JOR DELPHI Obesity and OA
Q15: Can/should we investigate the transgenerational or intergenerational effects of diet and obesity on OA risk, and how these effects are mediated?
Prepared by: Arin K Oestreich, Shirley (Nina) Tang, and Farshid Guilak

LEVEL OF EVIDENCE: Strong

RATIONALE: Obesity and Osteoarthritis (OA) are both pandemics that continue to rise in prevalence despite modern-day dietary and lifestyle changes, warranting the need to explore genetics and generational mechanisms linking OA, obesity, and generational transmission. A cursory literature search was conducted on "parental obesity", "generational obesity", "intergenerational", "transgenerational", and "osteoarthritis" focused on pre-clinical and translational studies.

Yes, we should investigate the generational effects of diet and obesity on OA risk. Maternal obesity increases the risk of adult offspring developing obesity and cardiometabolic disease (*1-8*) even when maintaining a healthy diet and lifestyle. Paternal obesity can also modulate gene expression in the embryo and placenta through altered seminal fluid composition, delivery of small non-coding RNAs, and nuclear epigenetic changes (*9*). This phenomenon, known as the developmental origins of health and disease (DoHAD), leads to a cycle of increased obesity and cardiometabolic disease in subsequent generations (*4*). In the United States, 40% of young adults (20-39 years old) in their key reproductive years are obese (BMI ≥ 30)(*10*). This creates an urgent need to develop therapeutic interventions to curtail generational transmission of obesity and its co-morbidities such as OA. Therefore, elucidating the mechanism by which parental obesity programs offspring OA risk is paramount.

Key cells of the knee joint are programmed by parental obesity
Cartilage: In mice, parental high fat diet (HFD) increases the risk for developing injury-induced OA in offspring raised on a control diet (*6*) demonstrating OA has developmental origins that are modifiable by parental HFD. Recent work specifically shows that *maternal* HFD increases OA severity in female offspring following destabilization of the medial meniscus (DMM) as an injury induced OA model (*11*) but does not promote early onset OA in animals raised to 1-year of age (*12*). Others have shown maternal exposures to HFD reduce glycosaminoglycan content in young offspring (*13*). This suggests that maternal HFD-induced obesity is a risk factor for PTOA in offspring, but further work is necessary to determine if and how chondrocytes might be programmed during development, and how different dietary composition could influence these effects.

Bone: Both epidemiological studies and animal models strongly indicate that nutrient disruptions and obesity during pregnancy can alter bone mass and mineral density in the offspring during development and as they age into adulthood, varying by anatomical cite and dietary regime (*6, 12, 14-21*), for review see (*1*). Maternal HFD exposure impairs mitochondrial respiration in osteoblasts and osteoclasts resulting in low bone turnover, reduced cortical bone mass, and decreased biomechanical strength (*7*). Subchondral bone remodeling is a hallmark of OA pathology characterized by bone plate thickening and thinning of the underlying trabecular bone with disease progression. In an injury-induced OA model, parental HFD increased trabecular separation in the subchondral bone of femurs from female mice (*6*). However, future work is necessary to determine if individuals with low bone mass exposed to parental or maternal obesity have accelerated OA progression, cartilage degradation, or pain in the knee joint.

Neurobiological responses to chronic OA pain: Chronic pain and sensitization of the sensory neurons innervating the synovium and subchondral bone is a primary hallmark of OA (*22, 23*). While few studies have investigated the impact of maternal diet on OA pain outcomes, many studies have examined the relationship of adverse developmental events on pain responses. For example, maternal stress increases sensitivity of nociceptive neurons (*24-26*) and exacerbates pain responses in offspring (*27*). Gestational diabetes increases the quantity of nociceptive neurons in the DRG and sensitizes behavioral responses to mechanical pain following inflammatory challenge (*28, 29*). Finally, painful experiences during neonatal development exacerbate chronic pain responses in adult mice with OA (*30, 31*). Together these studies provide strong evidence that the nociceptive peripheral nervous system is susceptible to environmental exposures during critical developmental windows, although more work is needed to fully define the mechanism by which maternal obesity may program pain responses in adult offspring.

Intergenerational effects of parental obesity on OA: During pregnancy both the fetus (F1 generation) and their developing gametes (future F2 generation) are exposed to the obese uterine environment, eliciting an intergenerational impact on health and disease. Maternal obesity can also elicit transgenerational effects by increasing the risk of obesity in the F3 generation (*4*). Ancestral exposure to altered nutrition, such as HFD, can increase obesity and susceptibility to metabolic diseases in subsequent offspring generations through reprogramming of the germline epigenome. To evidence, maternal HFD in female mice resulted in increased body size in third-generation (F3) offspring despite consuming control diets (*32*) paternal HFD resulted in increased tissue adiposity and metabolic dysfunction in 2 subsequent generations fed on chow (*33-35*) and

results in offspring hyperglycemia (*36*). Similarly, maternal and paternal famine result in an increased rate of chronic diseases, increased BMI, cardiovascular diseases, and diabetes in subsequent generations (*37-39*). These studies support the detrimental effects of generational diet and obesity on the systemic health of subsequent offspring, warranting the need to study generational effects on OA. While parental studies have been conducted, the field lacks intergenerational and transgenerational mechanistic elucidation of obesity and OA. Harasymowicz et al., showed that intergenerational transmission of diet-induced obesity (maternal/paternal HFD with 2 generations of offspring on chow diet) resulted in increased offspring weight gain, with female F2 offspring exhibiting predisposition to OA along with bone microarchitectural changes (*6*). Further studies on the epigenetic and hereditary targets are critical for investigating the mechanistic pathways and translational approaches for treating OA predisposition.

MECHANISTIC OUTCOMES AND RECOMMENDATIONS FOR STUDY DESIGN:
Epigenetics: Epigenetic mechanisms integrate environmental factors with heritable changes in gene expression and are a fundamental link between the environment and OA disease progression (*40-48*). Several reports show altered epigenetic mechanisms in bone cells of offspring exposed to a maternal obese environment (*49-51*). Recent work using multiomic sequencing has revealed a differentially regulated chromatin landscape in regulatory sequences of cartilage developmental genes in fetal chondrocytes exposed to a maternal obese environment (*52*). However, future work is necessary to determine if such epigenetic changes persist across the lifespan to predispose OA and if they are propagated to future generations.

Metabolic reprogramming: Obesity impairs oocyte mitochondria which are passed to the embryo (*53*) and maintained in the somatic cells of the offspring (*4, 8, 54*). Dysfunctional mitochondria in oocytes of female mice fed a high-fat, high-sugar diet were inherited into the somatic cells of the skeletal muscle, heart, liver, and bone (*2, 5, 7, 8*) and increased the risk of cardiometabolic disease in the offspring despite being raised on a healthy diet. These key studies implicate maternal transmission of defective mitochondria as a mechanism of transgenerational maternal metabolic programming. It is unknown if chondrocytes exposed to maternal obesity also inherit impaired mitochondria. However, recent work using single nucleus RNAseq has shown chondrocytes from fetal mouse knees exposed to maternal obesity have decreased expression of key glycolytic genes (*55*). It is conceivable that early metabolic insults may program decreased metabolic plasticity in chondrocytes throughout the lifespan to increase susceptibility to OA. However, it is yet to be determined if metabolic shifts in the chondrocytes exposed to the maternal obese environment persist into adulthood.

Microbiome dysbiosis: Although the timing is debated, the maternal gut and vaginal microbiome along with lactational composition influence the initial colonization of the offspring's gut microbiome (*56, 57*). The vertical transmission of the microbiome is a potential mechanism for intergenerational programming (*58*) which has been demonstrated in OA mouse models. Fecal transplants from superhealer mice protect recipient mice from cartilage damage following DMM and the protection is transmitted to the F1 and F2 progeny (*59*). Others have shown evidence of microbiome alterations in offspring exposed to maternal caffeine exacerbates injury-induced OA following cecal transplant (*60*). While there is evidence for intergenerational heritability of the microbiome impacting OA severity, there are no studies investigating how intergenerational microbiome transmission in pregnant or lactating individuals with obesity impacts OA severity in the offspring. Obesity restricts the diversity of the microbiome which can alter nutrient breakdown, increase systemic inflammation, and exacerbate OA progression (*61-64*). It has also been hypothesized that maternal HFD may program the hematopoietic immune cell populations in the synovial membrane to exacerbate joint inflammation (*65*). Therefore, it is plausible that intergenerational transmission of a dysbiotic gut microbiome programs immune responses in the offspring to exacerbate synovial inflammation. However, future work is necessary to understand if and how these potential mechanisms act synergistically to promote OA.

Study design considerations: Early developmental exposure to obesity sets the stage for life-long health and disease and risk factors can be inherited to the next generation. Future mechanistic work is necessary to determine how the developmental environment programs an increased intergenerational risk for OA to design targeted therapeutics to prevent transmission. Preventative interventions may target maternal-fetal health during pregnancy or reversing the detrimental consequences of developmental exposure to obesity in the offspring's postnatal life. Although these studies are urgently needed, they will be difficult to uncover in the clinic due to the longer lifespan of humans. Therefore, animal studies will be critical to develop therapeutic interventions. Since littermates share a developmental environment, they are not entirely independent. Therefore, each pregnancy should be evaluated as an experimental replicate in studies of dietary or genetic manipulations in pregnant mice.

CONCLUSIONS: There is strong evidence to support the investigation of intergenerational or transgenerational effects of diet and obesity on OA risk, and how these effects are mediated. The developmental programming of health and disease field provides incredibly strong evidence that intergenerational transmission of obesity is a prominent problem and contributing to the growing obesity epidemic. Given the complex concordant relationship between obesity and OA, there is a great need to unravel mechanisms of intergenerational transmission to design targeted intervention strategies for preventing obesity and OA.

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