Journal of Adolescent Health 52 (2013) S14–S21

ELSEVIER

JOURNAL OF ADOLESCENT HEALTH

www.jahonline.org

Review article

Epigenetics and Early Life Origins of Chronic Noncommunicable Diseases

Guoying Wang, M.D., Ph.D.[a], Sheila O. Walker, Ph.D.[a,b], Xiumei Hong, M.D., Ph.D.[a], Tami R. Bartell[c], and Xiaobin Wang, M.D., M.P.H., Sc.D.[a,c,*]

[a] *Center on Early Life Origins of Disease, Department of Population, Family and Reproductive Health, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland*

[b] *Department of Psychology, Georgetown University, Washington, DC*

[c] *Mary Ann, and J. Milburn Smith Child Health Research Program, Department of Pediatrics, Northwestern University Feinberg School of Medicine, Children's Memorial Hospital and Children's Memorial Research Center, Chicago, Illinois*

Article history: Received January 22, 2012; Accepted April 27, 2012
Keywords: Epigenetics; Chronic disease; Early life origin; Obesity; Mental health; Addiction

A B S T R A C T

In light of the increasing threats of chronic noncommunicable diseases in developing countries, the growing recognition of the early life origins of chronic disease, and innovative breakthroughs in biomedical research and technology, it is imperative that we harness cutting-edge data to improve health promotion and maintenance. It is well recognized that chronic diseases are complex traits affected by a wide range of environmental and genetic factors; however, the role of epigenetic factors, particularly with regard to early life origins, remains largely unexplored. Given the unique properties of the epigenome—functionality during critical time windows, such as the intrauterine period, heritability, and reversibility—enhancing our understanding of epigenetic mechanisms may offer new opportunities for the development of novel early prediction and prevention paradigms. This may present an unparalleled opportunity to offer maternal and child health professionals important tools with the translational value to predict, detect, and prevent disease at an early age, long before its clinical occurrence, and as such, break lifelong and transgenerational cycles of disease. In doing so, modern technology can be leveraged to make great contributions to population health, quality of life, and reducing the burdensome economic costs of noncommunicable diseases in developing countries.

Human health is interconnected throughout the life span from conception to fetal life to early childhood and adolescence and on into adulthood and the senior years. Each stage presents its own unique health needs and problems, yet each of them is interconnected. There is compelling evidence that early life may have a profound impact on health and disease in later life [1–3]. For example, there are four critical periods for the development of obesity: prenatal, early childhood, adolescence, and pregnancy [4]. As related to the prenatal period, with few nutrients, fetal systems develop to thrive in a world of scarcity, which manifests in reduced fetal growth. However, after birth, this "thrifty phenotype" becomes a liability when the postnatal environment provides many more calories and nutrients than the fetal adaptations have predicted. These "double hits" can lead to metabolically disadvantageous phenotypes and increased susceptibility to disease in later life.

Despite the extensive efforts of biomedical research taking place mostly in developed countries, we have made little progress toward preventing chronic noncommunicable diseases. In light of the increasing threats of chronic noncommunicable diseases in developing countries, the growing recognition of early life origins of chronic diseases, and the remarkable breakthroughs in biomedical research and technology, a new approach to health promotion and maintenance in developing countries needs to be explored and developed. The new focus must be on shifting the timing of our interventions from clinical disease to preclinical precursors that allow

* **Address correspondence to:** Xiaobin Wang, M.D., M.P.H., Sc.D., Department of Population, Family and Reproductive Health, Center on Early Life Origins of Disease, Johns Hopkins University, Bloomberg School of Public Health, 615 N. Wolfe Street, E4132, Baltimore, MD 21205-2179.
E-mail address: Xiwang@jhsph.edu (X. Wang).

1054-139X
http://dx.doi.org/10.1016/j.jadohealth.2012.04.019

us to prevent and/or intervene prior to disease onset. By doing so, we will be able to improve child and adolescent health, as well as population health and quality of life, and also work to reduce health care costs.

It is well recognized that chronic diseases are complex traits that are affected by a wide range of environmental and genetic factors. The epigenome is an important link between genetic inheritance and environmental factors, playing a particularly crucial role in the early life origins of chronic diseases. The excitement and promise of epigenetic research stem from its unique properties, including heritability, functionality during critical developmental windows, and reversibility. Regarding critical windows, evidence from animal models and human studies implicates the intrauterine period as a highly sensitive time for the establishment of epigenetic variability, which in turn influences risk for a range of disorders that can develop later in life [5–7]. Moreover, developmental plasticity from preconception to early childhood involves epigenetic responses to environmental influences, which exert long-term health effects. These epigenetic responses shape development, cell- and tissue-specific gene expression, and sexual dimorphism. A more substantive review of epigenetics can be found in the Epigenetics and Early Life Origins of Disease section.

Using the examples of obesity and mental illness, both of which are highly prevalent in developing and developed countries alike, this review underscores the importance of understanding early life origins of chronic noncommunicable diseases with a particular focus on epigenetics as a possible biological mechanism. Given the distinctive properties of the epigenome and its relation to gene expression and environmental factors, understanding epigenetic mechanisms could offer new opportunities for the development of novel early prediction and prevention paradigms. We are optimistic that this new paradigm will not only contribute to more cost-effective health care over the long term, but will also help to break intransigent lifelong and transgenerational cycles of chronic noncommunicable diseases prevalent in developing countries.

Evolving Paradigms of Early Life Origins of Disease

Early in 1934, the Early Life Origins of Adult Disease hypothesis was proposed by Kermack et al, who suggested that decreased death rates due to all causes in the United Kingdom and Sweden between 1751 and 1930 were the result of improved childhood living conditions [8]. In 1962, Neel extended on this hypothesis by proposing that exposure to periods of famine resulted in selection pressures in favor of a "thrifty genotype," which led to maladaptive levels of overly efficient fat storage during periods of abundance [9]. In 1977, Forsdahl reported that nutritional deficit during childhood may exacerbate later-life vulnerability to arteriosclerotic heart disease when exposed to a more affluent and nutritionally abundant adult lifestyle [10]. Subsequently, Baker et al found that the restraint of growth during fetal life and infancy may increase the risk for cardiovascular disease and reduced glucose tolerance in adult life. Based on this finding, he proposed the "thrifty phenotype hypothesis," which espouses the idea that poor nutrition in fetal and early infancy is detrimental to beta cell function and predisposes the individual to developing type 2 diabetes later in life [11–13]. Further development in the field extended this paradigm into what became known as the Fetal Origin of Adult Disease hypothesis. The Fetal Origin of Adult Disease hypothesis contends that environmental influences during fetal life can influence adult health through various mechanisms including developmental plasticity, fetal programming, and epigenetics [14–16]. This idea was further expanded into the developmental origins of health and disease paradigm, which has received tremendous attention over the past 25 years and reflects ideas that have been debated since the field of genetics gained widespread acceptance [17,18].

Nutrition in early life and its effect on obesity

Prenatal nutrition is arguably one of the most important contributing factors to obesity. Abundant evidence supports the relationship between the prenatal nutritional environment, patterns of postnatal growth, and adult adiposity. For example, a high prevalence of obesity was found at both high and low birth weights, which were associated with obesity in childhood and adult life [19,20]. Additionally, roughly half of the children who were large for gestational age at birth were overweight at age 8 years [21]. Alternatively, although infants who were small for gestational age tended to have a lower body mass index (BMI) in adulthood, they were prone to a higher level of central obesity than individuals who were large at birth [22–24]. A final example is provided by the well-known Dutch Winter Famine ("Hongerwinter") study, which examined long-term health outcomes of children born to mothers starved during pregnancy because of a Nazi blockage of the food supply lines during the Second World War. As adults, these children experienced significantly higher rates of type 2 diabetes and cardiovascular disease relative to their peers whose mothers had adequate nutritional intake during pregnancy [25].

Exposure to environmental toxins in early life and its effect on obesity

Research has also linked early life exposure to environmental toxins with obesity and chronic illness later in life. Numerous studies have found that maternal cigarette smoking during pregnancy is associated with reduced birth weight or increased risk of lower birth weight [26,27]. Additionally, associations have been found between maternal smoking in pregnancy and offspring obesity [28]. Previous work from our research team found that smoking mothers with specific genotypes were at a higher risk of delivering low-birth-weight infants [29]. These findings suggest that a specific gene–environment (GxE) interaction between maternal metabolic genes and cigarette smoking may contribute to offspring obesity later in life. Further evidence comes from a study on endocrine-disrupting chemicals, which may alter the normal functioning of hormones and other signaling molecules, including estrogens, androgens, thyroid, hypothalamic, and pituitary hormones [30,31]. Prenatal exposure to these endocrine-disrupting chemicals may play a role in shaping BMI later in life. For example, a correlation was found between prenatal exposure to dichlorodiphenyl dichloroethene, a known endocrine disrupter, and increased BMI in young children [32]. Similar effects were also found in boys at puberty [33].

Epigenetics and early life origins of disease

Epigenetic programming may be a mechanism underlying the early life origins of chronic disease via regulation of gene expression through DNA methylation, histone modifications, chromatin

remodeling, and/or regulatory feedback by way of microRNAs. Epigenetic mechanisms are important because of the effect they can have on the roughly 25,000 genes that comprise human DNA. Stated simply, genes or alleles (specific forms of genes) can be thought of as "recipes" for unique protein products that interact to create the biochemical blueprint underlying development. Epigenetic effects can silence genes entirely, or cause them to overproduce/overexpress (hypomethylate) or underproduce/underexpress (hypermethylate) the gene's protein product, influencing the downstream biochemical milieu that underpins all dimensions of complex behavior, including human health. Growing evidence supports the likelihood that the overwhelming majority of chronic human diseases are driven by acquired changes in genomic expression over the life course.

Research shows that epigenetic patterns are dynamic in response to both internal and external environmental stimuli throughout the life cycle [34,35]. For example, demographic factors (e.g., age and gender), environmental exposures (cigarette smoke, diet, lifestyle, maternal nurturing, air pollution, microbial infections), and genetic variations can all influence epigenetic patterns [36–40]. Converging these lines of evidence supports the possibility that epigenetics may be a causal link between the genotype and environment, and hence, between the phenotype and disease. Of note, although epigenetic expression patterns can persist over the long term, they are nonetheless potentially reversible, presenting as-yet undefined opportunities to optimize gene expression and health outcomes over the life course.

As described earlier, epigenetic changes may reflect the molecular consequences of genetic variants, environmental exposures, and GxE interactions. One example is provided by the finding that a low-protein diet during pregnancy was associated with decreased DNA methylation of the angiotensin receptor gene in offspring, explaining the increase in blood pressure among the study animals [41]. Another study in rats found that epigenetic modifications were associated with differential patterns of insulin-like growth factor 1 gene expression in intrauterine growth-restricted offspring, and suggested that these differences may have been associated with either rapid or delayed postnatal catch-up growth [42]. More evidence comes from an animal study that found epigenetic alterations induced by in utero and postnatal exposure to chemical compounds, such as bisphenol A [43–45], polybrominated diphenyl ethers [46], and polychlorinated biphenyls [47]. Interestingly, the hypomethylating effects of BPA can be mitigated by maternal folic acid supplementation, providing a preventative environmental solution to an adverse epigenetic effect [43]. In summary, animal research in epigenetics has revealed novel mechanisms to elucidate detrimental health effects arising from early life adversities, as suggested by the metabolic imprinting theory [48]. The basic hypothesis is that intrauterine exposure can permanently change fetal metabolic patterns and modify long-term risk for disease. This "fetal programming" appears to be largely independent of the genomic DNA sequence, and is likely mediated by epigenetic mechanisms.

Research in humans found that impaired glucose metabolism during pregnancy was associated with increased leptin gene methylation in offspring [49], exacerbating the long-term risk of developing obesity and type 2 diabetes in children born to women with gestational diabetes. Another human study provided evidence for differential methylation levels in response to dietary intervention. After an 8-week hypocaloric diet, methylation patterns in 170 locations on particular genes were substantially changed: 70 were demethylated by >20% (overexpressed) and 100 were methylated by >20% (underexpressed), which resulted in either over- or underproduction of the gene's protein product [50]. Moreover, there is evidence for epigenetic activity in transgenerational inheritance in humans [51]. Support comes from studies of human imprinting disorders, where alleles of particular genes are silenced (incorrectly expressed) because of a specific epigenetic flaw in the DNA of one parent [52,53]. In short, epigenetic mechanisms may operate in conjunction with environmental influences, but there is also evidence that aspects of methylation maintenance and methylation changes over time are under genetic control [6].

Early Life Origins of Obesity and Epigenetic Patterns

There is increasing epidemiologic evidence linking early life factors to later adiposity [1,25,54]. Although our present understanding of the underlying mechanisms is limited, some evidence suggests that epigenetic processes represent an important link between the early environment and obesity later in life [55,56]. For example, diet/nutrition represents a major risk factor for the development of obesity. A few studies have indicated that diet-induced obesity is under epigenetic regulation [57–62]. For example, methylation levels in the promoter region of the retinoid X receptor-α gene at birth were associated with maternal carbohydrate intake in early pregnancy, as well as adiposity in later childhood [60]. Periconceptional exposure to famine was associated with a decrease in DNA methylation of insulin-like growth factor 2 [61] and an increase in methylation of interleukin 10 and leptin, two obesity-related candidate genes [63]. Table 1 summarizes several examples of nutritionally induced alterations of methylation patterns.

A growing body of evidence points to epigenetic mechanisms as mediators of obesity risk, as has recently been reviewed [64]. Limited studies in humans have demonstrated that not only is global DNA methylation positively associated with BMI [65], but also that DNA methylation levels in specific genes (including UBASH3A and TRIM3) vary between obese and lean individuals [66]. In addition, the role of imprinted genes in body weight [67] and the development of obesity [68] have previously been summarized. Current evidence also supports the role of epigenetic effects in the regulation of key genes involved in adipogenesis, glucose homeostasis, inflammation, and/or insulin signaling [58,69–77]. These genes are summarized in Table 2.

Further evidence connecting obesity with epigenetic mechanisms comes from findings linking histone (an intracellular protein that packages and organizes DNA) modification with microRNA activity in the development of obesity [78,79]. In the early stages of adipogenesis, hyperacetylation of histone H3 and trimethylation of histone H3 Lys4 (H3K4) are positively associated with apM1 gene transcription. Conversely, inhibition of H3K4 methylation decreases apM1 gene expression and modifies adipogenesis, indicating an important role of epigenetic factors [75]. Another example is provided by an animal study, which found that the loss of function on an area of histone H3 may regulate peroxisome proliferator–activated receptor α and its target genes via modified levels of the gene's protein product, resulting in obesity and hyperlipidemia [78]. Finally, a human study reported that 70 microRNAs were highly and significantly up- or downregulated

Table 1
Examples of nutritionally induced alterations of methylation patterns

Diet	Modified gene		Alteration in methylation	Reference
	Gene name	Abbreviation		
High-fat diet	Melanocortin 4 receptor	Mc4r	↑	57
	Leptin	LEP	↑	58
Neonatal overfeeding	Pro-opiomelanocortin	POMC	↑	59
Lower maternal carbohydrate intake in early pregnancy	Retinoid X receptor α	RXRA	↑	60
Periconceptional exposure to famine	Insulin-like growth factor 2	IGF-2	↓	61
	Interleukin 10	IL-10	↑	63
	Leptin	LEP	↑	63
A low-protein diet during pregnancy	Imprinted maternally expressed transcript	H19	↑	62
	Insulin-like growth factor 2	IGF-2	↑	62

↑ = increased level of methylation; ↓ = decreased level of methylation.

(resulting in over- or underexpression of the gene's protein product) in mature adipocytes as compared with preadipocytes; 17 microRNAs were correlated with BMI, fasting glucose, and/or triglycerides, and 11 microRNAs were significantly deregulated in subcutaneous fat from obese subjects with and without type 2 diabetes [80]. In conclusion, a growing body of research supports the role of epigenetics as an important mechanism underlying the development of obesity. Further studies elucidating the association between DNA methylation status, increased fat mass, and obesity are warranted to validate existing research.

Epigenetics and Early Life Origins of Mental Health Problems

Although the primary focus of this review relates to the epigenetics of obesity and its related long-term health issues, evidence for differential gene expression patterns and related health outcomes also exists in the arena of psychiatric illness. Several studies have pointed to the association between prenatal and early life epigenetic mechanisms and long-term psychiatric outcomes [81–84]. Research in rodents found that variations in maternal care alter the expression of genes regulating behavioral and endocrine responses to stress, as well as hippocampal synaptic development [81]. Data from a human population found that a gene that codes for a glucocorticoid receptor co-chaperone protein was implicated in child abuse–associated risk of a major depressive disorder and posttraumatic stress syndrome [82,83]. Further evidence for the link between psychosocial stress and epigenetics stems from the finding that social isolation can impair the transcription of glucocorticoid response genes, and moreover increase proinflammatory activity in humans [69]. Epigenetics also have been shown to play a role in the link between stress and addiction [85], as well as the development of habit-forming behaviors [86], particularly when substance abuse begins early in life [85,87]. One study found that ethanol administration in rats during a developmental stage equivalent to human adolescence led to increased voluntary alcohol intake as adults [88], an outcome associated with epigenetic changes in the frontal cortex, striatum, and nucleus accumbens, as well as decreased dopamine expression in dopamine receptors 1 and 2. This suggests that epigenetic changes in adolescents contribute to long-lasting neurobiological consequences associated with early life ethanol administration by causing brain region–specific changes in signaling and neuroplasticity [88].

Research findings for drug abuse yield a similar pattern. Emerging data suggest that epigenetic regulation may be the molecular basis of drug-induced changes in gene expression in brain reward regions, contributing to the lasting neural and behavioral plasticity that underlies addiction [89]. Recreational drugs activate neural reward centers, such as the mesolimbic dopamine system, exerting rapid effects on behavior. For example, transient increases in members of the transcription factor Fos family are observed on acute exposure to drugs of abuse [90]. The expression of transcription factor FosB in neurons has led to the theory that it plays a significant role in the onset of addiction [91–93]. Manipulation of these genes in rodent models has been associated with the regulation of drug relapse behavior [92,94–96]. In short, epigenetic changes mediated by the interaction of inherited predispositions, environmental stimuli, and exposure to drugs can trigger long-lasting alterations in gene expression that influence susceptibility to addictive behaviors [97].

Table 2
Examples of genes involved in the regulation of adipogenesis, glucose homeostasis, inflammation, and/or insulin signaling

Gene name	Abbreviation	Chr[a]	Pathway	Reference
Peroxisome proliferator–activated receptor γ	PPARG	3	PPAR signaling pathway	70,74
The adipose most abundant transcript 1	apM1	3	Adipocytokine signaling pathway	75
Fatty acid-binding protein 4	FABP4	4	PPAR signaling pathway	70
Tumor necrosis factor	TNF	6	Apoptosis and autophagy	76
Leptin	LEP	7	Adipocytokine signaling pathway	58
Lipoprotein lipase	LPL	8	PPAR signaling pathway	70
Insulin	INS	11	Insulin signaling pathway	71,69
Glucose transporter	GLUT4	17	Insulin signaling pathway	73
Melanin-concentrating hormone receptor 1	MCHR1	22	G protein-coupled receptor signaling	72
Fat mass and obesity associated	FTO	16	Regulation of lipid storage	77

[a] Chr = chromosome.

Opportunities for Research and the Early Prevention of Chronic Disease

Epigenetics as a biological mechanism of the early life origin of disease

To date, few longitudinal studies have been designed to examine the role of epigenetic alterations in relation to early life adversities and the development of chronic noncommunicable diseases. Given the rising prevalence and burgeoning economic costs of noncommunicable diseases such as obesity and psychiatric illness worldwide, it is critical to harness cutting-edge research to examine the many important questions that remain unanswered. For example, to what degree do early life adversities (e.g., nutrition, stress, abuse, smoking, endocrine disrupters, and sleep) affect the epigenome? What are the critical time windows for imprinting, metabolic reprogramming, and epigenomic reversibility? Which early life risk factors are most closely linked to epigenetic alterations, and are biologically embedded to cause lifelong or even transgenerational consequences? How can we apply new scientific evidence and knowledge, and in particular, information related to critical time windows of developmental reprogramming, and reversibility of the epigenome to transform our approach to research and prevention of chronic diseases? Longitudinal birth cohort studies harnessing the expertise of interdisciplinary researchers are critically needed to identify links among community and family influences, early life adversities, genetics, epigenomic alterations, and the development of chronic diseases in children and adolescents. Such multilevel research has the potential to provide important insight into the biological mechanisms by which environmental exposures affect growth, development, and diseases over a life course and across generations.

Epigenetics and translational medicine

Much of the excitement surrounding epigenetics today relates to the reversible nature of epigenetic alterations and the promise of therapies that may restore the "normal epigenome" by activating or silencing disease-related genes. For example, two epigenetic drugs that reactivate tumor suppressor genes have recently received approval of the Food and Drug Administration [98,99], highlighting the tremendous promise of translational medicine through mapping and understanding epigenetic mechanisms. Translational epigenetic research in children's health is a reiterative process that ranges from research in the basic sciences to preclinical research and pediatric clinical research. Applying the latest scientific discoveries and subsequent clinical studies in pediatric and later years, we have the potential to maximize the impact of newly developed and tested interventions across the life span, preventing childhood and adult onset of disease by identifying risk at a very young age. This may allow clinicians to deliver targeted counteractive measures before symptoms of the disease become manifest. For example, identifying the epigenetic consequences of fetal programming creates potential applications in clinical practice: the development of epigenetic biomarkers for early diagnosis of disease, the ability to identify susceptible individuals at risk for adult diseases, and the development of novel preventive and curative measures that are based on diet, exercise, and/or novel epigenetic drugs [100].The completion of the human genome and epigenome projects will enhance our understanding of the genetics and epigenetics underlying growth, development, health, and disease. At present, genome-wide association study (GWAS) is the most powerful tool we have for dissecting the genetic basis of complex human diseases. GWAS to date have led to the identification of important susceptibility genes; however, we still lack a complete understanding of the global architecture of genetic and epigenetic regulatory networks that lead to the development of complex human diseases. It is anticipated that epigenomic studies in conjunction with GWAS will help us gain important new insight into the interrelationships between early life exposures, epigenetic alterations, and the development of chronic diseases: data that can ultimately be harnessed in clinical settings for preventative purposes [101,102].

Although there are significant costs associated with conducting genomic and epigenetic research, sequencing prices are dropping precipitously. The commensurate decreases in cost and increases in processing speed will greatly bolster the time and cost efficiencies involved in gathering this critically needed data. Falling costs and increasing efficiencies notwithstanding, it is important to consider that effective translation of epigenetic data into clinical settings will require a sizeable investment, although the timeline for the return on this investment is as yet unclear. However, the tremendous potential for epigenetic research to provide valuable translational data, which will allow the medical community to understand, treat, and ultimately prevent chronic disease, makes the long-term investment not only worthwhile but essential. For economic reasons, investment and research related to these technologies will be led primarily by developed countries. However, the ultimate aim is to reach a milestone where economic benefits outweigh the costs, which will spur translation into clinical settings, bolstering health outcomes and quality of life in developed and underdeveloped countries alike.

Interdisciplinary and international collaborations to advance 21st century medicine and public health

The rapid advancement in biomedical research and biotechnologies has offered unprecedented opportunities to improve human health in developing countries. Although it remains a tremendous challenge to translate these advancements into practice, it is critical that we strive for lofty short- and long-term goals. Although we have learned to treat disease, using increasingly sophisticated technologies and agents, we lack a pragmatic understanding of how to prevent it. "P4 Medicine" with each P representing predictive, preventive, personalized, and participatory, is the optimal, if ambitious, direction for 21st century medicine and public health.

Our ability to predict future risk will be greatly improved by combining information related to genetic susceptibility, environmental exposures, GxE interactions, and epigenetic and biochemical markers. Accurate early prediction is a key to preemptive prevention, a strategy that emphasizes using biomarkers at the earliest possible point to identify susceptible populations and initiate preventative strategies before the onset of disease, that is, at the preclinical stage. By shifting the timing of our focus from clinical disease to preclinical precursors, we will be able to move toward the ultimate goal of 21st century medicine—preventing and intervening before the onset of clinical disease. By doing so, we will be able to improve child and adolescent health, population health and quality of life, and thereby reduce health care costs.

This vision is not without challenges; however, despite the many scientific, social, regulatory, political, and economic difficulties, broad-reaching agencies such as the Food and Drug Administration and National Institutes of Health have placed high priority on the use of biological data to optimize health outcomes and the effectiveness of public health policy [103]. Although this article uses the noncommunicable diseases of obesity and psychiatric illness as examples, we must consider individual biological characteristics and how they interact with accrued environmental experiences over critical time windows to move the field forward. These types of complex studies will also require novel study designs, including large longitudinal birth cohorts, multilevel and multi-faceted data collection, and innovative analytical methods, to be effective. Understanding the etiology of chronic diseases will require massive data sets generated from -omics research and close collaborations among investigators from many disciplines, across the country and around the globe.

Summary

In light of the increasing threats of chronic noncommunicable diseases in developing countries, the growing recognition of early life origins of disease, and the remarkable breakthroughs in biomedical research and technology, a new approach to health promotion and maintenance in developing countries needs to be explored and developed. The new focus must be on shifting the timing of our interventions from clinical disease to preclinical precursors, to allow us to prevent and/or intervene before the onset of clinical disease. This approach places great emphasis on women's and children's health, and underscores the importance of early risk assessment, identification, and prevention.

It is well recognized that chronic diseases are complex traits that are affected by a wide range of environmental and genetic factors. In contrast, the role of epigenetic factors, particularly with regard to early life origins of chronic disease, remains largely unexplored. Evidence from animal models and human studies implicates the intrauterine period as a most sensitive time for the establishment of epigenetic variability, which in turn influences development, cell- and tissue-specific gene expression, sexual dimorphism, and risk for a range of disorders that can develop later in life. Given the unique properties of the epigenome—critical time windows, heritability, and reversibility—and its relation to gene expression and environmental factors, a deeper understanding of epigenetic mechanisms could offer important new opportunities for the development of a novel early prediction and prevention paradigm. We expect that this new paradigm holds the promise to develop cost-effective prevention and intervention strategies, but may also help break vicious lifelong and transgenerational cycles of chronic noncommunicable disease. Pediatricians and maternal and child health professionals have an unprecedented opportunity to play an important role in predicting, detecting, and preventing disease at an early age, long before its clinical occurrence. In doing so, great strides can be made in maternal and child health as well as population health, to ultimately enhance quality of life and reduce health care costs in developing countries.

References

[1] Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. N Engl J Med 2008;359:61–73.
[2] Bhargava SK, Sachdev HS, Fall CH, et al. Relation of serial changes in childhood body-mass index to impaired glucose tolerance in young adulthood. N Engl J Med 2004;350:865–75.
[3] Barker DJP. Fetal and Infant Origins of Adult Disease. London: BMJ Books, 1992.
[4] Dietz WH. Overweight in childhood and adolescence. N Engl J Med 2004;350:855–7.
[5] Petronis A, Gottesman II, Kan P, et al. Monozygotic twins exhibit numerous epigenetic differences: Clues to twin discordance? Schizophr Bull 2003;29:169–78.
[6] Bjornsson HT, Sigurdsson MI, Fallin MD, et al. Intra-individual change over time in DNA methylation with familial clustering. JAMA 2008;299:2877–83.
[7] Ollikainen M, Smith KR, Joo EJ, et al. DNA methylation analysis of multiple tissues from newborn twins reveals both genetic and intrauterine components to variation in the human neonatal epigenome. Hum Mol Genet 2010;19:4176–88.
[8] Kermack WO, McKendrick AG, McKinlay PL. Death-rates in Great Britain and Sweden: Expression of specific mortality rates as products of two factors, and some consequences thereof. J Hyg (Lond) 1934;34:433–57.
[9] Neel JV. Diabetes mellitus: A "thrifty" genotype rendered detrimental by "progress"? Am J Hum Genet 1962;14:353–62.
[10] Forsdahl A. Are poor living conditions in childhood and adolescence an important risk factor for arteriosclerotic heart disease? Br J Prev Soc Med 1977;31:91–5.
[11] Barker DJ. The intrauterine origins of cardiovascular and obstructive lung disease in adult life. The Marc Daniels lecture 1990. J R Coll Physicians Lond 1991;25:129–33.
[12] Hales CN, Barker DJ, Clark PM, et al. Fetal and infant growth and impaired glucose tolerance at age 64. BMJ 1991;303:1019–22.
[13] Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: The thrifty phenotype hypothesis. Diabetologia 1992;35:595–601.
[14] Shekhawat PS, Garland JS, Shivpuri C, et al. Neonatal cord blood leptin: Its relationship to birth weight, body mass index, maternal diabetes, and steroids. Pediatr Res 1998;43:338–43.
[15] Lepercq J, Lahlou N, Timsit J, et al. Macrosomia revisited: Ponderal index and leptin delineate subtypes of fetal overgrowth. Am J Obstet Gynecol 1999;181:621–5.
[16] Wiznitzer A, Furman B, Zuili I, et al. Cord leptin level and fetal macrosomia. Obstet Gynecol 2000;96:707–13.
[17] Lazar MA. How obesity causes diabetes: Not a tall tale. Science 2005;307:373–5.
[18] Prentice AM, Rayco-Solon P, Moore SE. Insights from the developing world: Thrifty genotypes and thrifty phenotypes. Proc Nutr Soc 2005;64:153–61.
[19] Parsons TJ, Power C, Manor O. Fetal and early life growth and body mass index from birth to early adulthood in 1958 British cohort: Longitudinal study. BMJ 2001;323:1331–5.
[20] Sørensen HT, Sabroe S, Rothman KJ, et al. Relation between weight and length at birth and body mass index in young adulthood: Cohort study. BMJ 1997;315:1137.
[21] Silverman BL, Rizzo T, Green OC, et al. Long-term prospective evaluation of offspring of diabetic mothers. Diabetes 1991;40(Suppl 2):121–5.
[22] Law CM, Barker DJ, Osmond C, et al. Early growth and abdominal fatness in adult life. J Epidemiol Community Health 1992;46:184–6.
[23] Loos RJ, Beunen G, Fagard R, et al. Birth weight and body composition in young adult men–A prospective twin study. Int J Obes Relat Metab Disord 2001;25:1537–45.
[24] Loos RJ, Beunen G, Fagard R, et al. Birth weight and body composition in young women: A prospective twin study. Am J Clin Nutr 2002;75:676–82.
[25] Ravelli GP, Stein ZA, Susser MW. Obesity in young men after famine exposure in utero and early infancy. N Engl J Med 1976;295:349–53.
[26] Hellerstedt WL, Himes JH, Story M, et al. The effects of cigarette smoking and gestational weight change on birth outcomes in obese and normal-weight women. Am J Public Health 1997;87:591–6.
[27] Wang X, Tager IB, Van Vunakis H, et al. Maternal smoking during pregnancy, urine cotinine concentrations, and birth outcomes. A prospective cohort study. Int J Epidemiol 1997;26:978–88.
[28] Widerøe M, Vik T, Jacobsen G, Bakketeig LS. Does maternal smoking during pregnancy cause childhood overweight? Paediatr Perinat Epidemiol 2003;17:171–9.
[29] Wang X, Zuckerman B, Pearson C, et al. Maternal cigarette smoking, metabolic gene polymorphism, and infant birth weight. JAMA 2002;287:195–202.
[30] Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, et al. Endocrine-disrupting chemicals: An Endocrine Society scientific statement. Endocr Rev 2009;30:293–342.
[31] Newbold RR, Padilla-Banks E, Snyder RJ, Phillips TM, Jefferson WN. Developmental exposure to endocrine disruptors and the obesity epidemic. Reprod Toxicol 2007;23:290–6.

[32] Verhulst SL, Nelen V, Hond ED, et al. Intrauterine exposure to environmental pollutants and body mass index during the first 3 years of life. Environ Health Perspect 2009;117:122–6.
[33] Gladen BC, Ragan NB, Rogan WJ. Pubertal growth and development and prenatal and lactational exposure to polychlorinated biphenyls and dichlorodiphenyl dichloroethene. J Pediatr 2000;136:490–6.
[34] Edwards TM, Myers JP. Environmental exposures and gene regulation in disease etiology. Environ Health Perspect 2007;115:1264–70.
[35] Feinberg AP. Epigenetics at the epicenter of modern medicine. JAMA 2008; 299:1345–50.
[36] Boks MP, Derks EM, Weisenberger DJ, et al. The relationship of DNA methylation with age, gender and genotype in twins and healthy controls. PLoS One 2009;4:e6767.
[37] El-Maarri O, Becker T, Junen J, et al. Gender specific differences in levels of DNA methylation at selected loci from human total blood: A tendency toward higher methylation levels in males. Hum Genet 2007;122:505–14.
[38] Liu J, Morgan M, Hutchison K, Calhoun VD. A study of the influence of sex on genome wide methylation. PLoS One 2010;5:e10028.
[39] Christensen BC, Houseman EA, Marsit CJ, et al. Aging and environmental exposures alter tissue-specific DNA methylation dependent upon CpG island context. PLoS Genet 2009;5:e1000602
[40] Madrigano J, Baccarelli A, Mittleman MA, et al. Prolonged exposure to particulate pollution, genes associated with glutathione pathways, and DNA methylation in a cohort of older men. Environ Health Perspect 2011; 119:977–82.
[41] Bogdarina I, Welham S, King PJ, et al. Epigenetic modification of the renin-angiotensin system in the fetal programming of hypertension. Circ Res 2007;100:520–6.
[42] Tosh DN, Fu Q, Callaway CW, et al. Epigenetics of programmed obesity: Alteration in IUGR rat hepatic IGF1 mRNA expression and histone structure in rapid vs. delayed postnatal catch-up growth. Am J Physiol Gastrointest Liver Physiol 2010;299:G1023–9.
[43] Dolinoy DC, Huang D, Jirtle RL. Maternal nutrient supplementation counteracts bisphenol A-induced DNA hypomethylation in early development. Proc Natl Acad Sci U S A 2007;104:13056–61.
[44] Bromer JG, Zhou Y, Taylor MB, et al. Bisphenol-A exposure in utero leads to epigenetic alterations in the developmental programming of uterine estrogen response. FASEB J 2010;24:2273–80.
[45] Ho SM, Tang WY, Belmonte de Frausto J, Prins GS. Developmental exposure to estradiol and bisphenol A increases susceptibility to prostate carcinogenesis and epigenetically regulates phosphodiesterase type 4 variant 4. Cancer Res 2006;66:5624–32.
[46] Chen J, Liufu C, Sun W, et al. Assessment of the neurotoxic mechanisms of decabrominated diphenyl ether (PBDE-209) in primary cultured neonatal rat hippocampal neurons includes alterations in second messenger signaling and oxidative stress. Toxicol Lett 2010;192:431–9.
[47] Desaulniers D, Xiao GH, Lian H, et al. Effects of mixtures of polychlorinated biphenyls, methylmercury, and organochlorine pesticides on hepatic DNA methylation in prepubertal female Sprague-Dawley rats. Int J Toxicol 2009;28:294–307.
[48] Waterland RA, Garza C. Potential mechanisms of metabolic imprinting that lead to chronic disease. Am J Clin Nutr 1999;69:179–97.
[49] Bouchard L, Thibault S, Guay SP, et al. Leptin gene epigenetic adaptation to impaired glucose metabolism during pregnancy. Diabetes Care 2010;33: 2436–41.
[50] Milagro FI, Campión J, Cordero P, et al. A dual epigenomic approach for the search of obesity biomarkers: DNA methylation in relation to diet-induced weight loss. FASEB J 2011;25:1378–89.
[51] Stöger R. The thrifty epigenotype: An acquired and heritable predisposition for obesity and diabetes? Bioessays 2008;30:156–66.
[52] Reik W. Genomic imprinting and genetic disorders in man. Trends Genet 1989;5:331–6.
[53] Nicholls RD, Knoll JH, Butler MG, et al. Genetic imprinting suggested by maternal heterodisomy in nondeletion Prader-Willi syndrome. Nature 1989;342:281–5.
[54] Godfrey KM, Barker DJ. Fetal programming and adult health. Public Health Nutr 2001;4:611–24.
[55] Burdge GC, Slater-Jefferies J, Torrens C, et al. Dietary protein restriction of pregnant rats in the F0 generation induces altered methylation of hepatic gene promoters in the adult male offspring in the F1 and F2 generations. Br J Nutr 2007;97:435–9.
[56] Drake AJ, Walker BR, Seckl JR. Intergenerational consequences of fetal programming by in utero exposure to glucocorticoids in rats. Am J Physiol Regul Integr Comp Physiol 2005;288:R34–8.
[57] Widiker S, Karst S, Wagener A, Brockmann GA. High-fat diet leads to a decreased methylation of the Mc4r gene in the obese BFMI and the lean B6 mouse lines. J Appl Genet 2010;51:193–7.
[58] Milagro FI, Campión J, García-Díaz DF, et al. High fat diet-induced obesity modifies the methylation pattern of leptin promoter in rats. J Physiol Biochem 2009;65:1–9.
[59] Plagemann A, Harder T, Brunn M, et al. Hypothalamic proopiomelanocortin promoter methylation becomes altered by early overfeeding: An epigenetic model of obesity and the metabolic syndrome. J Physiol 2009;587: 4963–76.
[60] Godfrey KM, Sheppard A, Gluckman PD, et al. Epigenetic gene promoter methylation at birth is associated with child's later adiposity. Diabetes 2011;60:1528–34.
[61] Heijmans BT, Tobi EW, Stein AD, et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. Proc Natl Acad Sci U S A 2008;105:17046–9.
[62] Gong L, Pan YX, Chen H. Gestational low protein diet in the rat mediates IGF2 gene expression in male offspring via altered hepatic DNA methylation. Epigenetics 2010;5:619–26.
[63] Tobi EW, Lumey LH, Talens RP, et al. DNA methylation differences after exposure to prenatal famine are common and timing- and sex-specific. Hum Mol Genet 2009;18:4046–53.
[64] Waterland RA. Epigenetic epidemiology of obesity: Application of epigenomic technology. Nutr Rev 2008;66(Suppl 1):S21–3.
[65] Kim M, Long TI, Arakawa K, et al. DNA methylation as a biomarker for cardiovascular disease risk. PLoS One 2010;5:e9692.
[66] Wang X, Zhu H, Snieder H, et al. Obesity related methylation changes in DNA of peripheral blood leukocytes. BMC Med 2010;8:87.
[67] Aasheim ET, Hofsø D, Hjelmesaeth J, et al. Vitamin status in morbidly obese patients: A cross-sectional study. Am J Clin Nutr 2008;87:362–9.
[68] Weinstein LS, Xie T, Qasem A, et al. The role of GNAS and other imprinted genes in the development of obesity. Int J Obes (Lond) 2010;34:6–17.
[69] Yang BT, Dayeh TA, Kirkpatrick CL, et al. Insulin promoter DNA methylation correlates negatively with insulin gene expression and positively with HbA(1c) levels in human pancreatic islets. Diabetologia 2011;54: 360–7.
[70] Noer A, Boquest AC, Collas P. Dynamics of adipogenic promoter DNA methylation during clonal culture of human adipose stem cells to senescence. BMC Cell Biol 2007;8:18.
[71] Kuroda A, Rauch TA, Todorov I, et al. Insulin gene expression is regulated by DNA methylation. PLoS One 2009;4:e6953.
[72] Stepanow S, Reichwald K, Huse K, et al. Allele-specific, age-dependent and BMI-associated DNA methylation of human MCHR1. PLoS One 2011;6: e17711.
[73] Yokomori N, Tawata M, Onaya T. DNA demethylation during the differentiation of 3T3-L1 cells affects the expression of the mouse GLUT4 gene. Diabetes 1999;48:685–90.
[74] Fujiki K, Kano F, Shiota K, Murata M. Expression of the peroxisome proliferator activated receptor gamma gene is repressed by DNA methylation in visceral adipose tissue of mouse models of diabetes. BMC Biol 2009;7:38.
[75] Musri MM, Corominola H, Casamitjana R, et al. Histone H3 lysine 4 dimethylation signals the transcriptional competence of the adiponectin promoter in preadipocytes. J Biol Chem 2006;281:17180–8.
[76] Sullivan KE, Reddy AB, Dietzmann K, et al. Epigenetic regulation of tumor necrosis factor alpha. Mol Cell Biol 2007;27:5147–60.
[77] Kilpeläinen TO, Zillikens MC, Stančákova A, et al. Genetic variation near IRS1 associates with reduced adiposity and an impaired metabolic profile. Nat Genet 2011;43:753–60.
[78] Tateishi K, Okada Y, Kallin EM, Zhang Y. Role of Jhdm2a in regulating metabolic gene expression and obesity resistance. Nature 2009;458: 757–61.
[79] Inagaki T, Tachibana M, Magoori K, et al. Obesity and metabolic syndrome in histone demethylase JHDM2a-deficient mice. Genes Cells 2009;14: 991–1001.
[80] Ortega FJ, Moreno-Navarrete JM, Pardo G, et al. MiRNA expression profile of human subcutaneous adipose and during adipocyte differentiation. PLoS One 2010;5:e9022.
[81] Meaney MJ. Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. Annu Rev Neurosci 2001;24:1161–92.
[82] Binder EB, Bradley RG, Liu W, et al. Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. JAMA 2008;299:1291–305.
[83] Bradley RG, Binder EB, Epstein MP, et al. Influence of child abuse on adult depression: Moderation by the corticotropin-releasing hormone receptor gene. Arch Gen Psychiatry 2008;65:190–200.
[84] McGowan PO, Sasaki A, D'Alessio AC, et al. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nat Neurosci 2009;12:342–8.
[85] Enoch MA. The role of early life stress as a predictor for alcohol and drug dependence. Psychopharmacol (Berl) 2011;214:17–31.
[86] Bönsch D, Lenz B, Reulbach U, et al. Homocysteine associated genomic DNA hypermethylation in patients with chronic alcoholism. J Neural Transm 2004;111:1611–6.
[87] Black YD, Maclaren FR, Naydenov AV, et al. Altered attention and prefrontal cortex gene expression in rats after binge-like exposure to cocaine during adolescence. J Neurosci 2006;26:9656–65.

[88] Pascual M, Boix J, Felipo V, Guerri C. Repeated alcohol administration during adolescence causes changes in the mesolimbic dopaminergic and glutamatergic systems and promotes alcohol intake in the adult rat. J Neurochem 2009;108:920–31.
[89] Colvis CM, Pollock JD, Goodman RH, et al. Epigenetic mechanisms and gene networks in the nervous system. J Neurosci 2005;25:10379–89.
[90] Nestler EJ, Barrot M, Self DW, DeltaFosB: A sustained molecular switch for addiction. Proc Natl Acad Sci U S A 2001;98:11042–6.
[91] Kalivas PW, O'Brien C. Drug addiction as a pathology of staged neuroplasticity. Neuropsychopharmacology 2008;33:166–80.
[92] Bowers MS, McFarland K, Lake RW, et al. Activator of G protein signaling 3: A gatekeeper of cocaine sensitization and drug seeking. Neuron 2004;42:269–81.
[93] McClung CA, Ulery PG, Perrotti LI, et al. DeltaFosB: A molecular switch for long-term adaptation in the brain. Brain Res Mol Brain Res 2004;132:146–54.
[94] Graham DL, Edwards S, Bachtell RK, et al. Dynamic BDNF activity in nucleus accumbens with cocaine use increases self-administration and relapse. Nat Neurosci 2007;10:1029–37.
[95] Grimm JW, Lu L, Hayashi T, et al. Time-dependent increases in brain-derived neurotrophic factor protein levels within the mesolimbic dopamine system after withdrawal from cocaine: Implications for incubation of cocaine craving. J Neurosci 2003;23:742–7.
[96] Lu L, Dempsey J, Liu SY, et al. A single infusion of brain-derived neurotrophic factor into the ventral tegmental area induces long-lasting potentiation of cocaine seeking after withdrawal. J Neurosci 2004;24:1604–11.
[97] Wong CC, Mill J, Fernandes C. Drugs and addiction: An introduction to epigenetics. Addiction 2011;106:480–9.
[98] Sharma S, Kelly TK, Jones PA. Epigenetics in cancer. Carcinogenesis 2010;31:27–36.
[99] Kaminskas E, Farrell A, Abraham S, et al. Approval summary: Azacitidine for treatment of myelodysplastic syndrome subtypes. Clin Cancer Res 2005;11:3604–8.
[100] Hochberg Z, Feil R, Constancia M, et al. Child health, developmental plasticity, and epigenetic programming. Endocr Rev 2011;32:159–224.
[101] Bjornsson HT, Fallin MD, Feinberg AP. An integrated epigenetic and genetic approach to common human disease. Trends Genet 2004;20:350–8.
[102] Butcher LM, Beck S. Future impact of integrated high-throughput methylome analyses on human health and disease. J Genet Genomics 2008;35:391–401.
[103] Hamburg MA, Collins FS. The path to personalized medicine. N Engl J Med 2010;363:301–4.