Mol Biol Rep (2015) 42:791–797
DOI 10.1007/s11033-014-3766-5

The early life origin theory in the development of cardiovascular disease and type 2 diabetes

Runa Lindblom · Katherine Ververis · Stephanie M. Tortorella · Tom C Karagiannis

Abstract Life expectancy has been examined from a variety of perspectives in recent history. Epidemiology is one perspective which examines causes of morbidity and mortality at the population level. Over the past few 100 years there have been dramatic shifts in the major causes of death and expected life length. This change has suffered from inconsistency across time and space with vast inequalities observed between population groups. In current focus is the challenge of rising non-communicable diseases (NCD), such as cardiovascular disease and type 2 diabetes mellitus. In the search to discover methods to combat the rising incidence of these diseases, a number of new theories on the development of morbidity have arisen. A pertinent example is the hypothesis published by David Barker in 1995 which postulates the prenatal and early developmental origin of adult onset disease, and highlights the importance of the maternal environment. This theory has been subject to criticism however it has gradually gained acceptance. In addition, the relatively new field of epigenetics is contributing evidence in support of the theory. This review aims to explore the implication and limitations of the developmental origin hypothesis, via an historical perspective, in order to enhance understanding of the increasing incidence of NCDs, and facilitate an improvement in planning public health policy.

Keywords Development origin hypothesis · Epigenetics · Early life origins of disease · Cardiovascular disease · Type 2 diabetes

R. Lindblom · K. Ververis · T. CKaragiannis (✉)
Epigenomic Medicine, Baker IDI Heart and Diabetes Institute, The Alfred Medical Research and Education Precinct, 75 Commercial Road, Melbourne, VIC, Australia
e-mail: tom.karagiannis@bakeridi.edu.au

R. Lindblom · K. Ververis · T. CKaragiannis
Department of Pathology, The University of Melbourne, Parkville, VIC, Australia

S. M. Tortorella
Melbourne School of Land and Environment, Department of Agriculture and Food Systems, The University of Melbourne, Parkville, VIC, Australia

S. M. Tortorella
Department of Chemical and Biomolecular Engineering, The University of Melbourne, Parkville, VIC, Australia

Introduction

In the developed world today, the number of infectious causes of death is very small. Public health policy of the past has enabled a degree of protection from contagious pathogens through the advent of hygiene and sanitation improvements; vaccination programs and cultural practice shifts (i.e. hygiene) [1]. Life expectancy has risen over time in correlation with these improvements. Currently the biggest threats upon mortality include a range of non-communicable diseases (NCD), which normally present in later adult life [2]. These include cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM), amongst others. Total burden from NCDs worldwide has been estimated at 63 % of total deaths by the World Health Organisation in 2008 [2]. Additionally the global incidence of diabetes has been projected to increase exponentially over the next 20 years and beyond [2]. The situation is similar in developing regions. NCDs have long been known to contribute significantly to mortality and morbidity even against the backdrop of prevalent infectious disease [2, 3]. It is in the public interest to find ways of reducing the impact in both developed and developing

regions. Research is currently being conducted into both preventions and treatments which may alleviate the burden. The aetiologies of these diseases remain the subject of ongoing research however some theories are gaining ground, including the early life origin theory. Public health provides an important context for consideration as the ability to prevent adult chronic disease has implications in the general spectrum of advancing life expectancy. In order to improve knowledge regarding the rising incidence of NCDs and to improve the forum for public health planning, this review aims to discuss the implication and limitations of the development origin hypothesis in a historical context.

The early life origin of health and disease theory

The general theory of the developmental origin of human health and disease is widely known. Published as a theory in 1995, the early life origin theory proposes the foetal and developmental origin of non-communicable disease risk [4]. Current public health policies aimed at CVD and T2DM tend to focus on providing individual lifestyle advice on diet and exercise to reduce the incidence of heart disease and diabetes. In addition there is a focus on medical care and therapeutic interventions such as that experienced in a clinical setting [2]. This relates to the theory of risk determined by adult life style. In comparison, the early life origin hypothesis suggests that the earliest stages of life convey significant CVD and T2DM risk. In particular focus, the theory has examined the correlations between low birth weight and adult onset of these diseases. Evidence produced has been compelling with a large number of studies across the globe revealing similar results, including the original studies in England [4, 5], comprehensive cohort studies in the Nordic countries [6–9], and more recent studies in non-western countries such as China [10] and also indigenous populations [11, 12]. Studies have generally correlated low birth weight, as a result of slowed foetal growth, to be an important indicator in the development of CVD and T2DM. More recent studies have aimed to address limitations in early studies, including the finding that birth weight alone may not be a significant marker in the development of adult onset disease, as well as the uncertainty in low cohort follow-up studies [9–11]. For example, the rate of foetal development was identified as a relatively better indicator of disease rather than birth weight alone [11]. Targeting the limitations of the research remains an ongoing factor in order to completely elucidate the importance of the developmental origin of health and disease hypothesis, and to determine its place within the risk spectrum [13].

Epigenetics

The early life origin hypothesis has been advanced by the field of epigenetic science. Epigenetics is the study of how changes in phenotype beyond the DNA sequence alone can be inherited and has been associated with an incredible range of adult chronic disease [14]. Epigenetic mechanisms generally describe regulators of gene expression such as DNA methylation status, histone post-translational modifications, and interference by miRNA (Fig. 1). The term ‘Epigenetics’ developed through the mid 20th century in response to the philosophical ideas surrounding genetic heritability combined with the Aristotelian idea of ‘Epigenesis’ [15].

Nature versus nurture has long been considered for their influence on NCD incidence rates. Genetic technologies have enhanced our ability to examine the underlying genetic causes but fail to adequately account for the observed incidence of CVD and T2DM alone. In addition, environmental consequences examined through epidemiology have supported the social and lifestyle effects of disease, but has also been subject to limitations due in part to the uncertainty between correlation and causation. The rapid changes in incidence of NCDs, particularly T2DM, produces an apparent disparity between genetic or environmental factors within population groups [16]. It is likely that this may be at least partially explained through epigenetics [17–20]. The epigenetic basis of disease has gained strength over the past two decades, with research expanding in this field to determine its significance in disease heritability. In particular the molecular basis for the involvement of epigenetics in disease has been evaluated in a number of animal models, including an extensive evaluation of the effects of methylation of the Agouti gene in mice, with studies revealing epigenetic methylation patterns can directly determine the risk of disease phenotype development [18, 21–23]. Therapeutic interventions aimed at favourably altering epigenetic profiles in this model have been promisingly explored [24, 25].

In an evolutionary context, adaptation responses to short term environmental cues has given rise to the adaptive developmental plasticity model that proposes a critical role for epigenetics in appropriating phenotypic development [26]. Within the scope of developmental biology, this model assists in bridging the gap between Darwinian evolution and individual phenotypic adaption. The concept of environment-phenotype mismatch as a result of this plasticity, representing the disparity between the energy environment of the foetus in utero and that experienced postnatally [27], has the potential to validate the mechanisms of the model. This would occur by highlighting the importance of the foetal environment in the determination of the overall gene expression profiles through to

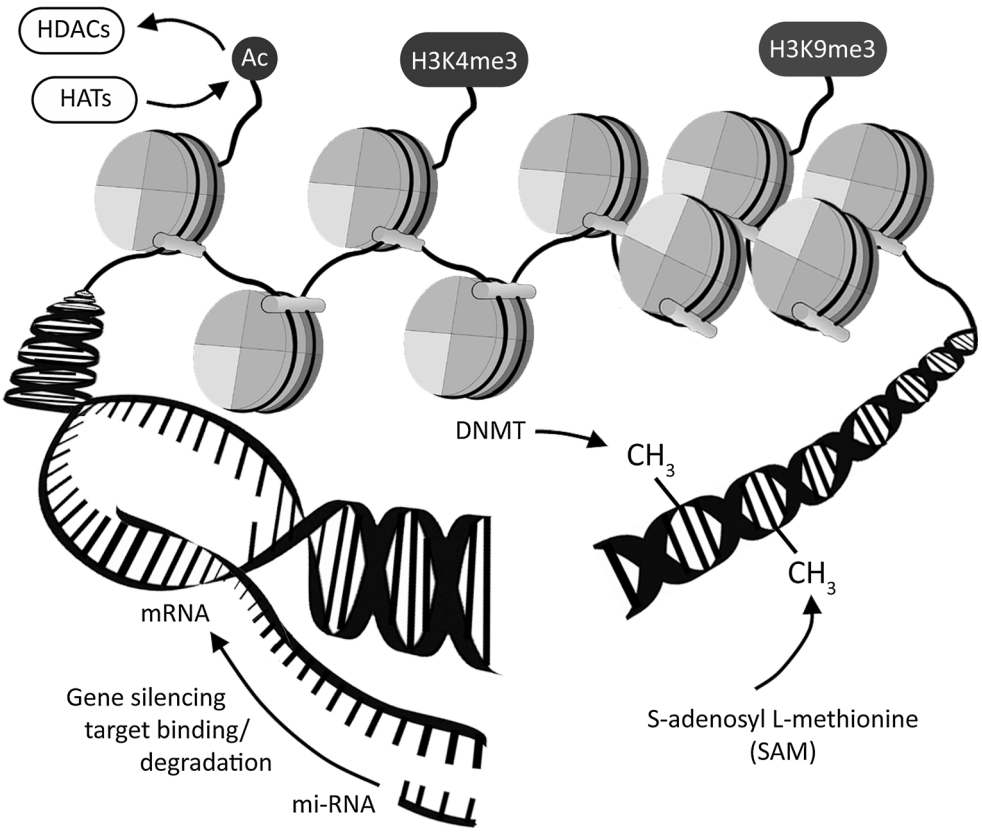

Fig. 1 Epigenetic mechanisms involves the modification of gene expression without modification to the DNA sequence. Epigenetic mechanisms include DNA methylation, histone post-translational modifications and interference by miRNA. The chromatin proteins associated with DNA or histones may be activated or silenced. Post translational modification of the amino acids that make up histone proteins include acetylation by histone acetyltransferases (HATs) or histone deacetylases (HDACs) or methylation at specific sites on the histone tails. DNA methylation occurs via DNA methyltransferses (DNMT) which utilises S-adenosyl L-methionine (SAM) as the methyl donor, mostly at CpG sites to convert cytosine to 5-methylcytosine

adulthood. This is in addition to the established body of evidence demonstrating how the maternal environment impacts the foetus' birth weight, for example through nutrition and smoking [28–30] (Fig. 2).

Influence on public health

In addition to the volume of biomedical research, the developmental origin theory has been well established and is generally accepted in the field of economic science as outlined in a review by Almond and Curri [31]. This has been an important area due to the financial burden of health, and the projected dominance of medical intervention costs in the future [2]. Economics has long been closely associated with public health interventions. Unfortunately the system is subject to uncertainty in expenditure due to the large variation in ideologies when it comes to intervention and treatments which affect mortality [31]. In the past, significant public health achievements have been found to correlate to increases in life expectancy [1]. These have often but not always been spurred by scientific research, with current public health interventions mostly aimed at altering diet and exercise at the individual level [2].

Overall, the evidence both from epidemiological and epigenetic studies has established the early life origin hypothesis as an important consideration when understanding the risk factors for CVD and T2DM [32]. Indeed, it has been proposed that epigenetic mechanisms have a likely involvement in the developmental origins of health and disease, with the requirement of epidemiology to explore and identify associations between early life exposures, changes in epigenetic regulation, and disease [33]. Research in both fields is ongoing in the hope of further elucidating the correlations and causations involved in what are now a significant cause of mortality and morbidity in our community. Acceptance of the early life origin theory has the potential to influence the management of disease risks associated with early life development via careful public health planning.

Maternal health

Maternal health and lifestyle choice is one area of public health which has been influenced by foetal and early life development theories. This has been more of a cultural change rather than a legislative change with negative social views of smoking, alcohol, stress and a positive view for nutritional supplementation during pregnancy [34]. Studies

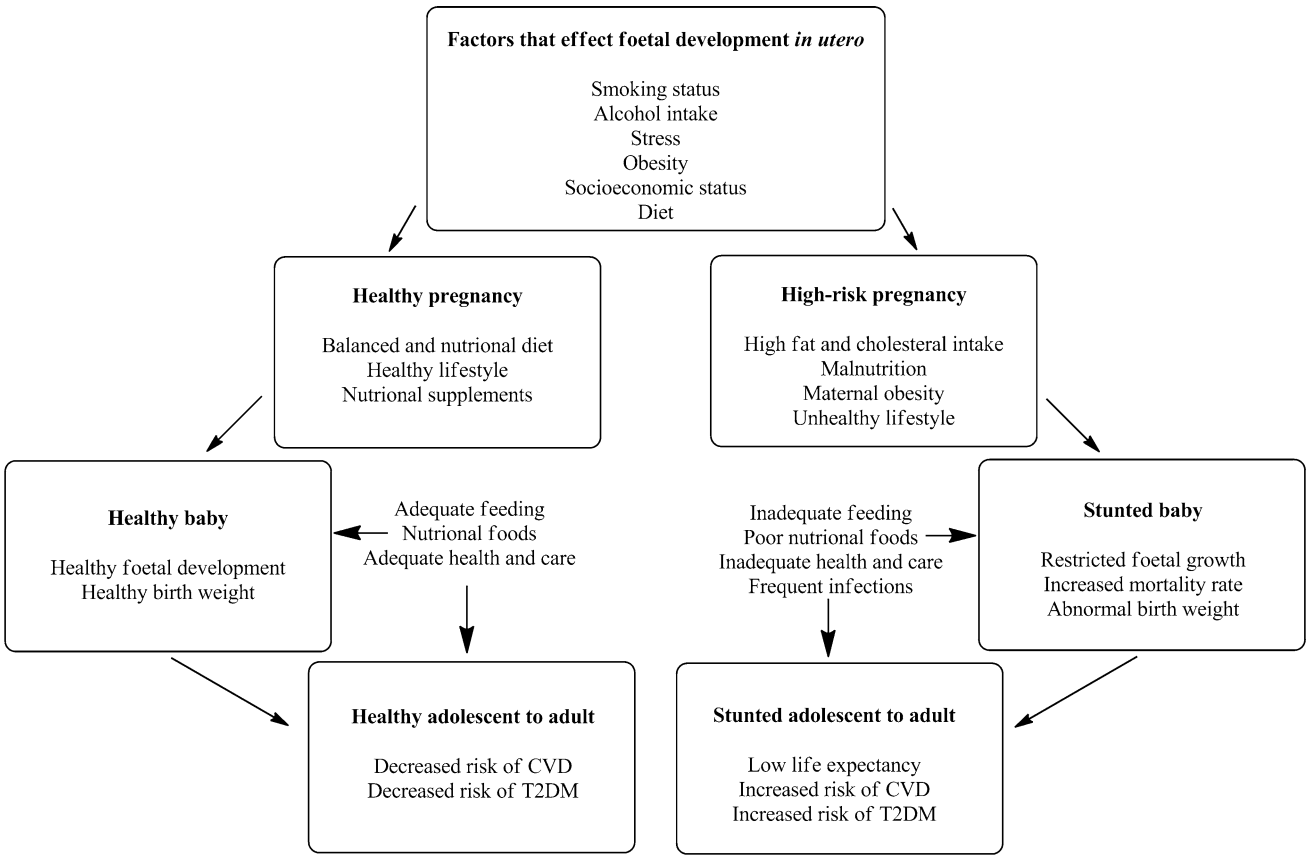

Fig. 2 The developmental origin of human health and disease. A summary of the early life origin of health and disease hypothesis which involves the role of maternal health and lifestyle in impaired foetal development leading to the increased risk of cardiovascular disease and type 2 diabetes mellitus in adulthood

have also examined the role of both under and over nutrition in the context of foetal development, and have identified a large range of mechanisms correlating to birth weight which produces the effects of the developmental origins theory for both CVD and T2DM [8, 30, 35–37]. In addition, birth weight and diabetes risk within aboriginal populations have been examined and have highlighted the importance of nutritional intervention in influencing the foetal development risk [11, 12]. The role of maternal diabetes status has also been correlated to the risk of development of T2DM and CVD for both small and large for gestational age (SGA and LGA) children representing an important area for public health interventions [38]. Nutritional studies have previously examined data from the prominent Dutch Hunger Winter study of the negative impact of maternal famine on offspring's adult disease profile [39]. A comparative study in Germany has examined the economic impact of a corresponding war environment on intergenerational economic outcomes [40]. Maternal obesity is also a major concern, with increased risk of both short-term and long-term factors involved in foetal and early life development [41]. For example, a recent study involving over 8,400 children in the USA reported that children born to obese mothers were twice as likely to be obese by 2 years of age [42]. These studies, amongst others [19, 43], highlight the importance of the maternal environment for later life disease as tracked through historical studies, and provide a potential point for intervention strategies to impact NCD incidence into the future. This is particularly intriguing considering the role of epigenetic determination in utero influencing later disease risk.

Beyond this, developing regions may be an important consideration for the developmental origin hypothesis in public health planning. This arises from the situations where by poor and vulnerable populations currently experiencing, or recently experienced maternal nutritional inadequacies will be paired in the future with the incorporation of westernised diets [30]. It has been predicted that this could underlie an increase in NCDs in the future following the foetal/postnatal energy environment mismatch theory [44, 45]. The knowledge that the mother's life situation can impact her offspring's life expectancy highlights the importance for consideration of the developmental origin of disease in public health policy.

Criticism in context

The early life origin theory is just one of the many factors thought to contribute to the development of cardiovascular disease. As yet however, the developmental origin hypothesis remains subject to criticism and overall influence on public health remains low. The most prevalent risk factor associated with disease involves the consumption of dietary fats and cholesterol, as well as obesity in the development of CVD, and as a result many public health campaigns exist which encourage individuals to reduce their dietary fat intake. This can be seen in the advent of low fat and low cholesterol products in the food industry. The evaluation of these risk factors has itself been reviewed with additional aspects now revealing significant involvement. These include the role of smoking, stress, and salt and sugar intake in raising individual risk which are all included in the WHO reports [2]. These factors are of public interest considering the evidence for both correlation and causation with NCDs. The difference between the developmental origin hypothesis and the lifestyle factors of CVD aetiology is that the latter are well established risks, and are more easily applied to the current intervention methodology on a case-by-case basis. In contrast, the early life origin hypothesis involves thinking for the future and targeting a particular group of people (future mothers) who may not show obvious symptoms of disease themselves. This may explain some of the criticism, and one reason why this hypothesis is not as prominent as other factors studied for intervention. The role of maternal diet, stress, and smoking however have all been related to restricting foetal growth, and thus birth weight, which is the major focus within the early life origin theory [23, 28]. In addition, maternal obesity or overnutrition before or during pregnancy may also result in foetal growth restriction, and increased risk of neonatal mortality and morbidity in humans [30, 46]. One other prominent criticism is that the hypothesis should not be an individual theory but rather form part of the overall lifetime "weathering" hypothesis [19, 43]. This purports that all life stages contribute significant cumulative risk for disease outcomes in later life.

Further considerations

By far the most criticism of the early life origin hypothesis comes from the correlating effect of birth weight with low socioeconomic status (SES). Here the idea of causation is removed from birth weight alone and instead placed upon other factors associated with low income. How can we be sure that slowed foetal development increases the risk of heart disease and diabetes when in general these particular groups of people are already more vulnerable? This effect has been reviewed with varying results, but generally appears to support the developmental origin hypothesis [6, 31]. Factors associated with low SES have been independently linked to causing low birth weight including the previous examples of smoking and nutrition [11, 28, 35]. The direct influence of the early life origin theory within this social context is still being elucidated regarding the underlying mechanisms of perceived correlation in vulnerable groups with NCD risk. Studies in both epidemiology and epigenetics, with an interdisciplinary approach, will enable a greater understanding of the causation of risk factors independent to SES.

Conclusion

The rising burden of Non-Communicable Disease upon life expectancy and life quality has contributed to the current research aims of evaluating effective prevention. The early life origin of health and disease theory is continuing to emerge as an important consideration amongst the current prevailing contributing factors to adult disease, with the potential for important implications in future policy planning and public health interventions. This has been considered most important for the world's poorest and most vulnerable populations due to associated risks. It is possible that additional public health interventions assisting maternal health may help alleviate the burden of Non-Communicable Disease for subsequent generations. If we can better understand the causes of death then perhaps we can find better prevention strategies. The theory of the developmental origins of adult chronic disease, through the combination of epidemiology and epigenetics, may be an important contribution to the advancement of current life expectancy. To date, the developmental origin theory of human health and disease remains as only one part in the overall perceived spectrum of risk.

Acknowledgments TCK is a Future Fellow and Epigenomic Medicine Laboratory is supported by the Australian Research Council. Supported by McCord Research and the authors would like to acknowledge the intellectual contribution of Dr. Darlene McCord. Supported in part by the Victorian Government's Operational Infrastructure Support Program.

References

1. Riley JC (2001) rising life expectancy a global perspective. Cambridge University Press, Cambridge
2. WHO (2011) Global status report on noncommunicable diseases 2010: description of the global burden of NCDs, their risk factors and determinants. World Health Organisation, Geneva
3. Reddy KS, Yusuf S (1998) Emerging epidemic of cardiovascular disease in developing countries. Circulation 97(6):596–601. doi:10.1161/01.cir.97.6.596

4. Barker DJP (1995) Fetal origins of coronary heart disease. BMJ: Br Med J 311 (6998):171-174. doi:10.1136/bmj.311.6998.171
5. Barker DJ, Martyn CN (1992) The maternal and fetal origins of cardiovascular disease. J Epidemiol Community Health 46(1):8–11
6. Leon DA, Lithell HO, Vågerö D, Koupilová I, Mohsen R, Berglund L, Lithell U-B, McKeigue PM (1998) Reduced fetal growth rate and increased risk of death from ischaemic heart disease: cohort study of 15 000 Swedish men and women born 1915–1929. BMJ Br Med J 7153:241. doi:10.2307/25179920
7. Whincup PH, Kaye SJ, Owen CG, Huxley R, Cook DG, Anazawa S, Barrett-Connor E, Bhargava SK, Birgisdottir BE, Carlsson S, de Rooij SR, Dyck RF, Eriksson JG, Falkner B, Fall C, Forsen T, Grill V, Gudnason V, Hulman S, Hypponen E, Jeffreys M, Lawlor DA, Leon DA, Minami J, Mishra G, Osmond C, Power C, Rich-Edwards JW, Roseboom TJ, Sachdev HS, Syddall H, Thorsdottir I, Vanhala M, Wadsworth M, Yarbrough DE (2008) Birth weight and risk of type 2 diabetes: a systematic review. JAMA 300(24):2886–2897. doi:10.1001/jama.2008.886
8. Andersen LG, Ängquist L, Eriksson JG, Forsen T, Gamborg M, Osmond C, Baker JL, Sørensen TIA (2010) Birth weight, childhood body mass index and risk of coronary heart disease in adults: combined historical cohort studies. PLoS ONE 5(11):e14126
9. Kajantie E, Osmond C, Barker DJP, Eriksson JG (2010) Preterm birth—a risk factor for type 2 diabetes?: the Helsinki Birth cohort study. Diabetes Care 33(12):2623–2625. doi:10.2337/dc10-0912
10. Fan Z, Zhang Z-X, Li Y, Wang Z, Xu T, Gong X, Zhou X, Wen H, Zeng Y (2010) Relationship between birth size and coronary heart disease in China. Ann Med 42(8):596–602. doi:10.3109/07853890.2010.514283
11. McNamara BJ, Gubhaju L, Chamberlain C, Stanley F, Eades SJ (2012) Early life influences on cardio-metabolic disease risk in aboriginal populations–what is the evidence? A systematic review of longitudinal and case-control studies. Int J Epidemiol 41(6):1661–1682. doi:10.1093/ije/dys190
12. Chamberlain C, McNamara B, Williams ED, Yore D, Oldenburg B, Oats J, Eades S Diabetes in pregnancy among indigenous women in Australia, Canada, New Zealand and the United States. Diabetes Metab Res Rev 29 (4):241-256. doi:10.1002/dmrr.2389
13. Bouchard L (2013) Epigenetics and fetal metabolic programming: a call for integrated research on larger cohorts. Diabetes 62(4):1026–1028. doi:10.2337/db12-1763
14. Karagiannis TC, Maulik N (2012) Factors influencing epigenetic mechanisms and related diseases. Antioxid Redox Signal 17(2):192–194
15. Van Speybroeck L (2002) From epigenesis to epigenetics: the case of C. H Waddington. Ann NY Acad Sci 981:61–81
16. Fradin D, Bougneres P (2011) T2DM: why epigenetics? J Nutr Metab 2011:647514. doi:10.1155/2011/647514
17. Feinberg AP (2013) The epigenetic basis of common human disease. Trans Am Clin Climatol Assoc 124:84
18. Seki Y, Williams L, Vuguin PM, Charron MJ (2012) Minireview: epigenetic programming of diabetes and obesity: animal models. Endocrinology 153(3):1031–1038. doi:10.1210/en.2011-1805
19. Vaag AA, Grunnet LG, Arora GP, Brøns C (2012) The thrifty phenotype hypothesis revisited. Diabetologia 55(8):2085–2088. doi:10.1007/s00125-012-2589-y
20. Jackson FL, Niculescu MD, Jackson RT (2013) Conceptual shifts needed to understand the dynamic interactions of genes, environment, epigenetics, social processes, and behavioral choices. Am J Public Health 103(Suppl 1):S33–S42. doi:10.2105/AJPH.2013.301221
21. Morgan HD, Sutherland HGE, Martin DIK, Whitelaw E (1999) Epigenetic inheritance at the agouti locus in the mouse. Nature genetics, vol 23. Nature Publishing Group
22. Rosenfeld CS (2010) Animal models to study environmental epigenetics. Biol Reprod 82(3):473–488. doi:10.1095/biolreprod.109.080952
23. Dolinoy DC, Weidman JR, Jirtle RL (2007) Epigenetic gene regulation: Linking early developmental environment to adult disease. Reprod Toxicol 23(3):297–307. doi:10.1016/j.reprotox.2006.08.012
24. Adamo KB, Ferraro ZM, Brett KE (2012) Can we modify the intrauterine environment to halt the intergenerational cycle of obesity? Int J Environ Res Public Health 9(4):1263–1307. doi:10.3390/ijerph9041263
25. Lillycrop KA (2011) Effect of maternal diet on the epigenome: implications for human metabolic disease. Proc Nutr Soc 70(1):64–72. doi:10.1017/S0029665110004027
26. Pc Beldade, Mateus ARA, Keller RA (2011) Evolution and molecular mechanisms of adaptive developmental plasticity. Mol Ecol 20(7):1347–1363
27. Godfrey KM, Lillycrop KA, Burdge GC, Gluckman PD, Hanson MA (2007) Epigenetic mechanisms and the mismatch concept of the developmental origins of health and disease. Pediatr Res 61 (5 Part 2):5R–10R
28. Suter M, Ma J, Harris A, Patterson L, Brown KA, Shope C, Showalter L, Abramovici A, Aagaard-Tillery KM (2011) Maternal tobacco use modestly alters correlated epigenome-wide placental DNA methylation and gene expression. Epigenetics 6(11):1284–1294. doi:10.4161/epi.6.11.17819
29. Talens RP, Jukema JW, Trompet S, Kremer D, Westendorp RG, Lumey LH, Sattar N, Putter H, Slagboom PE, Heijmans BT (2012) Hypermethylation at loci sensitive to the prenatal environment is associated with increased incidence of myocardial infarction. Int J Epidemiol 41(1):106–115. doi:10.1093/ije/dyr153
30. Wu G, Bazer FW, Cudd TA, Meininger CJ, Spencer TE (2004) Maternal nutrition and fetal development. J Nutr 134(9):2169–2172
31. Almond D, Curri J (2011) Killing me softly: the fetal origins hypothesis. J Econ Perspect (3)
32. Barker DJ (2002) Fetal programming of coronary heart disease. Trends Endocrinol Metab 13(9):364–368
33. Waterland RA, Michels KB (2007) Epigenetic epidemiology of the developmental origins hypothesis. Annu Rev Nutr 27:363–388
34. Lechtig A, Habicht J-P, Delgado H, Klein RE, Yarbrough C, Martorell R (1975) Effect of food supplementation during pregnancy on birthweight. Pediatrics 56(4):508–520
35. Brenseke B, Prater MR, Bahamonde J, Gutierrez JC (2013) Current thoughts on maternal nutrition and fetal programming of the metabolic syndrome. J Pregnancy 2013:13. doi:10.1155/2013/368461
36. van Abeelen AF, Elias SG, Bossuyt PM, Grobbee DE, van der Schouw YT, Roseboom TJ, Uiterwaal CS (2012) Famine exposure in the young and the risk of type 2 diabetes in adulthood. Diabetes 61(9):2255–2260. doi:10.2337/db11-1559
37. Eriksson JG (2011) Early growth and coronary heart disease and type 2 diabetes: findings from the Helsinki Birth Cohort Study (HBCS). Am J Clin Nutr 94(6 Suppl):1799S–1802S. doi:10.3945/ajcn.110.000638
38. Ramírez-Torres MA (2013) The importance of gestational diabetes beyond pregnancy. Nutr Rev 71:S37–S41. doi:10.1111/nure.12070
39. Heijmans BT, Tobi EW, Stein AD, Putter H, Blauw GJ, Susser ES, Slagboom PE, Lumey LH (2008) Persistent epigenetic differences associated with prenatal exposure to famine in humans. Proc Natl Acad Sci 105(44):17046–17049. doi:10.1073/pnas.0806560105
40. Jürges H (2013) Collateral damage: the German food crisis, educational attainment and labor market outcomes of German

post-war cohorts. J Health Econ 32(1):286–303. doi:10.1016/j.jhealeco.2012.11.001
41. Catalano P, Ehrenberg H (2006) Review article: the short-and long-term implications of maternal obesity on the mother and her offspring. BJOG Int J Obstet Gynaecol 113(10):1126–1133
42. Whitaker RC (2004) Predicting preschooler obesity at birth: the role of maternal obesity in early pregnancy. Pediatrics 114(1):e29–e36
43. Varvarigou AA (2010) Intrauterine growth restriction as a potential risk factor for disease onset in adulthood. J Pediatr Endocrinol Metab 23(3):215–224
44. Harvey LB, Ricciotti HA (2013) Nutrition for a Healthy Pregnancy. Am J Lifestyle Med. doi:10.1177/1559827613498695
45. Arnuna P, Zotor FB (2008) Epidemiological and nutrition transition in developing countries: impact on human health and development. Proc Nutr Soc 67(1):82–90
46. Castro LC, Avina RL (2002) Maternal obesity and pregnancy outcomes. Curr Opin Obstet Gynecol 14(6):601–606