Review Article
ISSN: **3051-8814**
Journal homepage: https://www.harrisonacademicpress.com/index.php/FBEMD
Frontiers in Biomedical Engineering and Medical Devices

Harrison Academic Press

Maternal High-Fat Diet and Transgenerational Epigenetic Inheritance of Adipose Dysfunction in Offspring

Ferrari D[1*], Correia J[2] and Cerny T[3]

[1]*Department of Molecular Biology, Sapienza University of Rome, Rome, Italy*
[2]*Department of Obstetrics and Gynaecology, University of Coimbra, Coimbra, Portugal*
[3]*Department of Nutrition Science, Masaryk University, Brno, Czech Republic*

ABSTRACT

Background: Maternal high-fat diet (HFD) and obesity during pregnancy are linked to persistent adipose dysfunction in offspring, with effects that may extend beyond the directly exposed generation. Objective: This narrative review synthesises rodent and human evidence on maternal HFD-induced adipose programming and the epigenetic mechanisms proposed to mediate its intergenerational and transgenerational transmission. Methods: Published rodent models of maternal and paternal HFD feeding, mechanistic studies of DNA methylation, histone modification and sperm small non-coding RNAs, and human cohort studies of perinatal methylation and offspring adiposity were reviewed. Findings: Maternal HFD consistently produces adipocyte hypertrophy, visceral adiposity, inflammation and insulin resistance in offspring, persisting into F2 and F3 generations, particularly via the paternal germline. DNA methylation at metastable epialleles and feeding-circuit genes, adipose hypomethylation of inflammatory loci, and sperm-borne tsRNAs are each mechanistically implicated, with tsRNA injection experiments providing direct causal evidence. Human cohorts corroborate methylation-adiposity associations but rarely track true multigenerational transmission. Conclusions: Epigenetic mechanisms plausibly carry nutritionally acquired adipose dysfunction across generations, though penetrance is incomplete and mechanistic hierarchy remains unresolved, warranting integrated multi-omic, multigenerational human studies.

Keywords: *maternal high-fat diet; transgenerational epigenetic inheritance; adipose tissue dysfunction; DNA methylation programming; developmental origins of disease*

Citation: Ferrari D, Correia J, Cerny T (2025) Maternal High-Fat Diet and Transgenerational Epigenetic Inheritance of Adipose Dysfunction in Offspring. Front Biomed Eng Med Devices, 3(1): 01-06.
DOI: 10.5281/zenodo.22502900

Corresponding Author: *Davide Ferrari*

E-mail Address: *davide.ferrari@uniroma1.edu*

Article History: *Received 13 January 2025 | Accepted 29 March 2025 | Published 12 June 2025*

Copyright: *© 2025 Davide Ferrari, et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited (**https://creativecommons.org/licenses/by/4.0/**).*

Introduction

Excess maternal adiposity and high-fat diet (HFD) consumption during pregnancy have become widespread, and a large body of experimental and epidemiological evidence now links the intrauterine and early postnatal nutritional environment to lifelong metabolic risk in offspring [1,2]. The developmental origins of health and disease (DOHaD) framework proposes that fetal and neonatal tissues, including adipose tissue, undergo plastic adaptations to maternal nutrient supply that permanently alter their structure and function [3,4]. Adipose tissue is a particularly informative target because its developmental trajectory - encompassing preadipocyte commitment, hyperplastic expansion, and the acquisition of insulin-responsive and endocrine functions - spans the fetal, neonatal, and early postnatal periods, all of which are sensitive to maternal metabolic cues [5,6]. Rodent models of maternal HFD feeding consistently produce offspring with adipocyte hypertrophy, increased fat mass, impaired insulin signalling, and low-grade adipose inflammation, phenotypes that frequently persist into adulthood and, notably, can appear in generations that were never themselves exposed to the maternal diet [7,8,9].

This apparent transmission of an acquired phenotype across generations has focused attention on epigenetic mechanisms - DNA methylation, histone post-translational modification, and small non-coding RNAs - as plausible carriers of nutritionally induced information through the germline and early embryo [10,11]. Unlike classical genetic inheritance, epigenetic marks are, in principle, reversible and environmentally responsive, which makes them attractive candidates for explaining how a grandmaternal or paternal dietary exposure can shape metabolic phenotypes in the F2 and F3 generations without any additional dietary challenge [12,13]. Distinguishing true transgenerational epigenetic inheritance, in which the germline itself carries an altered epigenetic state that is not directly exposed to the original

insult, from intergenerational effects, in which the F1 germ cells or the F2 conceptus are directly exposed in utero, remains a central conceptual and methodological challenge in this literature [14,15]. This review synthesises evidence from rodent models of maternal HFD exposure, the epigenetic mechanisms proposed to mediate transgenerational programming of adipose dysfunction, and the corroborating evidence emerging from human cohort and multigenerational studies.

Maternal High-Fat Diet Models and Adipose Phenotypes in Offspring

Rodent studies remain the primary experimental platform for dissecting how maternal HFD reshapes offspring adiposity because they allow controlled manipulation of diet composition, timing, and lactational exposure. In one influential mouse model, diet-induced obesity in dams before and during pregnancy produced first-generation offspring with hyperphagia, increased adiposity, hypertension, and insulin resistance despite offspring being weaned onto standard chow, indicating that the maternal metabolic environment, rather than the offspring's own diet, was sufficient to programme these outcomes [7]. Complementary work using a similar HFD paradigm showed that maternal obesity increased offspring body length and reduced insulin sensitivity in the second generation even when the F1 mothers were fed a control diet, implicating persistent, diet-independent transmission [8]. Extending this design to a third generation, the same group reported that increased body size was preferentially transmitted through the paternal lineage, a pattern inconsistent with simple continued exposure to an altered maternal milieu and more consistent with a heritable germline signal [12].

Systematic reviews of these rodent paradigms have highlighted substantial heterogeneity in diet composition, fat content, and exposure window, but converge on core offspring phenotypes: increased adiposity, impaired glucose tolerance, and dyslipidaemia that emerge with strikingly consistent frequency across studies regardless of species (rat or mouse) or strain [16,17]. At the tissue level, maternal HFD offspring show adipocyte hypertrophy, expanded visceral fat depots, and macrophage infiltration consistent with chronic low-grade inflammation, alongside blunted insulin-stimulated glucose uptake in adipose explants [4,18]. Maternal obesity also programmes hepatic and pancreatic tissues in parallel with adipose depots, producing a coordinated multi-organ metabolic phenotype that includes hepatic steatosis and beta-cell dysfunction, indicating that adipose dysfunction develops as part of a broader disturbance of metabolic tissue crosstalk rather than in isolation [9].

Paternal contributions to offspring adiposity have received growing attention as an independent, non-maternal route of nutritional programming. Chronic HFD feeding in male rats before mating produced first-generation daughters with impaired glucose tolerance and beta-cell dysfunction, despite no direct exposure of the offspring or their mothers to the paternal diet, implicating paternal germline signals as sufficient drivers of metabolic disease in progeny [19]. Similarly, diet-induced paternal obesity in mice altered the sperm transcriptome and small RNA content and produced metabolic disturbances - including altered adiposity and insulin sensitivity - in offspring across two generations, albeit with incomplete penetrance by the F2 generation, underscoring that transgenerational transmission is probabilistic rather than fully deterministic [14].

Epigenetic Mechanisms of Transgenerational Inheritance

Representative rodent models of maternal or paternal high-fat diet (HFD) exposure and the resulting adipose/metabolic phenotypes in offspring.

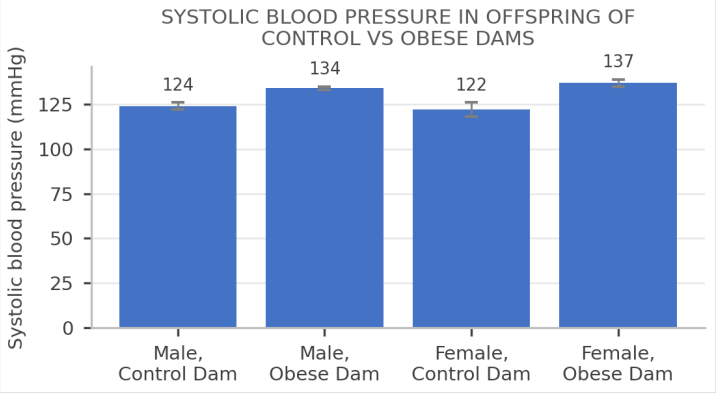
Model / Exposure	Species	Generation Affected	Key Adipose/Metabolic Phenotype	Reference
Maternal diet-induced obesity (pre-conception through lactation)	Mouse	F1	Hyperphagia, increased abdominal fat pad mass, hypertension, insulin resistance	[7]
Maternal HFD, F1 raised on control diet	Mouse	F2	Increased body length, reduced insulin sensitivity	[8]
Maternal HFD, paternal-lineage transmission	Mouse	F3	Increased body size transmitted via paternal lineage	[12]
Chronic paternal HFD before mating	Rat	F1 (daughters)	Beta-cell dysfunction, impaired glucose tolerance, reduced insulin secretion	[19]
Maternal obesity, first vs second generation comparison	Mouse	F1 and F2	Minimal F1 effect; pronounced adiposity/glucose intolerance emerges in F2	[9]
Cross-study synthesis of maternal HFD feeding paradigms	Rat/Mouse	F1	Consistent adipocyte hypertrophy, impaired glycaemic control across models	[16]

Epigenetic mechanisms proposed to mediate transgenerational or intergenerational transmission of maternal/paternal high-fat diet effects.

Mechanism	Locus / Molecule	Model System	Key Finding	Reference
DNA methylation of metastable epialleles	Transposable-element-associated loci	Mouse (Avy model)	Early nutrient supply alters CpG methylation at epigenetically labile loci	[10]
Hypothalamic promoter methylation	Pomc promoter	Rat	Hypermethylation in HFD-dam offspring persists despite chow diet switch	[20]
Neurotransmitter gene methylation	Dopamine/opioid-related genes	Mouse	Diet-dependent methylation changes linked to hedonic feeding	[21]
Adipose inflammatory gene hypomethylation	Tlr1, Tlr2, Lat promoters	Mouse, multigenerational HFD	Progressive hypomethylation and inflammation across F0-F2 generations	[22]

Mechanism	Locus / Molecule	Model System	Key Finding	Reference
Paternal germline small RNA (tsRNA)	Sperm tRNA-derived fragments	Mouse, zygote injection	Injected sperm tsRNAs from HFD males induce metabolic disorder in offspring	[15]
Maternal-diet -altered offspring sperm tsRNAs	Sperm tsRNA profile	Mouse	Maternal overnutrition reprograms F1 sperm tsRNAs, affecting F2 phenotype	[23]
Sperm methylome remodelling	Genome-wide sperm CpG methylation	Mouse, in utero undern utrition	Adult sperm methylome altered by early nutritional exposure	[13]

Systolic blood pressure at 6 months in male and female mouse offspring of control-fed versus diet-induced obese dams, illustrating the cardiometabolic component of maternal HFD programming alongside adipose dysfunction. Data from Samuelsson et al. [7].



DNA methylation at metastable epialleles and imprinted loci is the most extensively characterised epigenetic mechanism proposed to link maternal nutrition to offspring phenotype. Early work established that transposable-element-associated loci are particularly sensitive to methyl-donor availability during early development, providing a mechanistic template for how maternal nutrient supply can durably alter gene expression via changes in CpG methylation established around the time of implantation [10]. In the context of maternal HFD, hypothalamic feeding-circuit genes such as pro-opiomelanocortin (Pomc) show altered promoter methylation in offspring of HFD-fed dams, and this hypermethylated state is not corrected by subsequently switching offspring to a standard chow diet, demonstrating a stable, diet-independent epigenetic imprint that could plausibly extend to peripheral adipose regulatory genes [20]. Consistent with this, dopaminergic and opioid signalling genes implicated in hedonic feeding are similarly methylated in a diet-dependent manner in offspring brain, linking epigenetic reprogramming to the hyperphagic phenotype that in turn drives adiposity [21].

Within adipose tissue itself, multigenerational HFD feeding produces progressive DNA hypomethylation at inflammation-associated gene promoters, correlating with increased expression of inflammatory mediators and worsening insulin resistance with each successive generation of dietary exposure, providing direct tissue-level evidence that epigenetic marks accumulate and potentially amplify across generations [22]. Because DNA methylation patterns are substantially reset during primordial germ cell development and early embryogenesis, mechanisms capable of evading this erasure - incomplete demethylation at specific loci, or non-DNA-methylation carriers - are of particular interest for true transgenerational, as opposed to intergenerational, inheritance [6].

Small non-coding RNAs carried in sperm have emerged as compelling candidate vectors for paternal transmission of metabolic phenotypes. In a mouse model of paternal HFD-induced metabolic syndrome, injection of sperm-derived tRNA-derived small RNAs (tsRNAs) from HFD-fed males into normal zygotes was sufficient to induce metabolic disorders in the resulting offspring, directly demonstrating a causal, RNA-mediated route of intergenerational epigenetic inheritance independent of DNA methylation changes [15]. A related study in mice showed that maternal, rather than paternal, overnutrition altered sperm tsRNA profiles in male offspring, which were then associated with hedonic feeding and metabolic phenotypes in the subsequent generation, indicating that maternal diet can reprogram the paternal germline of the offspring themselves and thereby propagate a metabolic signal to grandoffspring [23]. Complementing the RNA and DNA methylation literature, studies of in utero undernutrition (a nutritional perturbation at the opposite end of the caloric spectrum) show that the adult sperm methylome is durably altered by early-life nutritional exposure, with these changes associated with altered metabolic gene expression in offspring, reinforcing the general principle that early nutritional insults of either direction can imprint the germline epigenome [13].

Evidence from Human Cohort and Multigenerational Studies

Translating mechanistic rodent findings to humans is constrained by the impossibility of directly manipulating maternal diet experimentally and by the long latency before multigenerational outcomes can be observed, but prospective human cohorts provide converging evidence for nutritionally sensitive epigenetic programming of adiposity. In the Southampton Women's Survey, methylation at the promoter of the retinoid X receptor-alpha (RXRA) gene measured in umbilical cord tissue at birth was associated with childhood adiposity measured years later, and this association was independent of conventional perinatal risk factors, providing some of the strongest human evidence that epigenetic state established in utero can predict later adipose phenotype [24]. Broader reviews of the human epigenetic obesity literature confirm that differential methylation at metabolically relevant loci - including genes governing adipogenesis, insulin signalling, and appetite regulation - is reproducibly associated with maternal obesity, gestational diabetes, and offspring adiposity across multiple independent cohorts, although the causal direction and functional consequences of many of these associations remain to be firmly established [11].

Clinical and epidemiological studies of maternal obesity during pregnancy report a consistent constellation of short- and long-term consequences for offspring, including increased risk of macrosomia, childhood obesity, and adult metabolic syndrome, mirroring the phenotypes observed in rodent models and supporting the biological plausibility of the developmental

programming hypothesis in humans [2]. Importantly, human data increasingly point toward paternal and multigenerational contributions analogous to those characterised in rodents: paternal obesity and metabolic status at conception have been associated with altered offspring metabolic risk independent of maternal factors, echoing the sperm-mediated epigenetic mechanisms demonstrated experimentally [14,19]. Nonetheless, human multigenerational studies capable of tracking epigenetic marks and metabolic phenotypes across three generations remain rare, and most human evidence to date is intergenerational (parent-to-child) rather than truly transgenerational, leaving open questions about the durability and penetrance of these signals analogous to the incomplete penetrance already documented in rodent F2 and F3 generations [12,9].

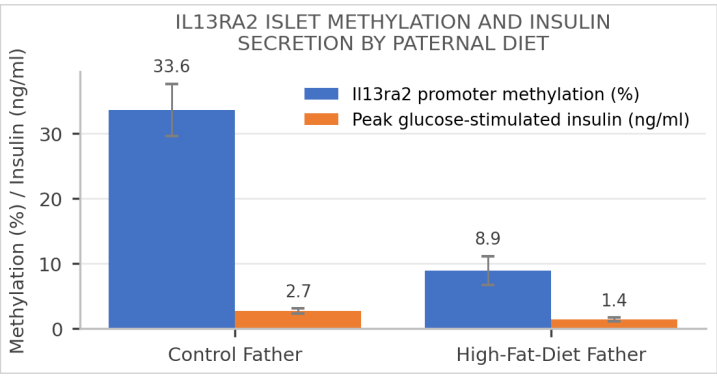
Conclusion

Maternal high-fat diet exposure programmes a robust and reproducible constellation of adipose tissue dysfunction in offspring - adipocyte hypertrophy, expanded and inflamed fat depots, and impaired insulin sensitivity - that is documented across rodent models and corroborated by human cohort data on maternal obesity and childhood adiposity [7,24,2]. Multiple, partially overlapping epigenetic mechanisms, including DNA methylation at metastable epialleles and feeding-circuit gene promoters, histone modification, and sperm-borne small non-coding RNAs, have each been mechanistically implicated in carrying this nutritional information across generations, with the sperm tsRNA literature providing the clearest causal demonstration to date [10,15,22]. Nevertheless, the field continues to grapple with distinguishing genuinely transgenerational inheritance from intergenerational carryover, with incomplete penetrance across successive generations in nearly every rodent model examined [14,12]. Future work integrating multi-omic germline profiling with well-powered, multigenerational human cohorts will be needed to establish which of these mechanisms are most clinically relevant, and whether early nutritional or pharmacological interventions can interrupt the epigenetic transmission of adipose dysfunction across generations [6,5].

Acknowledgements

The authors thank colleagues at Department of Molecular Biology, Sapienza University of Rome, Rome, Italy, Department of Obstetrics and Gynaecology, University of Coimbra, Coimbra, Portugal, and Department of Nutrition Science, Masaryk University, Brno, Czech Republic for helpful discussions during preparation of this review.

Il13ra2 promoter methylation and peak glucose-stimulated insulin secretion in pancreatic islets of female rat offspring of control versus chronic high-fat-diet-fed fathers, showing paternal germline-associated epigenetic and functional change. Data from Ng et al. [19].



Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Ferrari D conceived the review, conducted the literature search, and drafted the manuscript. Correia J contributed to the literature screening and technical framing and critically revised the manuscript for important intellectual content. Cerny T contributed additional context and approved the final version for submission.

Ethics Statement

Not applicable. This is a narrative review of previously published literature and did not involve new experimental data, human participants, or animal subjects.

Data Availability

No new data were generated or analyzed for this review. All sources synthesized are cited in the reference list and are available through their original publishers.

References

1. Gluckman PD, Hanson MA, Cooper C, Thornburg KL (2008) Effect of in utero and early-life conditions on adult health and disease. The New England Journal of Medicine, 359(1): 61-73. DOI: 10.1056/NEJMra0708473.

2. Catalano PM, Shankar K (2017) Obesity and pregnancy: mechanisms of short term and long term adverse consequences for mother and child. BMJ, 356: j1. DOI: 10.1136/bmj.j1.

3. Symonds ME, Sebert SP, Hyatt MA, Budge H (2009) Nutritional programming of the metabolic syndrome. Nature Reviews Endocrinology, 5(11): 604-610. DOI: 10.1038/nrendo.2009.195.

4. Heerwagen MJ, Miller MR, Barbour LA, Friedman JE (2010) Maternal obesity and fetal metabolic programming: a fertile epigenetic soil. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 299(3): R711-R722. DOI: 10.1152/ajpregu.00310.2010.

5. Lecoutre S, Breton C (2015) Maternal nutritional manipulations program adipose tissue dysfunction in offspring. Frontiers in Physiology, 6: 158. DOI: 10.3389/fphys.2015.00158.

6. Desai M, Jellyman JK, Ross MG (2015) Epigenomics, gestational programming and risk of metabolic syndrome. International Journal of Obesity, 39(4): 633-641. DOI: 10.1038/ijo.2015.13.

7. Samuelsson AM, Matthews PA, Argenton M, Christie MR, McConnell JM, Jansen EHJM, Piersma AH, Ozanne SE, Twinn DF, Remacle C, Rowlerson A, Poston L, Taylor PD (2008) Diet-induced obesity in female mice leads to offspring hyperphagia, adiposity, hypertension, and insulin resistance: a novel murine model of developmental programming. Hypertension, 51(2): 383-392. DOI: 10.1161/HYPERTENSIONAHA.107.101477.

8. Dunn GA, Bale TL (2009) Maternal high-fat diet promotes body length increases and insulin insensitivity in

second-generation mice. Endocrinology, 150(11): 4999-5009. DOI: 10.1210/en.2009-0500.

9. King V, Dakin RS, Liu L, Hadoke PWF, Walker BR, Seckl JR, Norman JE, Drake AJ (2013) Maternal obesity has little effect on the immediate offspring but impacts on the next generation. Endocrinology, 154(7): 2514-2524. DOI: 10.1210/en.2013-1013.

10. Waterland RA, Jirtle RL (2003) Transposable elements: targets for early nutritional effects on epigenetic gene regulation. Molecular and Cellular Biology, 23(15): 5293-5300. DOI: 10.1128/MCB.23.15.5293-5300.2003.

11. van Dijk SJ, Molloy PL, Varinli H, Morrison JL, Muhlhausler BS, Buckley M, Clark SJ, McMillen IC, Noakes M, Samaras K, Tellam RL (2015) Epigenetics and human obesity. International Journal of Obesity, 39(1): 85-97. DOI: 10.1038/ijo.2014.34.

12. Dunn GA, Bale TL (2011) Maternal high-fat diet effects on third-generation female body size via the paternal lineage. Endocrinology, 152(6): 2228-2236. DOI: 10.1210/en.2010-1461.

13. Radford EJ, Ito M, Shi H, Corish JA, Yamazawa K, Isganaitis E, Seisenberger S, Hore TA, Reik W, Erkek S, Peters AHFM, Patti ME, Ferguson-Smith AC (2014) In utero undernourishment perturbs the adult sperm methylome and intergenerational metabolism. Science, 345(6198): 1255903. DOI: 10.1126/science.1255903.

14. Fullston T, Ohlsson Teague EMC, Palmer NO, DeBlasio MJ, Mitchell M, Corbett M, Print CG, Owens JA, Lane M (2013) Paternal obesity initiates metabolic disturbances in two generations of mice with incomplete penetrance to the F2 generation and alters the transcriptional profile of testis and sperm microRNA content. The FASEB Journal, 27(10): 4226-4243. DOI: 10.1096/fj.12-224048.

15. Chen Q, Yan M, Cao Z, Li X, Zhang Y, Shi J, Feng GH, Peng H, Zhang X, Zhang Y, Qian J, Duan E, Zhai Q, Zhou Q (2016) Sperm tsRNAs contribute to intergenerational inheritance of an acquired metabolic disorder. Science, 351(6271): 397-400. DOI: 10.1126/science.aad7977.

16. Ainge H, Thompson C, Ozanne SE, Rooney KB (2011) A systematic review on animal models of maternal high fat feeding and offspring glycaemic control. International Journal of Obesity, 35(3): 325-335. DOI: 10.1038/ijo.2010.149.

17. Williams L, Seki Y, Vuguin PM, Charron MJ (2014) Animal models of in utero exposure to a high fat diet: a review. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 1842(3): 507-519. DOI: 10.1016/j.bbadis.2013.07.006.

18. Segovia SA, Vickers MH, Gray C, Reynolds CM (2014) Maternal obesity, inflammation, and developmental programming. BioMed Research International, 2014: 418975. DOI: 10.1155/2014/418975.

19. Ng SF, Lin RC, Laybutt DR, Barres R, Owens JA, Morris MJ (2010) Chronic high-fat diet in fathers programs β-cell dysfunction in female rat offspring. Nature, 467(7318): 963-966. DOI: 10.1038/nature09491.

20. Marco A, Kisliouk T, Tabachnik T, Meiri N, Weller A (2014) Overweight and CpG methylation of the Pomc promoter in offspring of high-fat-diet-fed dams are not "reprogrammed" by regular chow diet in rats. The FASEB Journal, 28(9): 4148-4157. DOI: 10.1096/fj.14-255620.

21. Vucetic Z, Kimmel J, Totoki K, Hollenbeck E, Reyes TM (2010) Maternal high-fat diet alters methylation and gene expression of dopamine and opioid-related genes. Endocrinology, 151(10): 4756-4764. DOI: 10.1210/en.2010-0505.

22. Ding Y, Li J, Liu S, Zhang L, Xiao H, Li J, Chen H, Petersen RB, Huang K, Zheng L (2014) DNA hypomethylation of inflammation-associated genes in adipose tissue of female mice after multigenerational high fat diet feeding. International Journal of Obesity, 38(2): 198-204. DOI: 10.1038/ijo.2013.98.

23. Sarker G, Sun W, Rosenkranz D, Pelczar P, Opitz L, Efthymiou V, Wolfrum C, Peleg-Raibstein D (2019) Maternal overnutrition programs hedonic and metabolic phenotypes across generations through sperm tsRNAs. Proceedings of the National Academy of Sciences of the USA, 116(21): 10547-10556. DOI: 10.1073/pnas.1820810116.

24. Godfrey KM, Sheppard A, Gluckman PD, Lillycrop KA, Burdge GC, McLean C, Rodford J, Slater-Jefferies JL, Garratt E, Crozier SR, Emerald BS, Gale CR, Inskip HM, Cooper C, Hanson MA (2011) Epigenetic gene promoter methylation at birth is associated with child's later adiposity. Diabetes, 60(5): 1528-1534. DOI: 10.2337/db10-0979.