the embryo than we see in the sperm,” says Pilsner, who holds provisional patents related to age-associated epigenetic changes in sperm. “There’s some sort of signal that’s being passed.” He adds that he’s now working with Sarah Kimmins, an epigeneticist at McGill University in Quebec whose wish that people would avoid thinking that there is only one mechanism.

Romain Barrès, an epigeneticist at the University of Copenhagen and the Université Côte d’Azur who heads up the Gametic Epigenetics Consortium against Obesity (GECKO), is of a similar opinion. “We think that the epigenetic modifications talk to each other,” he says. “The full picture ‘may be missed if you’re studying DNA methylation only, in only a set of tissues [such as] blood.” Failing to find a conserved signal across generations or within a single person during their lifetime “doesn’t mean that the signal is totally gone.” Rather, it is integrated into another epigenetic mark, like small RNA or chromatin conformation.

Conscious of the fact that the epigenome could change over time, Barrès’s group has been trying to study specific life events rather than lifelong exposures. A few years ago, his team tracked changes in DNA methylation patterns in the sperm of people undergoing bariatric surgery for obesity. Using another data set, the team found that slim and obese men showed differences in sperm DNA methylation patterns and non-coding RNA levels, even when controlling for genetic sequence variation. Using the new cohort, the researchers found that morbidly obese men showed remodeling of sperm DNA methylation just a week after undergoing surgery to reduce