A Brief Introduction to the Exposome and Human Health

Mark D Lucock*

School of Environmental & Life Sciences, University of Newcastle, Ourimbah, New South Wales, Australia

Received: November 26, 2020 | Revised: December 9, 2020 | Accepted: December 10, 2020 | Published: December 23, 2020

Abstract

The exposome refers to all environmental exposures (internal and specific/general external) that humans experience from conception through to death. This article examines the importance of both fundamental biological and public health perspectives within the context of the exposome, dealing with novel and well recognized concepts that include exposotype, issues of life stage/aging, and both short (epigenetic) and long-term (evolutionary) biological effects. The problem of scale, use of omics technology and database resources are also discussed. A special focus is also placed on the role of the ultraviolet light exposome in regard to the photolysis of folate and biosynthesis of vitamin D as important molecular mechanisms within human health and biology. Specifically, this includes critical nutrient genetic interactions. High-dimensional biology will permit extremely large scale initiatives in the future that will shed new light on the exposome by better characterizing a plethora of new and established biomarkers. However, smaller, delimited studies should not be ignored, as they can still help define aspects of the human exposome that remain unclear. Still, overall trends in the field are moving inexorably towards multiplexing metabolite and other omic analyses within large population studies. This article aims to reinforce the importance of exposomics via the idea, a fundamental tenet of biology, that human phenotype results from an amalgamation of genes and environment. What needs to be recognized is that phenotypes can be either adaptive or maladaptive. Within our phenome this process propagates disease or provides evolutionary advantage. In other words, the exposome is about more than simply public health.

Keywords: Exposome; Environment; Biomarkers; Vitamins; Epigenetics; Evolution.

Introduction

The exposome is a relatively new concept in health science that was initially laid out by Chris Wild in 2005. Few would deny that it represents a critically important field of study given the degree of negative anthropogenic change humanity is now subjected to. The exposome is broadly defined as “all environmental exposures that a person experiences from conception to death”, and is thus an extraordinarily wide topic to get to grips with from a health perspective.

This enormous breadth poses significant conceptual and analytical problems to scientists. Initially, the concept was intended to promote a wider assessment of exposure in epidemiological studies via the discovery of novel biomarkers that act as potential indicators of environmental influence on human health. The term “environmental” specifically implies non-genetic factors, although there is a clear need for genomic data to be integrated with exposomal information to allow for the most comprehensive understanding of how environmental exposures impact human biology over the life span. Therefore, temporal factors are also critical, with exposures possible during pregnancy, infancy, childhood, adolescence, adulthood and in old age.

To facilitate a better understanding of the exposome concept, Wild describes three non-genomic categories for evaluation: a) internal (endogenous), b) specific external and c) general external. These categories are fairly self-explanatory with internal exposomal factors encompassing hormones, oxidative challenges, inflammatory factors, allostatic load, microbiota, metabolism etc. Specific external factors are more varied and include electromagnetic radiation, pathogens, essential and non-essential dietary factors such as vitamins (indeed all food), environmental chemicals...
Lucock M.D. et al: The exposome and human health

The exposome and human health

Explor Res Hypothesis Med

Lucock M.D. et al:
The exposome and human health

DOI: 10.14218/ERHM.2020.00070  |  Volume 6 Issue 1, March 2021 19

and pollutants, noise and a vast array of lifestyle factors such as tobacco, betel nut, alcohol, caffeine, pharmacologic agents, phytochemicals and other xenobiotic substances. The general external factors are broad and embrace social, economic and psychological influences. Something as simple as where you live (geography) might be critical if you live in a polluted city or in one at high latitude where low seasonal ultraviolet light (UV) levels limit vitamin D synthesis. These three non-genomic categories exhibit obvious overlap—allotastic load is a consequence of stress, but manifests itself via metabolism, so categories a) and c) overlap. Anthropogenic climate change and its sequelae fit into all three categories (a–c).

With such a complex topic as the exposome, this partitioning is quite useful in organising important aspects within a human biology perspective (see Fig. 1).

The field of exposomics has evolved quite rapidly over the past decade and a half, and reflects ever greater complexity given recent exponential advances in omics technologies. As a topic, the exposome is critically important, yet at the time of writing this article (8th December 2020) a search of PubMed using the term “exposome” generated a mere 873 published articles. Despite this, recognition of the true importance of this field is emerging; a recent 2020 article in the journal Science states that given increased recognition of the dominant role that non-genetic factors play in disease, an effort to characterize the exposome at a scale comparable to that of the human genome is justified.

The problem of scale

The exposome is easy to conceptualize at its broadest level, but complexity/depth of information make it challenging to take a holistic approach whereby exposomal components are seen as being intimately interconnected within a human biology paradigm that is only explicable by reference to the whole. It is far easier to focus on individual component details (a delimited system), rather than adopting holism. Having said that, the tools are now becoming available to help quantify the chemicals we are exposed to and the metabolic profiles that ensue. Genomics (particularly the role of common polymorphisms), epigenomics, proteomics, transcriptomics, pharmacogenomics, nutrigenomics, lipidomics, metabolomics and fluxomics are all omic tools that are now mature technologies, and are therefore poised to greatly influence this field as the age of bioinformatics and big data moves forward. An insightful, holistic view of the impact of different facets within the exposome will transpire, indeed, we are now looking at the application of high-dimensional biology to environmental health modeling. Despite this, there are examples of simpler, delimited systems involving our exposome that are worthy of examination with respect to human biology, and which are elegant in their exposition (see below).

From genotype and phenotype to exposotype

High-dimension biology using a variety of omic technologies can now elucidate downstream biological changes that accrue and characterize the human exposure phenotype. This exposure phenotype derived from a specific exposure event has been referred to as an “exposotype”. By blending genotype, proteomics and metabolomic data (along with other information such as life stage, etc.), with detailed environmental exposure information, a route to understanding the molecular mechanisms that define specific exposotypes is possible. A good example of this would be that during the periconceptional period, a woman with elevated retinoids (vitamin A and/or synthetic analogues) due to treatment for skin complaints is more likely to experience a congenital malformation (e.g. neural crest/limb deformities) if she becomes pregnant. This mechanism is directly related to impaired HOX gene function during embryogenesis. Exposure can also mean deficit, although this term usually implies excess. A shortage of folic acid during this same time frame leads to a neural tube defect (NTD)-affected pregnancy (i.e. spina bifida). It has been established that several
genotypes can modify the occurrence and help define this exposome. The best example is the possession of the 677TT-MTHFR genotype, which increases the risk of NTD, as do other factors such as exposure to certain pharmacologic agents, for example, valproic acid.\textsuperscript{11,12}

Upstream processes that involve genes, transcription and proteins all contribute to the generation of metabolites. Being end-products, metabolites are therefore perhaps closest to phenotype, and where concomitant xenobiotics are present, it becomes possible to begin defining exposotype. In fact, this underscores the science of metabolomics.

Potential systemic xenobiotics cover an enormous array of chemicals; from air pollutants to aflatoxins in food. However, as will be discussed in a later section, human exposure to physical factors such as temperature, UV light, day length, and season also influence human biology and help characterize exposotype.

Cornucopia of data

As might be expected, identifying a vast array of metabolites is challenging and is a rate-limiting factor to fully opening up this field. Fortunately, many databases are available for this purpose: The Human Metabolome Database (HMDB) is freely available and contains information about small molecule metabolites found in the human body (http://www.hmdb.ca/metabolites). The HMDB is intended to be used for applications in metabolomics, clinical chemistry, biomarker discovery and general education. It provides three kinds of data: 1) chemical data, 2) clinical data, and 3) molecular biology/biochemistry data. The database contains 114,260 metabolite entries. Four extra databases, namely DrugBank (2,280 drugs/metabolites), Toxic Exposome Database-toxin and toxin target database (3,670 toxins/environmental pollutants), small molecule pathway database (25,000 human metabolic disease pathways) and FooDB (28,000 food components/additives) are part of the HMDB suite. Many other high-quality resources are also available. The Distributed Structure-Searchable Toxicity (DSTox) database provides a high-quality public chemistry resource for supporting improved predictive toxicology (https://www.epa.gov/chemical-research/distributed-structure-searchable-toxicity-dsstox-database), while the Exposome-Explorer database provides details on biomarkers of exposure to environmental risk factors related to disease (http://exposome-explorer.iarc.fr/). One of the largest data repositories is PubChem (https://pubchem.ncbi.nlm.nih.gov/), which is an open chemistry database at the National Institute of Health. It contains small molecules, but also larger ones (i.e., nucleotides, carbohydrates, lipids and peptides) and chemically modified macromolecules. PubChem acts as a repository of chemical structures, identifiers, chemical and physical properties, biological activities, patents, health, safety, toxicity data, and more. Another aspect adding to the complexity of this information involves recent advances in the human microbiome, a key internal exposomal factor. A relationship has been established between certain microbial signatures in the gastrointestinal tract and risk of diseases and maladapted phenotypes such as obesity. However, other dietary and biological factors are also thought to modify the microbiome, adding yet further complexity.\textsuperscript{13,14}

While databases and tools do exist, there are the usual confounding issues at play. Such issues involve controlling for biological variance (diet, sex, body mass index, risk factors, exposure risk, temporal factors, gene-environment interactions, circadian rhythm, and the sheer number of known genomic single nucleotide polymorphisms [SNPs], etc.), as well as analytical variance (sampling time and storage, sample processing technique, lack of harmonization with respect to the type and use of instrumentation, and available compound library, etc.).

**Lifecycle considerations**

Early lifecycle events are critical to future health outcomes. The embryo and fetus are particularly vulnerable to environmental exposure. There are critical windows in utero where environmental stressors can disrupt or deflect the normal developmental trajectory, and hence “hard wire” changes in body structures, metabolism and physiology that can lead to a potential maladaptation to postpartum life in well nourished, developed societies. This has been shown to lead to chronic pathologies in later life. Indeed, this scenario is a major element within the Developmental Origins of Health and Disease (DOHaD) paradigm. This paradigm is most often linked to prenatal diet, but evidence shows that air pollution and other environmental contaminants also impact fetal growth,\textsuperscript{15,16} with outcomes that influence individuals over their entire life span.\textsuperscript{17–19} It therefore seems likely that the “pregnancy exposome” is a critical starting point to life and hence an individual’s future health.\textsuperscript{17–19} By way of example, Tang and Ho\textsuperscript{20} examined epigenetic reprogramming and imprinting in the origin of disease, and discuss at length how early life environmental exposures can promote cancers.

The molecular mechanisms at play are many fold, but a critical factor is the maintenance of the methylome (epigenome). Gene CpG methylation profiles are critical to gene regulation and hence the provision of methyl groups is paramount. Dietary Methionine, methylfolate, vitamins B\textsubscript{12}, B\textsubscript{6} and B\textsubscript{2}, and choline are all critical in the provision of methyl groups, and any environmental exposure that modifies the availability of methyl groups is likely to have a significant impact. We now know that the provision of methyl groups is central to the DOHaD. In addition, several gene mutations and environmental factors interact with the methylome and hence, conspire to play an important role in human development.\textsuperscript{21}

It is important to note that environmental exposures can influence both germline and somatic cells via these types of molecular mechanisms.

Critical life stages extend beyond pregnancy and include lactation, infancy and late adulthood. All are subject to negative exposomal factors. Much has been written on this, particularly from a higher dimension perspective, so what follows are some thoughts on a simpler, yet important, delimited system, one that I have been fortunate enough to study for many years, and one that shifts perspective from more complex aspects of exposomal thinking.

**A novel example of a relatively delimited system**

The exposome is often discussed from a human health perspective, and this is fine. However, in truth it should also be considered from a human biology viewpoint. This is because environmental stressors can be adaptive as well as maladaptive. In that sense, they can contribute to evolutionarily adaptive phenotypes (one could argue a better term might be “adaptive exposotype”), and have acted over millennia to help shape human biology to the prevailing environmental conditions. Interestingly, the same environmental stressors can act over far shorter timescales (human lifespan) via their influence on epigenetic factors.

Both short-term human adaptation (epigenetic change) and long-term evolutionary change can occur due to variations in expo-
sure to key vitamins.\textsuperscript{2,21} The food exposome represents the total-
ity of dietary exposures,\textsuperscript{24} and is a substantial challenge to examine
due to the wide range of foods consumed and the variability in the
amount and frequency of intake, which are modulated by food
preference, season, and other factors.\textsuperscript{24} Fortunately, two vitamins
have such profound biological effects that their dietary abundance,
and physicochemical loss (folate) or biosynthesis (vitamin D)
through secondary environmental exposure (UV exposome) have
shaped the human phenotype from both evolutionary and health per-
spectives. Hence, these vitamins provide a good model for delim-
ted exposome study.

Natural folate coenzymes are water-soluble vitamins, while D
vitamins (i.e., 1, 25-dihydroxycholecalciferol/calcitriol) are fat-
soluble, and are often considered to be more hormone than vita-
min. Although these vitamins are very different at a chemical and
biomolecular level, both these vitamin families participate in a
common area of human biology. They are critical to the functional
integrity of the genome and epigenome, and are also both respons-
tive to the UV exposome,\textsuperscript{25} although their response to the UV
exposome differs. Natural reduced folate vitamins such as 5-me-
thyldHfolate are destroyed by UV,\textsuperscript{25} while vitamin D\textsubscript{3} is photo-
synthesized in our skin via the action of UV.\textsuperscript{27,28} In the short-term,
this can affect methyl group availability for epigenomic methyla-
tion, and thus regulated gene expression.\textsuperscript{21} As an example, the
CpG methylation profile facilitates normal spermatogenesis and
embryogenesis, with dysregulation linked to a number of clinically
relevant phenotypes. As stated earlier, epigenetics is a fundamental
mechanism within the DOHaD paradigm,\textsuperscript{29,30} a burgeoning sub-
discipline that was born out of the Barker Hypothesis.\textsuperscript{31} Methyl-
folate is important because it supplies a pool of de novo methio-
nine, which represents 50\% of the total methionine requirement;\textsuperscript{21}
it follows that anything affecting the availability or stability of re-
duced folate coenzymes will alter the provision of methyl groups,
with potential epigenetic consequences. A shortage of folate can
also lead to restricted one-carbon unit flow into dTMP and hence
DNA synthesis. This one-carbon shortage can lead to DNA fragili-
ity and may be important during embryogenesis. Therapeutically,
it is also important in cancer occurrence where antifolate cancer
treatments such as 5-fluorouracil block thymidylate synthase and
restrict dTMP synthesis in rapidly growing cancer cells. A simi-
lar principle exists when using methotrexate as an abortifacient or
as a chemotherapeutic agent for treating cancer. This drug blocks
dihydrofolate reductase, an enzyme further upstream from dTMP
synthesis, but one that still ultimately blocks one-carbon units for
DNA synthesis. A simple dietary shortage of folate can also sup-
press erythropoiesis via impaired dTMP synthesis. One gene that
influences the metabolic flow of folate derived one-carbon units is
\textit{C677T-MTHFR}. This SNP modifies the partitioning of carbon
units towards de novo methionine for maintaining the methyholme
or dTMP for the fidelity of DNA synthesis,\textsuperscript{32} and shows the import-
tance of genotype in folate-related cell survival and programming.
Either of these processes may be relevant early in the lifecycle and
in the occurrence and treatment of cancer. Early lifecycle changes
to gene methylation profile have now been shown to extend into
adulthood, and help substantiate the molecular basis of the DO-
HaD, especially where methylation profile affects key genes. Pre-
natal exposure to famine (1944–45 Dutch Hunger Winter) led to
less DNA methylation of imprinted insulin-like growth factor gene
(IGF2) and increased methylation in leptin (LEP), interleukin 10
(\textit{IL10}) and other genes in famine subjects compared to unexposed
same sex siblings 60 years after the famine exposome occurred.\textsuperscript{33} Lifecycle duration epigenetic changes in key metabolic regulatory
genes indicate a mechanism through which very early life famine
exposure influences adult metabolism and disease phenotype.

Vitamin D is also critical to the epigenome. The vitamin D\textsubscript{3} act-
vated vitamin D receptor (VDR) binds to 20,000 genome-wide
sites within accessible chromatin. This epigenomic effect is sig-
nificant as it modifies the transcriptome by activating or repress-
ing vitamin D related target genes. Although vitamin D\textsubscript{3} initiated
VDR action potentially modulates the expression of many genes,
it includes important chromatin modifiers and remodelers, and in
this way, can influence the DNA methylation profile itself.\textsuperscript{34} Addi-
tionally, the gene encoding VDR is itself modulated by CpG meth-
ylation, with differential methylation in promoter regions control-
gene expression. Critically, since vitamin D\textsubscript{3} is a steroid
hormone, it acts like other hormones and is pivotal in promoting
plasticity, modulating vitamin D in providing a reproductive
outcomes in response to environmentally originated cues. Where
those cues are unequivocally part of the human exposome, as with
UV exposure, the consequences for human biology are significant.

As with the Dutch Hunger Winter famine described above, it is
also thought that early lifecycle UV exposure calibrates adult vita-
moln D metabolism, with evidence for a developmentally originated
vitamin D homeostat that may alter related adult phenotypes (vita-
moln D metabolism, adult height and osteoporosis risk).\textsuperscript{35}

While most health scientists tap into this concept from a disease/
wellness perspective, most likely within the DOHaD construct, far
longer-term adaptive effects occur that reflect an evolutionary time
scale. This is true for both folate and vitamin D.

An evolutionary multiplex of critical factors capable of adapting
human skin phototype to an altering UV exposome seems likely to
have occurred.\textsuperscript{36} UV breakdown (photolysis) of folate in the skin is
thought to have acted as a selection pressure for a darker skin pho-
totype at tropical latitudes where human ancestors first evolved.
Conversely, early humans migrating out of Africa likely required
less skin pigmentation to allow for adequate vitamin D photo-
synthesis in the skin. The premise for this evolved trait revolves
around the role of folate in mitosis, and vitamin D in providing a
reproductive advantage, whereby natural selection operates on skin phototype to
optimize folate stability and vitamin D synthesis according to the
prevailing solar regime.\textsuperscript{37,38} Ultimately, the UV exposome-folate-
vitamin D multiplex interacts with a cassette of polymorphic genes
that are known to be altered in the longer term to adapt the human
skin phototype to the prevailing UV exposome.\textsuperscript{22,23,26}

Future direction

The magnitude of the exposome humans experience is so large
that no single individual could ever embrace the entire discipline.
Sources of pollution in the air, sea and fresh water are immense
and variable; radiation can be overt as per the Chernobyl acci-
dent, or clinically important as in UV as a source of skin cancers
that include melanoma. Although I give a single delimited exam-
ple involving the UV wavelengths relevant to folate and vitamin
D biology to show the scope of the field of exposome research,
some of the best known environmental stressors include asbestos,
heavy metals like lead and mercury, halogenated and polybromi-
nated diphenyl ether (flame retardants), perfluorinated compounds
(non-stick coatings etc), phthalates (plasticizers), formaldehyde
and polychlorinated phenyl chloride (releases phthalates in use and dioxin when
burnt). Many of the issues allied to the exposome have even broader
implications in relation to, for example, climate change, and so
the only way forward is to adopt a multidisciplinary approach. Ex-
pertise needs to focus on higher dimensional biology that utilizes
the latest omic technologies, along with advanced data handling/
statistical analysis commensurate with the large pool of data gen-

DOI: 10.14218/ERHM.2020.00070 | Volume 6 Issue 1, March 2021 21
erated. Of course, genetic variation can be included or excluded in studies, and this is quite acceptable where exposure-disease relationships are clearly established. However, from a prospective exploratory viewpoint, the more complete the analysis, the better understanding will be gained. Ultimately, as part of any future direction, research on the exposome should be linked to molecular pathological epidemiology (MPE) and tissue biomarker research. MPE is a relatively new integrated science that aims to better understand the interplay between etiological factors, cellular molecular characteristics, and disease evolution, and may help to address aspects of personalized medicine and disease prevention.

An important point to make is that the exposome can relate to the unnaturally low presence of a substance as much as it can to elevated levels of a substance. This is particularly true when considering the food exposome. Also, in this context, foods are seasonal, and this seasonality can lead to variance in phytochemicals and important vitamins such as folate. This may have had historical significance (Ca. last 100 years), since it has been suggested that the seasonal cycle of abundance of folate-rich foods may have regulated embryo viability by acting as a selection factor for 677T-MTHFR. Ultimately, for exposomal research to flourish, harmonization across techniques and sampling is essential. Already, several large consortiums are emerging and the future seems assured given the backdrop of negative anthropogenic change we have to face up to, particularly from a public health perspective.

Conclusions

As a final thought, it is interesting to consider whether the current coronavirus disease (COVID-19) pandemic has altered the human exposome. Humanity has been exposed to more indoor time, increased levels of stress, and altered dietary habits. Although likely short term, it is interesting to speculate whether there is any relevance, particularly within a DoHAD framework.

Acknowledgments

None.

Funding

None.

Conflict of interest

No conflicts of interest exist.

References

[1] Wild CP. Complementing the genome with an “exposome”: the outstanding challenge of environmental exposure measurement in molecular epidemiology. Cancer Epidemiol Biomarkers Prev 2005;14(8):1847–1850. doi:10.1158/1055-9965.EPI-05-0456.
[2] Lucock M. The Anthropocene: Exploring its origins, biology and future. Am J Hum Biol 2020:e23476. doi:10.1002/ajhb.23476.
[3] Wild CP. The exposome: from concept to utility. Int J Epidemiol 2012;41(1):24–32. doi:10.1093/ije/dyr236.
[4] Wild CP. Environmental exposure measurement in cancer epidemiology. Mutagenesis 2009;24(2):117–125. doi:10.1093/mutage/gen061.
[5] Wild CP. Future research perspectives on environment and health: the requirement for a more expansive concept of translational cancer research. Environ Health 2011;10(1):515. doi:10.1186/1476-069X-10-5151.
[6] Rappaport SM, Smith MT. Environment and disease risks. Science 2010;330(6003):460–461. doi:10.1126/science.1192603.
[7] Vermeulen R, Schymanski EL, Barabasi AL, Miller GW. The exposome and health: Where chemistry meets biology. Science 2020;367(6476):392–396. doi:10.1126/science.aaay316.
[8] Rattray JW, Deziel NC, Wallach JD, Khan SA, Vasiliiou V, Ioannidis JP, et al. Beyond genomics: understanding exposotypes through metabolomics. Human Genomics 2018;12(1):1. doi:10.1186/s40426-018-0134-x.
[9] Rattray NW, Charlkoftaki G, Rattray Z, Hansen JE, Vasiliiou V, Johnson CH. Environmental influences in the etiology of colorectal cancer: the premise of metabolomics. Curr Pharmacol Rep 2017;3(3):114–125. doi:10.1007/s40495-017-0088-z.
[10] van der Put NM, Steeggers-Theunissen RP, Frosst P, Trijbels FJ, Estes TK, van den Heuvel LP, et al. Mutated methylenetetrahydrofolate reductase as a risk factor for spina bifida. Lancet 1995;346(8982):1070–1071. doi:10.1016/s0140-6736(95)91743-8.
[11] Nau H. Valproic acid-induced neural tube defects. Ciba Found Symp 1994;181:144–160. doi:10.1002/9780470514599.ch9.
[12] Ornoy A. Valproic acid in pregnancy: how much are we endangering the embryo and fetus? Reprod Toxicol 2009;28(1):1–10. doi:10.1016/j.reprotox.2009.02.014.
[13] Turner A, Veysey M, Keely S, Scarlett C, Lucock M, Beckett EL. Interactions between Bitter Taste, Diet and Dysbiosis: Consequences for Appetite and Obesity. Nutrients 2018;10(10):1336. doi:10.3390/nu10101336.
[14] Ogino S, Nowak JA, Tamada T, Milner DA Jr, Nishihara R. Insights into Pathogenic Interactions Among Environment, Host, and Tumor at the Crossroads of Molecular Pathology and Epidemiology. Annu Rev Pathol 2019;14:83–103. doi:10.1146/annurev-pathmed-012418-012818.
[15] Pedersen M, Giorgis-Allemand L, Bernard C, Aguillera I, Andersen AM, Ballester F, et al. Ambient air pollution and low birthweight: a European cohort study (ESCAPE). Lancet Respir Med 2013;1(9):695–704. doi:10.1016/s2213-2600(13)70192-9.
[16] Wigle DT, Arbuckle TE, Turner MC, Berubé A, Yang Q, Liu S, et al. Epidemiologic evidence of relationships between reproductiv and child health outcomes and environmental chemical contaminants. J Toxicol Environ Health B Crit Rev 2008;11(5-6):373–517. doi:10.1080/10937400801921320.
[17] Godfrey KM, Gluckman PD, Hanson MA. Developmental origins of metabolic disease: life course and intergenerational perspectives. Trends Endocrinol Metab 2010;21(4):199–205. doi:10.1016/j.tem.2009.12.008.
[18] Van den Bergh BR. Developmental programming of early brain and behaviour development and mental health: a conceptual framework. Dev Med Child Neurol 2011;53(Suppl 4):19–23. doi:10.1111/j.1469-8749.2011.04057.x.
[19] Robinson O, Vrijheid M. The pregnancy exposome. Curr Envir Health Rep 2015;2(2):204–213. doi:10.1007/s40495-015-0043-2.
[20] Tang W, Ho SM. Epigenetic reprogramming and imprinting in origins of disease. Rev Endocr Metab Disord 2007;8(2):173–182. doi:10.1007/s11514-007-9042-4.
[21] Lucock M, Yates Z, Martin C, Choi JH, Beckett E, Boyd L, et al. Methylation diet and methyl group genetics in risk for adenomatous polyp occurrence. BBA Clin 2015;2015;3:107–112. doi:10.1016/j.bbacli.2014.11.005.
[22] Lucock MD. Folic acid: beyond metabolism. J Evid Based Complement Altern Med 2015;20(4):310–322. doi:10.1177/1533211015580491.
[23] Scalbert A, Hu BS, Gunter MJ. The Food Exposome. In: Dagnino S, Macherone A, eds. Unravelling the Exposome. Springer; 2019.
[25] Jones P, Lucock M, Veysey M, Beckett E. The Vitamin D-Folate Hypothesis as an Evolutionary Model for Skin Pigmentation: An Update and Integration of Current Ideas. Nutrients 2018;10(5):554. doi:10.3390/nu10050554.

[26] Lucock M, Beckett E, Martin C, Jones P, Forst J, Yates Z, et al. UV-associated decline in systemic folate: implications for human nutrigenetics, health, and evolutionary processes. Am J Hum Biol 2017;29(2):e22929. doi:10.1002/ajhb.22929.

[27] Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr 2004;80(6 Suppl):1678S–1685. doi:10.1093/ajcn/80.6.1678S.

[28] Martin CE, Veysey M, Yates ZR, Lucock M. Vitamin D: Genetics, Environment & Health. J Food Nutr Disor 2014;3:5. doi:10.4172/2324-9323.1000155.

[29] Kim KC, Friso S, Choi SW. DNA methylation, an epigenetic mechanism connecting folate to healthy embryonic development and aging. J Nutr Biochem 2009;20(12):917–926. doi:10.1016/j.jnutbio.2009.06.008.

[30] Clare CE, Brassington AH, Kwong WY, Sinclair KD. One-Carbon Metabolism: Linking Nutritional Biochemistry to Epigenetic Programming of Long-Term Development. Annu Rev Anim Biosci 2019;7:263–287. doi:10.1146/annurev-animal-020518-115206.

[31] Barker DJ. The origins of the developmental origins theory. J Intern Med 2007;261(5):412–417. doi:10.1111/j.1365-2796.2007.01809.x.

[32] Sohn KJ, Jang H, Campan M, Weisenberger DJ, Dickhout J, Wang YC, et al. The methylenetetrahydrofolate reductase C677T mutation induces cell-specific changes in genomic DNA methylation and uracil misincorporation: a possible molecular basis for the site-specific cancer risk modification. Int J Cancer 2009;124(9):1999–2005. doi:10.1002/ijc.24003.

[33] HeijmansBT, Tobi EW, Stein AD, Putter H, BlauwGJ, Susser ES, et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. PNAS 2008;105(44):17046–17049. doi:10.1073/pnas.0806561010.

[34] Fetahu IS, Höbaus J, Källay E. Vitamin D and the epigenome. Front Physiol 2014;5:164. doi:10.3389/fphys.2014.00164.

[35] Lucock M, Thota R, Garg M, Martin C, Jones P, Forst J, et al. Early lifecycle UV-exposure calibrates adult vitamin D metabolism: Evidence for a developmentally originated vitamin D homeostat that may alter related adult phenotypes. Am J Hum Biol 2019;31(4):e23272. doi:10.1002/ajhb.23272.

[36] Jablonski NG, Chaplin G. Colloquium paper: human skin pigmentation as an adaptation to UV radiation. PNAS 2010(Suppl 2):8962–8968. doi:10.1073/pnas.0914628107.

[37] Jones P, Lucock M, Veysey M, Jablonski N, Chaplin G, Beckett E. Frequency of folate related polymorphisms varies by skin pigmentation. Am J Hum Biol 2018;30(2):e23079. doi:10.1002/ajhb.23079.

[38] Jablonski NG. The evolution of human skin and skin colour. Annu Rev Anthropol 2004;33:585–623. doi:10.1146/annurev.anthro.33.307023.143955.

[39] Ogino S, Lochhead P, Chan AT, Nishihara R, Cho E, Wolpin BM, et al. Molecular pathological epidemiology of epigenetics: emerging integrative science to analyze environment, host, and disease. Mod Pathol 2013;26(4):465–484. doi:10.1038/modpathol.2012.214.

[40] Ogino S, Nishihara R, VanderWeele TJ, Wang M, Nishi A, Lochhead P, et al. Review Article: The Role of Molecular Pathological Epidemiology in the Study of Neoplastic and Non-neoplastic Diseases in the Era of Precision Medicine. Epidemiology 2016;27(4):602–611. doi:10.1097/EDE.0000000000000471.

[41] Lucock M, Yates Z, Ng X, Veysey M, Blades B, Travers C, et al. Preliminary evidence for genetic selection of 677T-MTHFR by natural annual cycle of folate abundance. J Nutrigenet Nutrigenomics 2008;1(1-2):24–29. doi:10.1159/000109872.