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Asthma, Allergy, and Responses to Methyl Donor Supplements and Nutrients

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Abstract

After a brief period of stabilization, recent data has shown that the prevalence of asthma and allergic diseases continue to increase. Atopic diseases are major public health problems resulting in significant disability and resource utilization globally. While environmental factors influence the development of atopic disease, dietary changes may partially explain the high burden of atopic disease. One mechanism by which diet is suspected to impact asthma and allergy susceptibility is through epigenetic mechanisms including DNA methylation. Dietary methyl donors are important in the one-carbon metabolism pathway that is essential for DNA methylation. Findings from both observational studies and interventional trials of dietary methyl donor supplementation on the development and treatment of asthma and allergy have produced mixed results. While issues related to the differences in study design partially explain the heterogeneous results, two other issues have been largely overlooked in these studies. Firstly, these nutrients affect one of many pathways and occur in many of the same foods. Secondly, it is now becoming clear that the human intestinal microbiome is involved in the metabolism and production of the B vitamins and other methyl donor nutrients. Future studies will need to account for both the interrelationships between these nutrients and the effects of the microbiome.

Keywords

Allergy; Asthma; Betaine; Choline; Vitamin B2; Vitamin B6; Vitamin B12; Folate; Methyl Donor; Microbiome

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Introduction

Asthma and allergic diseases including allergic rhinitis and atopic dermatitis continue to be major public health problems resulting in significant disability and resource utilization globally[1, 2]. Although the trend in asthma prevalence in the United States had initially stabilized, since 2003 the prevalence of asthma and allergic disease in the United States and abroad is rising[3-7]. There is substantial evidence for the genetic predisposition to complex diseases like asthma and allergy with multiple genetic loci demonstrating reproducible associations with these diseases, but genetics alone is unable to explain the overall burden of atopic disease. While the etiology of the rising prevalence is not definitively known, several factors have been proposed to account for this increase including environmental etiologies[8, 9]. Environmental exposures such as tobacco smoke have been shown to influence the incidence of both asthma and allergy in children[10-12] and in adults[13, 14]. Other environmental exposures including traffic related air pollution have also shown modest associations with atopic diseases in children[15-17]. However, even the contribution of these environmental exposures to asthma and allergy susceptibility is unlikely to fully explain the increasing prevalence of asthma and allergic diseases worldwide.

Epidemiologic data suggests that changes in dietary patterns may also partially explain the rising prevalence of asthma and allergy in industrialized countries[18-20]. However, the role of certain dietary nutrients in the development of atopic diseases has been conflicting in part due to the fact that the role of diet in the development of atopy is complex, difficult to measure, and is limited by a dearth of interventional trials investigating the impact of diet on atopic disease susceptibility.

Methyl Donors

One of the proposed mechanisms by which diet is suspected to impact asthma and allergy susceptibility is through epigenetic mechanisms including DNA methylation, which results in heritable changes in gene expression without alteration of the original DNA sequence[21]. Methylation of CpG islands within regulatory regions of DNA is an important mechanism for the control of gene expression and has been shown to be transmissible across generations[22]. DNA methylation results from the transfer of methyl groups to the cytosine in the CpG dinucleotide resulting in a reversible modification that can alter both chromosome stability and suppress gene transcription. Environmental exposures, including air pollution and dietary factors, have been shown to influence the epigenome[23]. Furthermore, recent evidence from the Normative Aging Study suggests that prior allergen sensitization is associated with increased methylation of the retrotransposon-derived element Alu, which is a proxy for global DNA methylation, ($\beta = 0.32$ for sensitized vs. nonsensitized patients; $p = 0.003$) even after adjustment for smoking status and air pollutants[24].

Dietary methyl donors including folate and choline are necessary for the one-carbon metabolism pathway that produces S-adenosylmethionine (SAM), which is the universal methyl donor that is essential for the DNA methylation process to occur (Figure 1). Vitamin B12 and betaine, which are additional agents derived from the diet, are also necessary for methionine synthesis, which is another step that is important in DNA methylation.

Therefore, differential intake of these nutrients may lead to differences in DNA methylation and ultimately alter gene expression. In an agouti mouse model, mothers on a diet supplemented with methyl donors resulted in hypermethylation of the metastable epiallele in the progeny resulting in a brown coat color, lower incidence of obesity, and increased longevity[25]. In a mouse model of allergic airway disease, *in utero* supplementation of a diet that is high in methyl donors (including folic acid, choline, and vitamin B12) resulted in increased atopy (IgE and eosinophils) and airway responsiveness in the exposed progeny[26]. In addition, *in utero* exposure to a high methyl donor diet was associated with increased methylation of the Runt-related transcription factor (*RUNX3*) gene in the progeny, which resulted in decreased expression of the gene. *Runx3* is known to negatively regulate allergic airway disease, suggesting that the methylation changes induced by a diet high in methyl donors may result in increased atopic diseases. Given the emerging evidence from animal models demonstrating a role for dietary methyl donors in the development of atopic diseases, dietary methyl donors have been investigated in human subjects as a possible etiology of the rising prevalence of atopic disease.

In humans dietary methyl groups such as folate, vitamin B12, and choline are a source of methyl donors for DNA methylation (Table 1). Methyl donors, especially folate, have been extensively studied in asthma and to a lesser degree in allergy. However, the data for the association of dietary methyl donors with the development of asthma and allergy in humans remains unclear. In this review we examine the existing evidence for the role of methyl donors in the development and treatment of asthma and allergy. We have limited this review to articles that have examined specific nutrients rather than foods or diets that contain the nutrient. Food intake and dietary patterns and asthma and allergies have recently been reviewed and the readers are directed to those reviews[18, 20, 27, 28]

Folate

Folate is a water-soluble B vitamin that is naturally present in a variety of foods and is available in nutritional supplements. It is naturally occurring in the diet as folate, and folic acid is the a fully oxidized monoglutamate form that is used as a dietary supplement[29]. Folic acid consists of a p-aminobenzoic molecule linked to a pteridine ring and one molecule of glutamic acid. Dietary folates are polyglutamates, which include additional glutamate residues[30]. Folate is found naturally in foods including dark leafy vegetables, fruits, nuts, beans, poultry, meat, eggs, seafood, and dairy products. In addition, it is found (in folic acid form) in fortified food products including breads, cereals, and grain products. Dietary supplements including multivitamins, however, are the major source of folic acid in humans. Unlike naturally-occurring folate, which is hydrolyzed in the intestines and reduced to tetrahydrofolate upon absorption, folic acid requires reduction and methylation in the liver via dihydrofolate reductase. It should be noted that controversy exists regarding how best to measure folate status in humans[31-33], but this is beyond the scope of the current review.

Folate is necessary for many biologic processes including purine and pyrimidine synthesis and amino acid production. Folate is also needed for the methylation of deoxyuridylate to thymidylate in the formation of DNA, which is required for normal cell division. Folate in the form of 5-methyl-tetrahydrofolate (5-methyl-THF) provides the methyl groups necessary

for the formation of S-adenosyl-methionine (SAM), which is the universal methyl donor required for DNA methylation. In addition to its role in DNA methylation, folate may have antioxidant effects, which is relevant to asthma and allergies[34, 35]. The use of folic acid supplements before and during the first trimester of pregnancy reduces the risk of neural tube defects and other congenital anomalies and is, therefore, recommended as part of public health guidelines worldwide[36-39]. Because asthma and allergies develop in early childhood, prenatal exposures are thought to play a role in the development of these disorders, and folate intake has been studied as a potential factor. The association between folate and asthma was recently extensively reviewed by Blatter and colleagues[40]. With regard to the question of prenatal folate intake, folic acid supplementation, or maternal folate status and the development of asthma and allergies in children, a few studies showed increased risks of early wheeze and lower respiratory illnesses,[41] asthma,[42, 43] and eczema (but not asthma)[44]. However, the bulk of birth cohort studies have shown no effect of folate intake or folic acid supplement use at various points in pregnancy[45-51] and asthma or allergies. We agree with Blatter and colleagues that given the weight of the evidence against a moderate to strong effect of maternal folate status on asthma and allergies, there is no reason to change the current recommendations regarding prenatal folic acid supplementation.

The effect of maternal folate intake on DNA methylation and the development of atopic disease in the offspring is a topic of recent interest[52]. In a study of 24 pregnant women, maternal folic acid intake during pregnancy and cord blood folate levels were correlated with cord blood LINE-1 methylation, a measure of global DNA methylation[53]. Furthermore, among 107 pregnant Korean women, serum folate levels were significantly associated with percent methylation of the placenta[54]. Additionally, peri-conceptional use of folic acid supplements was associated with higher methylation of insulin-like growth factor II (*IGF2)* in young children[55]. However, in a prospective cohort study of 534 pregnant women participating in Project Viva, there was no significant association found between maternal dietary intake of folate as assessed by questionnaire in both the first and second trimesters of pregnancy with cord blood LINE-1 methylation[56]. The discrepancy in these results may in part be due to relatively small sample sizes in the studies and in the assessment of DNA methylation. Studies using newer and more comprehensive methods[57, 58] of assessing DNA methylation (using genome-wide techniques) are underway, and using these methods together with folate intake assessment can better answer the question of whether DNA methylation of specific regions in the genome may modify the risk of asthma and allergies.

Post-natal studies of the association of folate and asthma have also resulted in mixed findings. Two studies have shown an increased risk with folate. In a small study of 138 at-risk children, those with higher folate levels in early childhood (<6yrs old) had increased risks of sensitization in later childhood to foods and aeroallergens compared with children who had lower levels.[59] However, there were no associations of increased folate level with asthma or wheezing. In a large cross-sectional study of 1601 Australian adults, dietary intake of folate was significantly associated with asthma, but not with markers of airway hyper- responsiveness or atopy.[60] Three large cross-sectional studies have found a protective effect. In a study of 6,784 Danish adults, higher serum folate levels were found to be associated with lower risks for an asthma diagnosis, but no associations were found with

lung function or atopy[61]. On the other hand, in the US NHANES cohort (both children and adults), higher serum folate levels were associated with decreased risks for wheeze, total serum IgE, and atopy, but no association was noted for physician-diagnosed asthma[62]. In a study of 1,030 English adults, dietary folate intake was associated with lower risks for physician-diagnosed asthma[63]. Finally, four studies have found no associations between either serum folate levels[34, 64, 65] or folate intake[66] with asthma or allergies.

As can be seen above, results of post natal studies of folate and asthma and allergy have been inconsistent. Furthermore, randomized controlled trials investigating folic acid supplementation on asthma and allergy susceptibility are lacking. We agree with the conclusion of Blatter and colleagues[40] that there is insufficient data to exclude an effect of folate on either asthma and allergy development or modification of disease course. Reasons for the heterogeneous results of these studies may include differences in study design and analytic approach, the difficulty of folate status measurements, timing of folate supplementation, confounding due to other exposures, sample size, age, differences in the phenotypic assessment of allergy and atopy, or differences in genetic predisposition. In addition to these study design considerations, Figure 1 shows that other methyl donor nutrients are involved in the pathway leading to DNA methylation. Thus, perturbations in folate intake may not be sufficient to derail the pathway unless there are also changes to the levels of the other methyl donor nutrients. While some of the reports reviewed above[47, 50, 51, 60, 61, 63, 66] investigated other nutrients or foods, these were studied individually and no consideration was given to the relationships between each of these nutrients. While studies of diet patterns[67, 68] address this issue to a certain extent, pathway-based or systems-based analyses[69] might help dissect the complex interrelationships between individual nutrients.

Studies investigating the association of genetic variants in genes in the folate metabolism pathway with asthma and allergy have been limited to date. The vast majority of studies investigating the role of genetic associations have been performed on genetic variants in the methylene-tetrahydrofolate reductase (*MTHFR*) gene due to the association of its common variant C677T with reduced enzymatic function of the gene[70]. The results of studies investigating genetic associations of the C677T *MTHFR* genotype with asthma and atopy have been variable. In a cross-sectional study of 1,671 subjects from Denmark, the *MTHFR* genotype was associated with specific IgE [71]. However, i*n* a population-based birth cohort that included genotypic information on 7,356 mothers and 5,364 children from the Avon Longitudinal Study of Parents and Children (ALSPAC) there was no genetic association of the *MTHFR* C677T genotype with atopy, allergy, or asthma in the mothers or children[46]. In addition, a smaller population-based study of 1,189 adults from Denmark also showed no association of the *MTHFR* polymorphism with allergy (IgE, skin-tests) or asthma [72]. Interestingly, in a population-based prospective cohort study of 2,001 children that investigated the interaction between *MTHFR* genetic variants and methyl donor levels on asthma and eczema, a significant interaction of the *MTHFR* C677T mutation and higher folate levels on an increased risk of eczema was identified[73]. Although there may be a difference in genetic predisposition that underlies the association of methyl donors with asthma and allergy disease susceptibility, these results suggest that there may also be

complex gene-by-environment or gene-gene interactions that have yet to be fully elucidated. Furthermore, genetic studies investigating other genes in this pathway may help elucidate the genetic predisposition to these allergy and asthma.

An additional reason for the heterogeneous effects of folate may be differences in intestinal microbiota in the study populations. It has been shown that bacteria commonly found in human large intestines can produce folate,[74] and whereas folate is mainly absorbed in the small intestines, absorption also occurs in the large intestines[75]. Several strains of bacteria from the genus *Bifidobacteria* have been shown to produce folate both in vitro[76] and in vivo.[77] Bacteria from the genus *Lactobacillus* generally need folate for growth, but one strain, *Lactobacillus plantarum*, has been shown to be a folate producer[78] It is easy to see how folate production by intestinal microbiota can modify the effects of folate ingested in the diet, and has already been considered in studies of diet and colon cancer risk[78, 79]. While there is keen interest in the gut microbiome and asthma and allergy risk,[80, 81] these studies are in their infancy and future studies in cohorts that are collecting both diet and microbiome data will be needed to investigate this link.

Choline

Choline is a tri-methylated water soluble B vitamin that is important in many biologic functions[82]. Although it is synthesized in small quantities by the liver, choline is present in many foods and is a component of nutritional supplements and multivitamins. Choline is naturally found in many food sources including soybeans, egg, peanuts, cauliflower, lentils, and flax seeds[83]. Choline is a precursor of phosphatidylcholine and sphingomyelin, which are phospholipids that are components of biologic membranes and are involved in maintaining cell structure. Choline has also been shown to aid in the movement of lipids in and out of cells[84, 85]. In addition, it is a precursor to platelet-activating factor and acetylcholine. Choline can be oxidized into betaine, which provides the methyl groups needed to resynthesize methionine from homocysteine thereby providing methionine for methylation reactions[86]. This pathway is an alternative to one that uses the co-factor 5-methyltetrahydrofolate (Figure 1).

Animal models have demonstrated the anti-inflammatory properties of choline supplementation in inflammatory arthritis[87]. In addition, an in vitro model showed that choline deficiency resulted in the loss of membrane phosphatidyl choline and resulted in the induction of apoptosis[88]. Mice fed with a choline deficient diet showed altered antioxidant properties and an increase in oxidative stress[89]. Furthermore, dietary choline supplementation resulted in decreased reactive oxygen species and a suppressed the inflammatory response to ovalbumin challenge in a murine model of allergic airway disease[90]

Human data for the association of choline with the development of asthma and allergy is limited. A small study of 23 asthmatic subjects with documented aspirin sensitivity treated with choline magnesium trisalicylate (CMT), demonstrated the safety of choline supplementation, but did not result in an improvement in pulmonary function, nasal congestion, or rhinorrhea[91]. However, studies of the treatment of asthmatic subjects with tricholine citrate demonstrated symptomatic improvement in their asthma with decreased

symptom scores, increased symptom-free days, and decreased rescue medication use[92, 93]. Furthermore, individuals treated with high-dose choline were also noted to have improvements in lung function[92] and had decreased airway responsiveness[93]. In a treatment trial of 76 patients with asthma treated with choline or standard pharmacotherapy, choline supplementation resulted in improved quality of life, decreased asthma medication use, improvements in airway responsiveness, and significantly reduced markers of inflammation including interleukin-4 (IL-4), IL-5, and tumor necrosis factor alpha (TNF-α)[94]. Interestingly, in a case-control study investigating the metabolomic signature of the serum of asthmatics compared to non-asthmatic controls, choline was significantly lower in asthmatic subjects[95]. In addition, this metabolomic profile was associated with decreased lung function including the forced expiratory volume in one second (FEV_1) percent predicted[95], demonstrating a possible role for choline in the pathogenesis of asthma.

More studies are needed to elucidate the effects of choline in the development of asthma and allergies. As with folate, there appears to be a role of the intestinal microbiome in mediating the effects of dietary choline. Through metabolomics studies, the role of gut microbiome metabolism of dietary choline in atherosclerosis has been elucidated. Gut microbiome metabolism of choline and phosphatidylcholine lead to the formation of trimethylamine N-oxide (TMAO),[96, 97] which was recently shown to increase the risk of major cardiovascular events such as death, myocardial infarction, or stroke.[98] The role of TMAO in asthma and allergies is unknown, however, the metabolomic study[95] cited above linking lower choline levels in serum with asthma suggests that this line of research should be investigated further.

Vitamin B12

Vitamin B12 (B12) is a water-soluble vitamin that plays a key role in one-carbon metabolism. Vitamin B12 is naturally found in several foods including fish, meat, poultry, eggs, and dairy products. Vitamin B12 is also found in fortified foods including cereals and grains as well as in dietary supplements[29]. B12 exists in several forms and contains the mineral cobalt, giving them the name “cobalamins”. Methylcobalamin and 5-deoxyadenosylcobalamin are the forms of B12 that are important in human metabolism[99]. Vitamin B12 is required for red blood cell formation, DNA synthesis, and proper neurologic function[100]. Folate metabolism is influenced by vitamin B12 levels[101]. B12 acts as a co-factor for folate, and provides methyl groups for the synthesis of methionine and its derivate SAM, which is a universal methyl donor for multiple substrates: DNA, RNA, proteins, lipids, and hormones. B12 deficiency results in decreased methylation of deoxyuridylic acid (dUMP) to deoxythymidylic (dTMP), leading to an excessive incorporation of uracil into DNA as well as DNA hypomethylation[102]. Animal models have shown that increased B12 is associated with an increased risk of allergic airway disease that is mediated through epigenetic mechanisms including changes in DNA methylation[26].

The results of studies investigating B12 intake and the development of atopy in humans have been variable. In a single birth cohort, maternal serum B12 concentrations during pregnancy were significantly associated with an overall increased prevalence of atopic dermatitis in children[44]. However, a study of 763 asthmatic children in Japan, showed that maternal vitamin B12 intake during pregnancy was not associated with the development of

wheeze or eczema[50]. In addition, serum levels and dietary intake of B12 were not associated with asthma and atopy in a large, adult cohort study[61]. These studies have been limited by small sample sizes and a lack of interventional studies. Therefore, the role of vitamin B12 in the development of asthma and allergy remains unclear.

Vitamins B2 and B6

Vitamin B2, or riboflavin, is required for several cellular processes. There are a variety of dietary sources of vitamin B2 including eggs, meat, milk and cheese. In addition, it is found in many fortified foods including cereals and rice as well as in nutritional supplements including multivitamins. Vitamin B6 is a water-soluble vitamin that is naturally occurring in many foods. Vitamin B6 is the generic name for six compounds with vitamin B6 activity: pyridoxine, pyridoxal, pyridoxamine, and their respective 5′-phosphate esters. The vitamin B6 compounds are naturally occurring in fish, beef liver, fruits, vegetables, and grains[29]. In the United States, most adults obtain most of their vitamin B6 from fortified foods including cereals, beef, and poultry. Furthermore, vitamin B6 is found in multivitamins and supplements containing other B complex vitamins. Vitamin B2 and B6 perform a wide variety of biologic functions including assisting in the metabolic pathway of one-carbon compounds (Figure 1).

Although the data for the role of vitamins B2 and B6 in asthma pathogenesis is limited, several small studies have investigated the role of vitamins B2 and B6 on the risk of atopy. In a study investigating maternal vitamin B intake during pregnancy and the subsequent risk of wheeze and eczema in infants, Miyake and colleagues demonstrated no evidence of association of maternal vitamin B2 or B6 intakes with the subsequent risk of wheeze or eczema up to two years of age in Japanese children[50]. In a small cross-sectional study evaluating the prevalence of allergy in school children in Vietnam, vitamin B2 intake was found to be associated with a reduced risk of allergy ($p=0.038$)[103]. Using the European Respiratory Health Survey (ECRHS) data to determine the role of dietary intake on the prevalence of allergic sensitization, Heinrich and colleagues showed no association of vitamin B2 intake and the prevalence of allergy[104]. Finally, in a cross-sectional population based study of 1671 subjects with and without atopy in Denmark, dietary intake of vitamins B2 and B6 were not significantly associated with atopy[71]. However, there was noted to be at least a borderline interaction between *MTHFR* genotype (C677T) and the dietary intake of vitamins B2 and B6 with a decreased risk of atopy [71].

While there is data to suggest that vitamin B6 level is associated with homocysteine metabolism[105] and that increased dietary intake of vitamin B6 results in decreased plasma homocysteine levels[106], its role in asthma and allergy is not yet clear. A few studies have investigated these vitamins in established asthma. In a small study of 31 patients with asthma participating in a double-blind trial, vitamin B6 supplementation in steroid-dependent asthma was not associated with improvement in lung function, asthma symptom scores, or 24 hour urinary 5-HIAA levels[107]. However, in a different study of 15 adult patients with asthma, erythrocyte pyridoxal phosphate concentrations were significantly lower in asthmatics compared to non-asthmatic controls[108]. Furthermore, supplementation with vitamin B6 in these subjects was associated with decreased asthma symptoms and

decreased exacerbation rates[108]. In a double-blind study of 76 asthmatic children supplementation with vitamin B6 was associated with improvement in asthma symptoms resulting in a reduction in the dosage of asthma-treatment medications[109].

Although definitive clinical trials are lacking, a review of the current literature only supports a limited effect of vitamins B2 and B6 on atopic disease susceptibility and disease treatment due to the discrepancy of the results obtained to date. Some of the variability in the results of these studies may be due to study design, sample size, analytic approach, the difficulty of B vitamin status assessment, and age.

Betaine

Betaine is a water soluble molecule that is involved in a variety of biologic processes including DNA methylation. Betaine is found in a variety of food sources including beets, broccoli, spinach, seafood, and grains. In addition, it is found in small quantities in nutritional supplements and multivitamins[110]. It is essential in one-carbon metabolism playing an essential role in the transition from homocysteine to methionine. Studies investigating the role of betaine in the development of asthma and allergy are lacking. Furthermore, studies investigating the role of betaine in DNA methylation in humans is limited. In a large cohort study of 534 pregnant women in Project Viva, there was no significant association found between maternal dietary intake of betaine in both the first and second trimesters of pregnancy with cord blood LINE-1 methylation[56]. However, periconceptional intake of betaine was inversely associated with cord-blood methylation, but the effect of betaine on methylation was attenuated after adjustment for cadmium intake[56]. Given its importance in one-carbon metabolism, studies investigating the role of dietary betaine intake in the development of asthma and allergy are warranted.

Summary and Future Directions

Dietary changes are a proposed mechanism underlying the increasing prevalence of asthma and allergic disease worldwide. Several observational studies and a few small interventional trials have attempted to assess the role of dietary methyl donors in the development and treatment of asthma and allergy. Due to the interest in the early origins of asthma and allergic diseases, and because of recommendations for folic acid supplementation in pregnancy for the prevention of neural tube defects, folate intake has been investigated as a potentially modifiable exposure in pregnancy. However, the results of the studies investigating prenatal folate intake or folate status published to date have been mixed, limiting any definitive conclusions on the role of prenatal folate with regards to its association with asthma and allergy. Studies investigating postnatal folate intake or status in childhood or adulthood have also been mixed, and studies of other dietary methyl donors have been limited.

While more studies are needed to allow for more definitive conclusions regarding the effect of these nutrients on asthma and allergies, appropriate attention to study design is essential for future investigations. In addition, two other issues need to be considered in either analyzing existing datasets or designing new studies – broader approaches such as pathway or systems analyses and incorporation of the effects of the intestinal microbiome. Few of the

studies reviewed here have investigated more than one nutrient. Given that these nutrients are intricately related in pathways (Figure 1), future studies need to include analyses of multiple nutrients. Furthermore, given the complexities of the one-carbon metabolism pathway, analyses including a systems-based approach or pathway analyses may further our understanding of the role of dietary methyl donors in the development of atopic disease[69].

Finally, the role of the microbiome in health is gaining wider recognition. The intestinal microbiome has been shown to be actively involved in the production and metabolism of these nutrients. As reviewed, several strains of the genus *Bifidobacteria* have the ability to produce folate. The microbiome also has a role in either the production or metabolism of other B vitamins (reviewed in LeBlanc et al.[74]). B vitamin production by intestinal bacteria are mediating or modifying the effects of ingested nutrients, and may partly explain the heterogeneity in the results of the studies investigating these nutrients to date. The design of future studies will need to incorporate analyses of the intestinal microbiome to fully understand the effects of these nutrients on human health in general, and in the development of asthma and allergies in particular. For example, in the ongoing Vitamin D Antenatal Asthma Reduction Trial (VDAART, U01 HL091528 and ClinicalTrials.gov # NCT00920621), we are collecting both pre- and postnatal dietary information (including vitamins other than vitamin D) and stool samples (R01HL108818) to enable such studies. Integration of these types of datasets (i.e. dietary data and microbiome data) will lead to novel insights into the biologic basis of health and disease[111, 112].

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Abbreviations

(CMT)	Choline Magnesium Trisalicylate
(SAH)	S-Adenosyl-homocysteine
(SAM)	S-Adenosyl-methionine
(THF)	Tetrahyrdrofolate
(B2)	Vitamin B2
(B6)	Vitamin B6
(B12)	Vitamin B12

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Key Messages

- Results of studies investigating the effect of dietary methyl donors on asthma and allergy susceptibility have been variable.
- The current evidence does not support the routine supplementation of dietary methyl donors for the primary prevention or treatment of asthma and allergy.
- Future studies need to incorporate pathway or systems-based analyses and the effects of the microbiome on these nutrients.

Capsule Summary

Dietary changes in methyl donors may explain the increase in atopic disease. Studies investigating methyl donor supplementation with atopy have had variable results. Insufficient evidence exists to recommend dietary methyl donor supplementation to treat atopy.

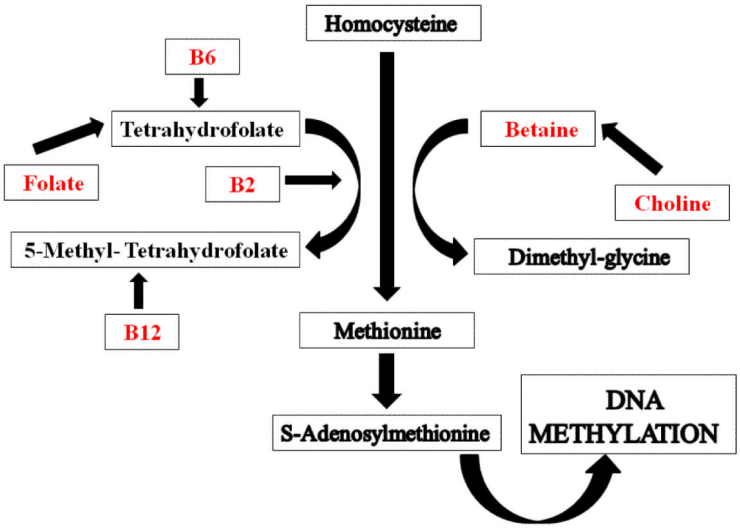

Figure 1.

Figure 1 represents a simplified diagram of the one-carbon metabolic pathway. The figure demonstrates where dietary methyl donors, identified in red, are involved in the one-carbon metabolic pathway and how they influence DNA methylation. DNA methylation depends upon the availability of methyl groups from *S*-adenosylmethionine, which is derived from methionine. This figure highlights the connection between folate, choline, methionine, betaine, and vitamins B2, B6, and B12 on DNA methylation. The pathways intersect at the formation of methionine from homocysteine.

Table 1

Methyl donor sources, function, and mechanisms of action

Methyl Donor	Dietary Sources*	Function	Mechanism of Action in Methylation Reactions
Folate	Green leafy vegetables, fruits, nuts, beans, grains, fortified cereals, eggs, dairy	Purine and pyrimidine production, amino acid production, and cell division	Production of S-adenosylmethionine (SAM)
Choline	Soybeans, egg, peanuts, cauliflower, lentils, and flax seeds	Precursor to phosphatidylcholine and sphingomyelin, Aids in the movement of lipids into and out of cells	Production of SAM
Vitamin B12	Fish, meat, poultry, eggs, and dairy products	Red blood cell formation, DNA synthesis, and neurologic function	Methionine Synthesis
Vitamin B2 (riboflavin)	Eggs, meat, milk and cheese	Energy production, antioxidant, red blood cell production	Methionine production
Vitamin B6 (pyridoxine)	Fish, beef liver, fruits, vegetables, and grains	Homocysteine metabolism, metabolism of fats and protein, nervous system development	Folate metabolism
Betaine	Beets, broccoli, spinach, seafood, and grains	Homocysteine metabolism, immune modulation	Methionine production

*Dietary sources other than nutritional supplements or fortified foods.

Table 2

Results of studies investigating the role of non-folate methyl donors in the primary prevention or treatment of asthma and allergy

Methyl donor	Potential mechanism of action	Observational studies*	Randomized-control trials
Choline	Animal models demonstrate anti-inflammatory properties and anti-oxidant properties of choline.	No observational studies.	No primary prevention studies.
			RCT of asthmatic subjects showed no improvement in asthma and allergy symptoms or lung function[91]. (n=23)
			RCT of asthmatic subjects showed choline supplementation resulted in decreased asthma symptom scores, increased symptom-free days, and decreased medication use[93].
			RCT of asthmatic patients showed choline supplementation resulted in improved quality of life, decreased airway responsiveness, and decreased inflammatory markers[92].
Vitamin B12	A co-factor for folate. Provides methyl groups for the synthesis of methionine and S-adenosyl-methionine.	Maternal serum vitamin B12 was associated with increased atopic dermatitis in a birth cohort[44]. (n=8,742)	No randomized controlled trials.
		Japanese birth cohort showed maternal vitamin B12 intake during pregnancy was not associated with wheeze or eczema[50]. (n=763)	
		Serum vitamin B12 level and dietary intake was not associated with asthma or atopy in an adult cohort study[61]. (n=6,784)	
Vitamin B2	Important in methionine synthesis and its role as a methyl donor.	Japanese birth cohort showed maternal vitamin B2 intake during pregnancy was not associated with wheeze or eczema[50]. (n=763)	No RCTs.
		Riboflavin intake was associated with a reduced risk of allergy[103]. (n=195)	
		Adult cohort study showed no association with vitamin B2 with the prevalence of allergy[104]. (n=3,872)	
		Cross-sectional study of adult subjects with and without atopy showed no association of vitamin B2 with atopy[71] (n=1,671)	

Methyl donor	Potential mechanism of action	Observational studies*	Randomized-control trials
Vitamin B6	Important in methionine synthesis and its role as a methyl donor.	Japanese birth cohort showed maternal vitamin B6 intake during pregnancy was not associated with wheeze or eczema[50]. (n=763)	RCT of asthmatic patients showed that pyridoxine supplementation was not associated with asthma symptoms or lung function[107]. (n=31)
		Cross-sectional study of adult subjects with and without atopy showed no association of vitamin B2 with atopy[71] (n=1,671)	RCT of adult asthmatics vitamin B6 levels were associated with decreased asthma symptoms and exacerbation rates[108]. (n=15)
			RCT of childhood asthmatics treated with pyridoxine showed significant improvement in use of bronchodilators and cortisone use[109] (n=76)
Betaine	Important in methionine synthesis and its role as a methyl donor. Involved in global methylation	No observational studies.	No RCTs.

* Observational studies include birth cohort studies and cross-sectional studies.