Autism is Shaped by Obesity, Even before Conception

1 message

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We tend to think of child health as something shaped during pregnancy or after birth, but a growing body of research suggests that critical biological programming actually begins weeks, months, and **even years before conception**, through processes like *epigenetics*.

Epigenetics, the process by which environmental and lifestyle factors switch genes "on" or "off" without altering the underlying DNA sequence, helps explain how parental health choices can reverberate across generations.

One of the most striking examples involves maternal obesity. A large-scale analysis involving over 3.6 million mother-child pairs show maternal obesity before and during pregnancy nearly doubles the risk of autism in offspring and increases ADHD risk by up to 57%.[1]

A groundbreaking new study brings clarity to exactly how—and when—this occurs. Using an elegant IVF model, researchers isolated the effects of obesity exposure to two distinct time points: before conception (preconception obesity) and during pregnancy (gestational obesity). The results highlight a critical window during which maternal metabolic health can alter neurodevelopmental trajectories of her offspring.[2]

Before diving deeper into this remarkable study, it's worth noting that maternal obesity **isn't the only factor currently raising alarms**. Recently, the FDA issued a cautionary advisory urging pregnant women to avoid acetaminophen (Tylenol), due to emerging evidence linking its use during pregnancy to neurodevelopmental disorders, including autism and ADHD. While controversial, this advisory underscores how profoundly prenatal factors can influence lifelong child health outcomes.

Here's what the researchers discovered about maternal obesity:

To tease apart whether maternal obesity influences offspring neurodevelopment before pregnancy, during pregnancy, or both, researchers used a clever in vitro fertilization (IVF) and embryo transfer design that allowed

them to control and isolate the *timing* of obesity exposure. They created three groups of mice:

1. **Preconception obesity**—eggs from obese donor mothers were fertilized and implanted into normal-weight surrogate mothers.
2. **Gestational obesity**—eggs from normal-weight donors were implanted into obese surrogate mothers.
3. **Controls**—eggs from normal-weight donors were implanted into normal-weight surrogates.

The structure was designed to answer two key questions: **does obesity *before* pregnancy alter neurodevelopment?** And separately, **does obesity *during* pregnancy (without prior exposure) do the same?** After birth, offspring were monitored for 41 days, undergoing a battery of behavioral tests that reflect the core domains used to diagnose autism spectrum disorder: sociability, communication, and repetitive behaviors.

Obesity Before (But Not During) Pregnancy Alters Offspring Behavior

Male offspring from obese donor mothers (preconception obesity) displayed abnormalities in all three domains: exhibiting altered communication, reduced sociability, and repetitive behaviors. Crucially, **these autism-like behaviors were not explained by general anxiety or stress**. When tested on a standard measure of anxiety-like behavior known as the elevated plus maze test, no differences were found between groups— the observed deficits were specific to autism-relevant behaviors.

By contrast, **male offspring from obese surrogate mothers (who were only exposed to obesity during gestation) behaved indistinguishably from controls**. This indicates that obesity before conception, not during gestation, was sufficient to induce autism-like traits.

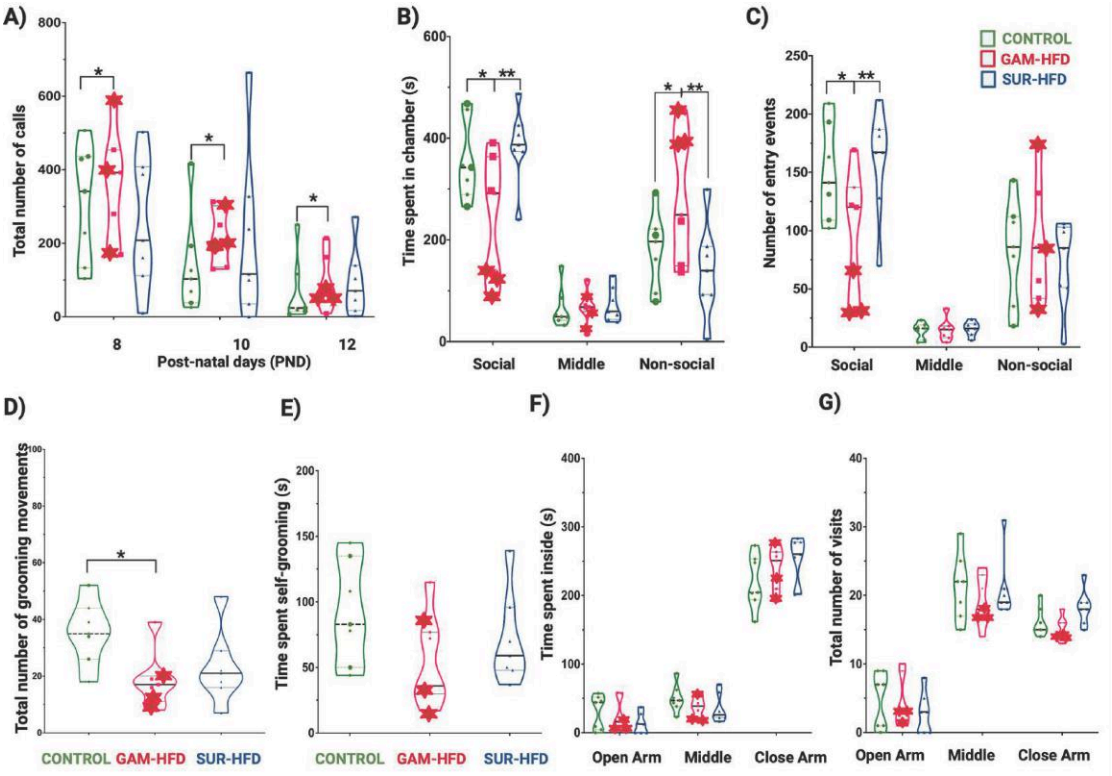
Female offspring, on the other hand, did not exhibit any of these alterations, regardless of group. This is consistent with the male-biased prevalence of autism in humans. And not every male mouse exposed to preconception obesity developed autism-like traits. There was considerable variability. Some mice showed strong deficits across all three domains, while others appeared unaffected. This heterogeneity echoes human autism, where **individuals with similar genetic or environmental risk factors may present with very different outcomes.**

To capture this variability, researchers stratified the offspring exposed to preconception obesity into two subgroups:

- **ASD-like:** individuals with clear behavioral abnormalities.
- **“Nested”:** individuals without significant deficits.

What might explain these behavioral differences among the subgroups?

Genetics provide some clues.



Preconception Obesity Causes Molecular Changes in the Brain

A look into gene expression in the cortex and DNA methylation patterns in the hippocampus (two brain regions crucial for neurodevelopment and highly responsive to environmental influences) revealed that **ASD-classified mice had a distinct gene expression profile**. Eight genes were uniquely dysregulated compared to controls, including two high-confidence autism susceptibility genes:

- *Homer1*, which encodes a synaptic scaffolding protein that helps organize connections between neurons.
- *Zswim6*, which has been linked to neurodevelopmental delay and autism-like traits.

Other dysregulated genes were tied to circadian rhythm regulation, neuronal excitability, and synaptic modulation—these are all processes previously implicated in autism. Importantly, **expression changes were far less pronounced in the "Nested" subgroup** (who didn't display behavioral abnormalities), suggesting that the severity of transcriptional disruption paralleled the severity of behavioral traits.

Epigenetic regulation of Homer1

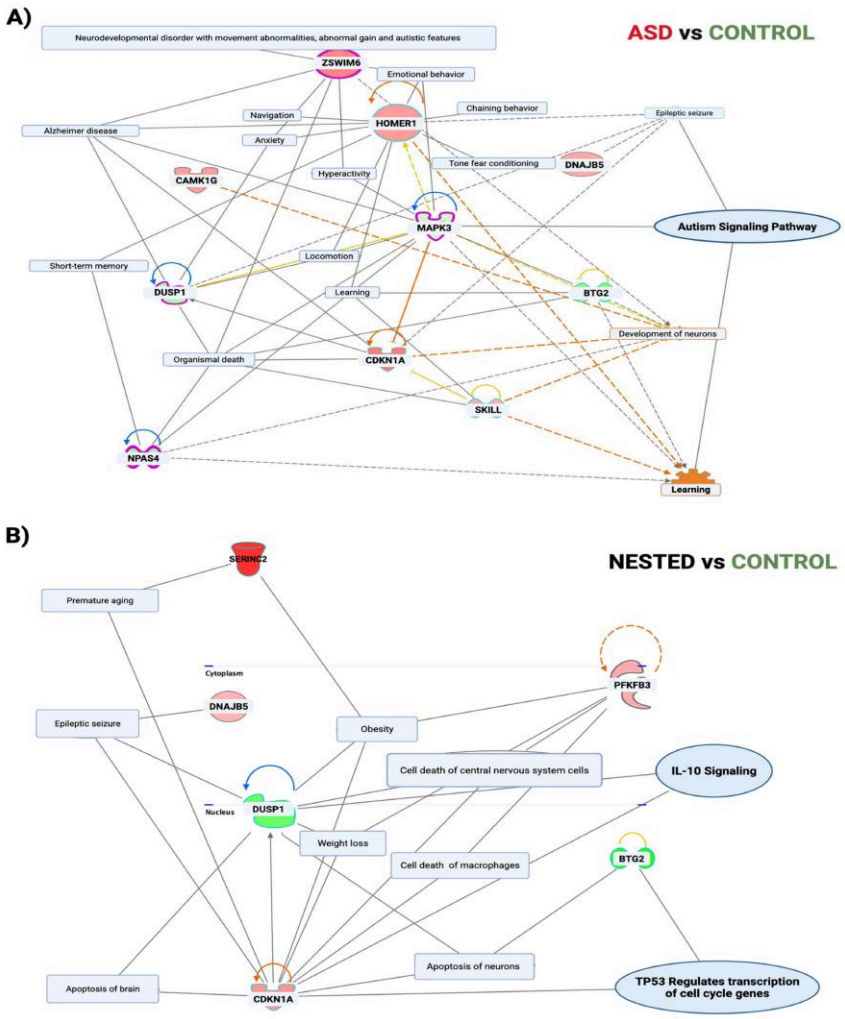
One of the most compelling findings centered on *Homer1*. This gene can be activated from two "start sites," or promoters: a main (canonical) one and an alternative one.

While the canonical promoter was unaffected across groups, the *alternative promoter* showed some clear group differences; **it was completely switched on (unmethylated) in ASD mice, switched off (heavily methylated) in ASD mice, and partially methylated in the "Nested" mice.**

This difference drove the expression of a specific isoform, Homer1a, which disrupts the structural scaffolding at synapses and interferes with synaptic plasticity. In short, **preconception obesity flipped on an alternative genetic switch that rewired the brain in a way consistent with autism-like behavior.** But this was not a global effect—there were no sweeping methylation changes across the genome. Instead, the alterations were highly targeted.

Together, these findings underscore that maternal obesity before pregnancy can reprogram the offspring brain through transcriptional and epigenetic changes. And even though obesity *during* pregnancy didn't exert the same influences on neurodevelopment, this contrasts with broader research in humans linking both preconception and gestational obesity to autism and ADHD in children.

As the authors put it, *“These findings identify a critical window where maternal environment programs long-term neurodevelopmental outcomes via transcriptional and epigenetic reprogramming.”* This critical window—the preconception period—is also a modifiable one, highlighting the importance of maternal health before pregnancy as a factor in reducing autism risk.



Aliquot episode #100 explores evidence-based recommendations for having a healthy pregnancy and baby, and shares some of Dr. Rhonda Patrick's personal decisions and experiences surrounding her pregnancy and parenting.

- Understanding the impact of caffeine, antioxidants, and B-vitamins on fertility
- What to do before reproducing – exercise, diet, and targeted supplements
- How to improve sperm quality
- Strategies for healthy fetal development after 40
- Navigating supplement use during pregnancy – essentials and exclusions
- And more!

Autism and the Role of Lifestyle Versus Genetics

Recent estimates place the heritability of autism around 80% after adding up common polygenic effects plus rare, "highly penetrant" variants. There's undoubtedly a genetic component to this condition. **But that leaves ~20% for**

environment and lifestyle factors—admittedly tricky terms to define and even trickier to parse out in terms of their individual contributions.

There are a number of lifestyle factors that potentially affect an unborn child's genes by altering the chemistry of DNA in sperm and egg cells (Dr. Elissa Epel discusses how the pre-pregnancy health of men *and* women shapes the health of their offspring in this clip from episode #46 of the podcast)

It's a concept known as **transgenerational epigenetic inheritance**, and while it was first discovered in animals, we now know it probably works in humans too. Children can inherit changes that are caused by behaviors—good and bad—their parents engaged in even prior to conception. My favorite one of these to talk about is (no surprise) exercise!

It's clear that when we exercise deliberately and frequently, our genes behave differently—an effect that not only benefits our own health, but one that can be passed down through generations.

One study in particular found that 3 months of high-intensity interval training "reprograms the sperm methylome" including changes in paternally inherited genes involved in the risk of autism, Alzheimer's disease, obsessive-compulsive disorder, obesity, type 2 diabetes, and atherosclerosis.[3] And while it isn't clear whether these changes are passed down to human offspring, animal studies have have shown that **the benefits of exercise on cognition, neurogenesis, and mitochondrial function can be passed down**.[4] Importantly, these changes are accompanied by alterations in gene expression and are directly transmitted through the father's sperm. Paternal physical activity drives the cognitive function of offspring through epigenetic inheritance. It's not just brain health that benefits. When either parent exercises, their offspring are protected against metabolic diseases, have better glucose regulation, less adiposity, improved heart health, and a lower risk for birth defects.[5]

Exercise is hardly the only environmental and lifestyle factor known to affect autism and ADHD risk. Other known contributors include:

• Maternal inflammation and infections
• Vitamin D deficiency (I've co-authored research with the late Dr. Bruce Ames in which we present evidence that the vitamin D hormone activates the transcription of serotonin-synthesizing genes in the brain; low serotonin being a core characteristic of autism spectrum disorder).
• Low omega-3 status (impacting brain development)
• Metabolic issues (insulin resistance, obesity)
• Immune dysregulation during pregnancy
• BPA and plastic chemicals (more on their effects in our episode on Microplastics)
• Sperm epigenetic factors

Final thoughts

Can autism be prevented with a healthy lifestyle, supplementation, and the avoidance of negative risk factors? No. Each of the modifiable environmental and lifestyle factors I've discussed may only shift risk modestly and probably can't outweigh a strong genetic predisposition to autism. But **even if non-genetic factors explain only a minority of one's liability to autism, it's worth doing what we can do to move the needle in the right direction.**

Even if autism prevention or passing down beneficial genes to your offspring isn't on your list of priorities, these are the same healthy lifestyle behaviors everyone should be engaging in anyway.

Warm regards

— Rhonda and the FoundMyFitness team