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Intergenerational metabolic effects of cold exposure

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Parental health during conception and gestation can affect offspring development and health. A study in humans now shows that adult individuals who were conceived during cold seasons exhibit greater brown adipose tissue activity, increased energy expenditure, lower body mass index and lower visceral fat accumulation.

Complex trait trajectories are shaped throughout development[1]. A growing body of evidence highlights how mammalian development – from fertilization and throughout preimplantation and fetal development – is under environmental pressure. Indeed, parental health and exposure to environmental challenges at conception, and maternal health and exposures during gestation and breast feeding, are emerging as key determinants of offspring health and prenatal risks of complex, noncommunicable diseases[2].

A common line across most intergenerational studies is that parental health and exposures can negatively influence offspring development and health trajectories. For example, parental overweight or obesity increase offspring risk of metabolic and cardiovascular diseases in humans[3,4], and parental stress exposures are implicated in the risk of offspring neurodevelopment and neuropsychiatric disorders[5]. Few studies have identified parental factors that might positively skew offspring development and health; parental preconception exercise, for example, improves pregnancy and fetal outcomes, as well as adult offspring metabolic and neurobehavioural health[6].

Climate change represents one of the most important global health challenges of the 21st century[7]. Beyond its immediate effects on reproductive health, climate-related events will shape the long-term and intergenerational risks of mortality and morbidity for both birthing individuals and their children[7]. Indeed, parental heat stress negatively affects reproduction and health across mammals[8,9].

In this issue of *Nature Metabolism*, Yoneshiro, Matsushita, Fuse-Hamaoka and colleagues[10] analysed energy expenditure in four different cohorts of Japanese volunteers and showed that individuals who were conceived in colder seasons exhibit significantly higher prevalence and activity of the thermogenic – and metabolically beneficial[11] – brown adipose tissue (BAT) compared to those who were conceived in warmer seasons (Fig. 1). These data complement a previously published study in which the season of conception was linked to offspring BAT activity and body mass index[12], and identified (through advanced statistical analyses) diurnal range of outdoor temperature before conception as the most significant meteorological factor associated with increased BAT activity in offspring. The new findings emphasize once more the critical role of the preconception environment in shaping offspring metabolism, and offer perspectives for understanding the co-existence of two global health challenges – obesity and warming – and addressing them with tailored lifestyle intervention strategies.

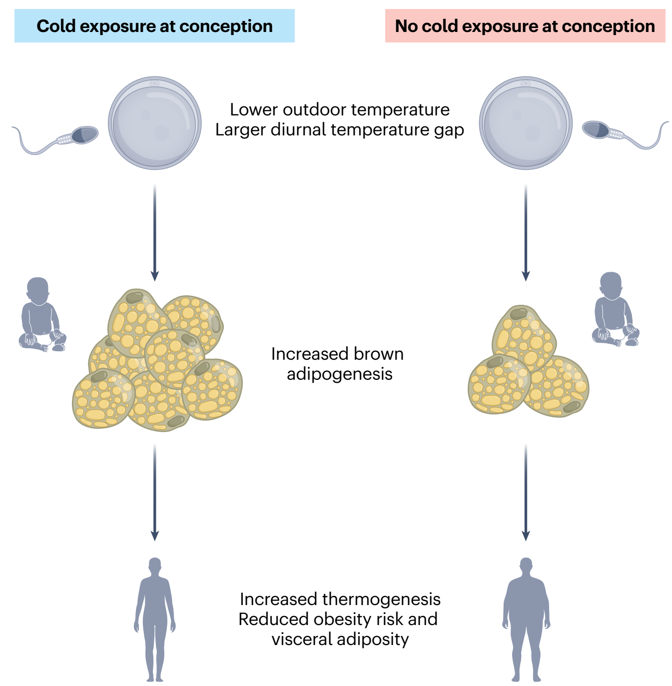

Fig. 1 | Intergenerational effects of parental cold exposure. Fertilization in cold seasons with lower outdoor temperatures and larger diurnal temperature gaps protects offspring from obesity and visceral adiposity by increased brown adipogenesis and cold- and diet-induced thermogenesis.

Mechanistically, Yoneshiro, Matsushita, Fuse-Hamaoka and colleagues hypothesized that paternal cold exposure – and therefore the paternal lineage – might be responsible for the intergenerational induction of BAT activity. Indeed, no meteorological parameter during the first, second and third trimesters correlated with BAT activity, which suggests minimal effects of the maternal lineage during gestation. Despite not being able to formally exclude maternal preconception effects, these findings are in keeping with the study from Sun et al.[12], which showed that, in mice, preconception cold exposure of males – but not females – results in BAT activation, improved systemic metabolism and protection from diet-induced obesity of the male offspring[12]. Sun et al. also associated cold exposure with significant reprogramming of DNA methylation in mature spermatozoa at genes that are probably involved in BAT formation and neurogenesis[12]. In other words, cold exposure leaves a signal in spermatozoa that – when inherited at fertilization — enables robust developmental programs for better metabolic adaptations to diet and cold.

The mechanistic exploration of paternal effects is complicated. Despite the transcriptional silence and the relatively simple epigenome of mature spermatozoa, different layers of epigenetic signals (DNA methylation, histone post-translational modifications and small non-coding RNAs) have been implicated in paternal effects[13], and recently sperm-borne and mitochondrial-encoded small RNAs have been demonstrated to dynamically respond to nutrition, be inherited at fertilization and accumulate in early embryos[4]. Nonetheless, non-germ cell factors, such as components of the seminal fluid, influence female receptivity and pregnancy outcomes[14] and contribute to the intergenerational effects of paternal preconception stress[15]. Given this complexity, further studies are needed to fully unravel the mechanistic underpinnings of the intergenerational effects of paternal preconception cold exposure in humans. This knowledge would build upon the already important implications of the discoveries from Yoneshiro, Matsushita, Fuse-Hamaoka and colleagues, and enable further understanding of the effects of the paternal preconception environment on offspring health.

With these data, the authors propose the prefertilization origins of health and disease concept, which is adapted from the developmental origins of health and disease concept, to further highlight the importance of considering preconception health in research and public health strategies. In a dynamic world, in which environmental factors are continuously and profoundly shaping human health, there is a continued need for public health investments towards fostering and nurturing parental preconception health — both maternal and paternal — as a universal strategy to reduce the global burden of non-communicable diseases and provide children with higher chances of a healthy start to life.

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Competing interests

The author declares no competing interests.