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# The Role of Over-Nutrition and Obesity in Multiple Sclerosis

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## Abstract

In countries with high standard of living, lowered risk of infectious diseases is parallel to increased incidence of autoimmune diseases. One of the autoimmune disorders, multiple sclerosis, affects genetically susceptible individuals. Genetic susceptibility is supposed to interact with lifestyle and environmental factors in developing autoimmunity in MS. From this point of view, epigenetics provides the bridge between the external environment and the internal genetic system. In MS, environmental burden can modulate gene expression by epigenetic modification of chromatin components, microRNAs or by subtle changes in DNA methylation. Our paper focuses on describing the epigenetic mechanisms linking environmental factors with pathogenesis of multiple sclerosis. We summarise current knowledge about the role of over-nutrition and obesity as epigenetic factors in multiple sclerosis.

**Keywords:** multiple sclerosis, epigenetics, early life environmental factors, obesity, microRNA, DNA methylation, histone acetylation

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## 1. Introduction

The genomewide association study (GWAS) conducted by International Multiple Sclerosis Genetics Consortium has identified genes conferring susceptibility to multiple sclerosis (MS) [1]. Many of these genes play a role in the immune system with a prominent role for major histocompatibility complex (MHC) class II molecules in particularly defined HLA-DRB1 alleles. GWAS found complete concordance between the rs 3135388A SNP and the HLA-DRB1\*1501 genotype [1].

In most cohorts, especially in Caucasian population, genetic burden for MS has been found to be associated with gene clusters in chromosome 6p21.3 [2]. Evident genetic heterogeneity of MS makes identification of single candidate gene impossible. This highlights the role of molecular markers rather than MS-susceptibility genes in indicating the disease status [3]. As the genetic background determines only about 26–30% of the risk of developing MS [4, 5], other factors have been considered to determine heterogeneity of clinical course and MS symptoms [6].

Epigenetics is defined as heritable changes in gene expression that are not due to any alteration in the primary DNA sequence. The changes are responsible for organisation and reading of genetic information [7]. The term epigenetics has evolved to define mechanisms underlying phenotype plasticity due to environmental influences, parent-of-origin effects, gene-dosage control, imprinting, and X-chromosome inactivation. At the molecular level, epigenetics includes modification of DNA base pairs, post-translational modification of histones, and the effects of non-coding RNAs [8]. Moreover, it was found that epigenetic alterations accumulate in time; consequently they can exert their effect on expressed genes longitudinally [9].

Our paper focuses on describing the epigenetic mechanisms linking environmental factors with pathogenesis of multiple sclerosis. We summarise current knowledge about roles of over-nutrition and obesity as epigenetic factors in multiple sclerosis.

### **1.1. Molecular epigenetic mechanisms**

In human DNA, cytosines in the CpG dinucleotide are commonly methylated, and methylation is well-balanced. DNA methylation is involved in normal development and sustaining of cellular homeostasis and functions in adult organisms (particularly for X-chromosome inactivation in females, genomic imprinting, silencing of repetitive DNA elements, regulation of chromatin structure, and control of gene expression). CpG sites are concentrated in short regions of the genome [7, 10, 13]. Another common mechanism that regulates chromatin structure inside a cell involves histone modification. In general, histone acetylation and phosphorylation act as activators of gene expression, whereas histone deacetylation, biotinylation and sumoylation inhibit gene expression [10, 12]. Other described mechanisms of epigenetic regulation of gene function are mediated by miRNAs. They are small non-coding RNAs, 16–29 nucleotides-long, that function primarily as negative gene regulators at the post-transcriptional level. Recently, novel microRNAs (miR) have been identified to be human-specific as well as tissue-specific [7, 11].

Different authors have suggested that epigenetic mechanisms could be directly controlled by metabolic and dietary constituents, metabolic state, or endocrine unbalances [10, 40].

### **1.2. Early life period and potential epigenetic risks**

Recently, studies on humans have indicated that adaptive changes made by foetus in response to intrauterine environment result in permanent changes in early life programming [14–16].

Currently, there are no prospective systematic studies conducted in humans that would evaluate the association of selective environmental factors and risk of MS in humans. However,

many environmental factors have been described to be potential epigenetic regulators of MS development [16, 17, 18]. Some of the metabolic and toxic epigenetic factors are listed and included in **Table 1**.

- lower levels of maternal vitamin D and lower exposure to UV light in childhood
- nutritional factors + obesity
- exposure to glucocorticoids, metabolic trigger
- smoking
- epigenetics of endocannabinoid system
- maternal psychosocial stress

Potential epigenetic factor	Mechanism of action	Clinical and immunological consequences	References number
Lower maternal vitamin D Decreased vitamin D in MS patients	blocking of NF for activated T-cells, sequestration of Runt-related TF-1 FokI gene polymorphism (rs10735810) Vitamin-D-mediated trans-repression of the CYP27B1 p450 27B1 gene methylation of CpG sites IL-17 gene expression by blocking of NF, necessary for activating Th-1 cells TF and by HDAC Vitamin-D mediated suppression of IL-12 via HDAC	1,25(OH)2D3 inhibits the production of IFN $\gamma$ , IL2 and IL12, expansion of dependent Th-1 cells, modification of dendritic cells 58% reduced risk of MS for each 400 IU/day evolution of MS, sex-differences	[19–25]
Lower UV exposure	Similar to vitamin D deficiency	Increase of TNF $\alpha$ and IL-10-impaired antigen-presenting cell function, and antigen-specific Th-cell tolerance, decreased Th-regulatory cells region of birth and low maternal exposure to UV radiation	[26, 27]

Potential epigenetic factor	Mechanism of action	Clinical and immunological consequences	References number
Higher maternal pre-pregnancy BMI	Oxidative stress, lower vitamin D exposure, over-expression of miR-145,146,155, cluster 17-92 on immune cells Over-expression of Notch1 signalling pathways on oligodendrocytes, impaired neural stem differentiation	in the first trimester are independently associated with subsequent risk of MS in offspring No significant relation of weight gain during pregnancy and MS risk when increased pre-pregnancy BMI (OR: 0.39; 0.18–0.85)	[18, 28–31]
Glucocorticoids hyperglycaemia/diabetes	Reduction of GLUT, dysfunction of cell membrane, impaired DNA methylation of central myelin and genes important in regulating cortisol levels	Blockage of the HPA axis increased risk to MS in offspring	[32–34]
Parental smoking, passive inhalation	Methyl group deficiency, loss of histone H3K9 and H4K20 methylation	24–50% increased risk of MS in women exposed to parental or passive smoking	[18, 30, 31, 35]
Cannabis consumption	Endocannabinoids influence gametogenesis, DNA modulation of reproductive cells, dysregulation of glutamatergic gene expression, findings that would be predictive of impaired synaptic plasticity	Trans-generational effect to next generation, potential modulatory effect to mesolimbic reward-related subregion of the striatum, risk of MS and neurodegenerative disorders	[34, 36]
Lower choline in diet	Impaired DNA methylation of PAD2 promotor, encoding oligodendrocyte activity, developmental type of myelin	Increased inflammatory cytokines: IL-6 and TNF $\alpha$ Increased risk of MS	[37, 38]

Potential epigenetic factor	Mechanism of action	Clinical and immunological consequences	References number
Psychosocial stress in pregnancy, inappropriate maternal immune activation due to stress, maternal separation and obesity	Increased DNA methylation of endocannabinoid receptor-1	Increased IL-6, IL-1, IL-10, increased CD4 and B lymphocytes, decreased Th-regulatory cells, increased permeability of BBB, altered the HPA axis in infants, risk of immune deregulations	[32, 38, 39]

Abbreviations: NF = nuclear factor, TF = transcriptional factor, 1.25(OH)2D3 = 1.25-dihydroxycholecalciferol, FokI = polymorphism of vitamin D receptor, IFN $\gamma$  = interferon gamma, TNF $\alpha$  = tumour necrosis factor alfa, IL-1,-2,-6,-10,-12,-17 = interleukine 1,-2,-6,-10,-12,-17, Th-1 = autoaggressive T lymphocytes, CYP27B1 p450 27B1 = cytochrome P450 family 27 subfamily B polypeptide 1, CpG = cytosine guanine islands - regions of DNA, HDAC = histone deacetylase, UV = ultraviolet, MS = multiple sclerosis, BMI = body mass index, HPA = hypothalamo-pituitary-adrenal, miR = microRNA, GLUT = glucocorticoid transporters, PAD2 = peptidylarginine deiminase 2, CD4 = Th lymphocytes - helpers, BBB = blood-brain barrier.

**Table 1.** The list of potential epigenetic risk factors.

### 1.3. Obesity, nutritional factors and multiple sclerosis

Over the last decade, obesity appears to be a new component of the complex mosaic of autoimmunity [41], suggesting that starvation leads to immunosuppression [42] and that over-nutrition or obesity promotes autoimmunity [8, 41, 43].

Maternal obesity in pre-pregnancy period [measured by body mass index (BMI)], correlated with higher risk of developing MS in children [18], suggests that obesity is a prenatal risk factor. Maternal obesogenic environment is considered to be an epigenetic modulator [40, 43, 44].

Trans-generational epigenetic effects have been supported by nutritional studies that identified a link between food supply during childhood and MS mortality in grandchildren [45, 46]. Although not clearly defined in MS, intergenerational epigenetic effects could explain why the HLA DRB 1\*15 frequency is significantly lower in the first-generation affected females, whereas it remains unchanged across the two generations in affected males [46].

Although in one of the retrospective studies, maternal obesity in pre-pregnancy period was associated with risk of MS in children [18], other studies analysed the association of body configuration in adolescence with risk of MS. They found a correlation between higher BMI in adolescence and subsequent development of MS [28, 29, 47], whereas the interaction of obesity and carriage of HLA DRB 1\*15 genotype was identified [48]. Munger et al. [28] found that a higher BMI at ages 7–13 years was associated with a significant 1.61–1.95-fold increased risk of MS only among girls. Similarly, another study [49] identified a higher risk of paediatric MS and clinically isolated syndrome (encompassing optic neuritis and transverse myelitis) in extremely obese adolescent girls (BMI  $\geq 35$  kg/m<sup>2</sup>) with an OR = 2.57. In age-adjusted analyses,



women with a BMI  $\geq 30$  kg/m<sup>2</sup> at an age of 18 had a greater than twofold risk of developing MS as compared to women with a BMI between 18.5 and 20.9 kg/m<sup>2</sup>. A higher percentage of women who were obese (BMI  $\geq 30$  kg/m<sup>2</sup>) at an age of 18 were smokers at baseline as compared to women with lower BMI [29]. However, body weight at age  $\geq 30$  was not associated with risk of MS [28], indicating that postnatal life period and adolescence are most important for future development of MS. Other authors did not prove the relationship between obesity and MS in adult patients with ongoing MS symptoms [50, 51]. Moreover, Emamgholipour and colleagues presented a study demonstrating a decreased adipose tissue mass in patients with definite MS compared with healthy individuals (18% MS versus 22.6% in controls) [52]. The negative correlation of MS severity and adipose tissue mass was supposed to result from increased lipolysis and loss of metabolic plasticity.

During over-nutrition, immune cells are increasingly activated and accumulated in adipose tissue, but pro-inflammatory cytokines and chemokines, released from immune cells can also affect other organs [53]. Obesity is associated with accumulation of macrophages, changed from anti-inflammatory M2 to pro-inflammatory M1 phenotype [53]. Obesity selectively promotes an expansion of the Th17 T-cell sub-lineage, producing progressively more IL-17 than lean subjects. IL-6-dependent Th17 expansion is a clinically prominent element in obesity [53]. The results of a small clinical study concurred with the previous investigations. These authors demonstrated stimulation of pro-inflammatory pathways through elevated IL-17 in serum of obese women [54].

Moreover, inflammatory peptides, originated from enlarged adipocytes, have a tendency to change the activity of the HPA axis via hypothalamic receptors [34, 71] and consequently modulate immune responses [58]. Obesity induced by high-fat diet increases blood-brain barrier (BBB) permeability [56] and leads to accumulation of lipids in brain tissue [60, 61], stimulating innate immunity responses. Over-nutrition was correlated with increased number of activated brain microglial cells and oligodendrocytes [61].

MS is one of the autoimmune disorders of the central nervous system (CNS) with not fully known aetiology [6]. Immunological assessments of MS patients have supported the concept of MS as the disorder driven by myelin-specific Th1 helper cells [6], and/or Th17 cells [52]. They were found to migrate into CNS, where they cause demyelination and axonal loss and subsequent neurological disability in MS [6]. Currently, it is known that both innate and adaptive immune processes contribute to MS pathogenesis [42]. Additionally, there is evidence indicating that MS has a neurodegenerative component since neuronal and axonal loss occurs even in the absence of overt inflammation [56]. However, interactions between infiltrating immune cells and resident cells of the CNS require co-stimulatory and additive factors that determine both disease evolution and clinical outcome of MS patients [57]. However, neuro-inflammation cross-talk can have either beneficial or destructive consequences [57], depending on the environmental influences interacting with genetic risks. In MS, environmental exposures might occur long before the disease becomes clinically evident. In addition, the onset of the disease is unknown. Changes in gene expression driven by epigenetic mechanisms play an important role in the predisposition to future disease development [17, 61].

## 1.4. Epigenetic links between over-nutrition or obesity and multiple sclerosis

### 1.4.1. Micro RNA

Until today many studies have demonstrated that miR have multiple functions in negative gene regulation and play important roles in neurological disorders, and it seems possible that several epigenetic mechanisms have multiple targets [62].

Interestingly, while obesity increases the expression of the miR-143–145 cluster in adipose tissue/adipocytes via increasing over-expression of tumour necrosis factor alpha (TNF $\alpha$ ) secretion and lipolysis [62], recent research has shown miR-145 to be expressed dramatically in peripheral blood mononuclear cells (PBMCs) from patients with MS [63]. Other miR-142-3p, miR-146a, miR-155 and miR-326 were also aberrantly expressed in the PBMCs of MS patients [64].

Obesity-induced over-expression of miR-155, miR-107, and miR-146-5p led to release of pro-inflammatory cytokines, adaptive and innate immune activation [65, 66], while miR-155 and miR-326 were up-regulated in both PBMCs and brain white matter lesions [67].

It has also been found that miR-146a increases IL-17 expression and miR-155 promotes Th1 and Th17 cells [65], determining severity of the disease course [64]. Th17 cell-associated miR-326 expression was highly correlated with disease severity in patients with MS. In vivo silencing of miR-326 resulted in fewer Th17 cells [65]. Moreover, a recent research has revealed that miR-155 over-expression could be implemented into acute BBB dysfunction, as miR-155 was increased at the neurovascular unit in MS lesions when compared to levels in MS normal-appearing white matter [68]. Pro-inflammatory cytokines, such as interferon gamma (IFN $\gamma$ ) and TNF $\alpha$  were able to up-regulate miR-155 in human cells. The findings indicate contribution of miR-155 to cytokine-induced disruption of the brain endothelium via cell-to-cell and cell-to-matrix interactions, leading to an increased permeability of BBB which is typical for MS [68]. Similarly, another study confirmed increased expression of miR-155 on astrocytes in acute MS demyelinated lesions [69], while miR-155-deficient macrophages had a decreased inflammatory potential, and miR-155 inhibited adipogenesis in adipocytes [62].

Pro-inflammatory cytokines, namely IFN $\gamma$ , secreted from auto-reactive Th-1 lymphocytes in not only MS patients [67] but also in obese individuals [53, 71] could be responsible for up-regulation of miR-155 and dysfunction of BBB.

Another possible cross-link between obesity and MS might be the expression of the miR-17-92 cluster, which was found down-regulated in B lymphocytes of MS patients [72] and also in blood and adipocytes in obese individuals [62]. The immunogenetic study by Steiner and colleagues proposed that miR-17-92 family members potentiate T helper cell proliferation, whereas miR-29 family members specifically inhibited IFN $\gamma$  [73].

Further studies are needed to investigate whether obesity-induced over-expression of specific miR and release of pro-inflammatory cytokines in periphery could trigger autoimmune reaction against brain structures in sensitive life periods. We hypothesise that maternal over-nutrition or high-fat diet in childhood might stimulate over-expression of miR-145, -146, -155



in several sites including adipocytes and peripheral blood cells. This allows inflammatory cells to release cytokines and cross the BBB and attack myelin in brain white matter.

Reported down-regulation of the cluster miR-17-92 in Th cells both in obese subjects and MS patients [62, 72] supports the theory of common immune pathways, and indirectly supports the role of over-nutrition in autoimmunity and development of MS.

#### 1.4.2. DNA methylation

One of the epigenetic mechanisms, methylation of myelin basic protein (MBP), is important for maintaining protein stability. In MS patients, methylation of MBP was reported to be higher than in healthy controls [74, 75], and some isoforms of MBP (such as the early developmental ones) are implicated in de- and re-myelination attempts during MS [74]. Since the myelin sheath has been described to be developmentally immature due to impaired myelin synthesis via oligodendrocyte failure [76], a post-translational pathogenetic mechanism has been proposed. A recent research confirmed the previous hypothesis, whereas re-expression of the developmental pathway was found to restrict oligodendrocyte maturation [77]. The authors showed that over-expression of Notch1 within and around active MS plaques lacking re-myelination was associated with immature oligodendrocyte phenotype and up-regulation of transforming growth factor beta1 in perivascular extracellular matrix [77]. It is of interest that animal studies proved maternal high-fat diet to be a potent epigenetic regulator of the Notch signalling pathway that impairs hippocampal development in the offspring. Notch signalling was involved in molecular mechanisms of neurogenesis, whereas over-expression of Notch1 in neural stem cells caused inhibition of the proliferation of neural progenitors [78]. Although in humans the relationship between high-fat diet and inhibition of neural progenitors has not been confirmed yet, we hypothesised that nutritional factors could exert the effect via the same mechanism.

Myelin structure can be altered when an alternative pathway for the reversal of arginine methylation involves the conversion of an arginine in either histone H3 or H4 to a citrulline. This is termed deimination because the methyl group is removed along with the imine group of arginine and is accelerated by peptidylarginine deiminase 4 (PAD4). Converting citrulline back to arginine has not yet been described [7, 10]. It was found that deimination of MBP-bound arginyl residues makes them more susceptible to myelin-associated proteases [75]. The accompanying loss of positive charge compromises the ability of MBP to interact with the lipid bilayer. The conversion of arginine to citrulline in brain is carried out by an enzyme peptidylarginine deiminase 2 (PAD2). The amount of PAD2 in brain was increased in MS normal-appearing white matter. The mechanism responsible for this increase involved hypomethylation of the promoter region in the PAD2 gene in MS [79]. The triggering factor is not fully known. However, the methylation process requires Vitamin B12, which transfers its methyl group to homocysteine via synthesis of methionine, which is then converted to S-adenosylmethionine, the methyl donor in all biological methylation reactions [79]. Choline, methionine and 5-methyl tetrahydrofolate are major sources of methyl groups in humans [10, 38]. Moreover, they have an importance in suppression of inflammatory processes. Individuals whose diet was rich in choline and betaine had the lowest levels of several inflammatory

markers, including C-reactive protein, homocysteine, IL-6 and TNF $\alpha$  [37]. Among the most concentrated sources of dietary choline are fish and fish-caviar, liver, eggs and wheat germ [37]. On the other hand, vulnerability of myelin sheath is caused by disturbed lipid metabolism, while the uptake of external lipids may also play a role in the formation and disturbances of myelin membranes. The pathogenic mechanisms are known from research of neurodegenerative brain disorders [81, 82].

#### 1.4.3. Histone acetylation

Histone acetylation is another epigenetic mechanism involved in the pathogenesis of MS. Histone deacetylases (HDACs) are responsible for the removal of the acetyl group from histones, with resulting ability to influence expression of genes encoded by DNA linked to the histone molecule. HDACs are also able to modify a large variety of non-histone proteins whose activity depends on their acetylation status, such as transcription factors, chaperone proteins, signal transduction mediators, structural proteins, and inflammation mediators [83].

Sirtuin-1 (SIRT1), a member of the HDAC class III family of proteins, can induce chromatin silencing through the deacetylation of histones and can modulate cell survival by regulating the transcriptional activities [84]. It was recently reported that SIRT1 was expressed by a significant number of cells in both acute and chronic active lesions in brains of MS patients. Authors found SIRT1 to co-locate with CD4, CD68, oligodendrocytes and glial fibrillar acidic protein (GFAP) cells in MS plaques, when statistically significant decrease in SIRT1 expression correlated with that of histone H3 lysine 9 acetylation (H3K9ac) and methylation (H3K9me2) [84].

HDAC9 has a key role in the development and differentiation of many types of cells, including regulatory Th cells. Dysfunction of Th cells in MS suggests that HDAC9 may act as an epigenetic switch in effector Th cell-mediated systemic autoimmunity [85]. Genetic variability in HDAC9, along with variants in HDAC11, SIRT4 and SIRT5, has also been shown to influence brain volume in MS patients, as assessed using neuroimaging methods [86].

A growing number of the dietary HDAC reported in the literature are generated as metabolites during the course of digestion [83]. Dietary constituents are formed by the metabolism of some vegetables and fruits, olive oil and nuts. Broccoli, cabbage, Brussel sprouts, cauliflower, kale, Savoy cabbage, citrus, grapes, berries and apples contain many HDAC regulators [83]. For example, resveratrol, naturally occurring compound found in grapes, wine and eucalyptus, is a potent activator of sirtuins (class III HDACs) and in particular, SIRT1 [83]. Thus, regular consumption of foods rich in this compound can have protective effect.

## 2. Conclusion

Until now, a lot of potential epigenetic mechanisms in MS have not been discovered, and also the hypotheses linking nutritional factors and obesity or nutritional compounds have not been proved by prospective epidemiological studies. The relationship among diet, obesity and

genetic risk of MS has been studied only occasionally. The included studies were usually focused on a role of vitamin D. Further studies based on both genetic-epigenetic factors and environmental triggers could bring new information about how to determine the MS risk factors more precisely and much earlier in life. Although at present, there is no particular preventive strategy in MS, new findings could help us to work out dietary interventions and other alternative non-conventional therapies.

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