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The association between atopy and factors influencing folate metabolism: is low folate status causally related to the development of atopy?

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Background Deficiency of folate has been associated with several disorders characterized by enhanced activation of the cellular immune system (non-allergic th1 type immune response). Whether folate status is also associated with atopic disease (allergic th2 type immune response) is unknown. We aimed at examining the association between atopy and markers of impaired folate metabolism, i.e. MTHFR(C677T) genotype, plasma total homocysteine, and dietary intakes of methionine, folates, and vitamins B12, B6, and B2.

Methods Cross-sectional population-based study of 1671 male and female residents of Copenhagen County, Denmark, aged 30–60 years participating in a health examination during 1999–2001. Atopy was defined as positive levels of specific IgE against a panel of inhalant allergens. MTHFR(C677T) genotype was determined by PCR followed by restriction fragment length polymorphism analyses. Total homocysteine was measured by fluorescent polarization immunoassay. Dietary vitamin intakes were estimated from a semi-quantitative food frequency questionnaire.

Results The prevalence of atopy was associated with MTHFR(C677T) genotype. TT individuals had a significantly higher risk of atopy compared with CC/CT individuals [odds ratio 1.76, 95% confidence interval (95% CI) 1.19–2.60]. Additionally, gene–diet interaction effects were identified. Dietary markers were negatively associated with risk of atopy in persons with the TT genotype. Total homocysteine was not related to atopy (odds ratio per 5 μmol/l = 1.12, 95% CI 0.98–1.29).

Conclusions The results suggest that an impaired folate metabolism may be causally related to the development of atopy.

Keywords Folic acid, allergy, methylenetetrahydrofolate reductase, vitamin B 12, vitamin B 6, vitamin B 2, methionine, homocysteine, atopy, IgE, folate

Atopy is defined as a personal and/or familial tendency to produce IgE antibodies (allergic th2 type immune response) against common environmental allergens, usually proteins.[1] Atopic persons are at increased risk of developing atopic diseases such as asthma, allergic rhinoconjunctivitis, and atopic eczema. There is evidence that the prevalence of atopic disease has increased over recent decades in Westernized affluent countries including Denmark.[2] The causes of this increase are

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not known, but changes in lifestyle and dietary factors have been proposed.

It has been suggested that the current recommendation of folate intake is not optimal, and that a large proportion of the population of Denmark and other European countries suffer from relative folate deficiency.[3] Thus folate deficiency may represent a significant health problem.

Deficiency of folate has been shown to increase susceptibility to infection[4] and is associated with several disorders characterized by enhanced activation of the cellular immune system (th1 immune response) like neurodegenerative disorders such as Alzheimer's disease,[5] autoimmune diseases such as rheumatoid arthritis,[6,7] and cardiovascular disease.[8,9] To our knowledge no previous study has examined the relationship between folate status and atopic disease.

Folate is an essential vitamin cofactor that appears in various different biochemical forms. Folates are involved in numerous biochemical reactions, where they function as donors/acceptors of different one-carbon units (Figure 1).[10] Thus folates are required for DNA synthesis and repair as well as for methyl transfer reactions essential in the synthesis and regulation of many biological molecules including gene expression. Elevated total homocysteine is a sensitive marker of an impaired folate metabolism; especially the methylation cycle.[11] Folate deficiency may result from insufficient dietary intake of folates. Moreover, a low intake of the vitamin cofactors B12, B6, and B2 may impair folate metabolism (Figure 1). In addition, a common single nucleotide polymorphism—C to T transition at nucleotide position 677 (C677T)—has been identified in the gene encoding methylenetetrahydrofolate reductase (MTHFR), which is considered a key regulatory enzyme in folate metabolism, as it directs folates towards either the DNA synthesis cycle or the methylation cycle (Figure 1).

The aim of the study was to examine the association between markers of impaired folate metabolism (total homocysteine, the MTHFR(C677T) polymorphism, and dietary intake of folate and vitamins B12, B6, and B2) and the prevalence of atopy in a population-based study of 1671 Danish men and women aged 30–60 years.

Materials and methods

Study population

The subjects were participants in the Inter99 study, a population-based randomized controlled trial, investigating the effect of non-pharmacological intervention on cardiovascular disease and diabetes. The Inter99 study has been described in detail elsewhere.[12,13] An age-specific and sex-stratified random sample of 13 016 persons born in 1939–40, 1944–45, 1949–50, 1954–55, 1959–60, 1964–65, 1969–70 and living in 11 municipalities in the South-western part of the Copenhagen County was drawn from the Civil Registration System and invited to a health examination from March 1999 through January 2001. Data were collected using a self-administered questionnaire, a physical examination, and blood tests. Individuals born in 1940, 1945, 1950, 1955, 1960, 1965, and 1970 were a priori selected for homocysteine measurement and MTHFR(C677T) genotype determination. Individuals born in 1939–40, 1949–50, 1959–60, and 1969–70 were selected for IgE assessment. Thus the current study population was based on a random sample of 3504 individuals born in 1940, 1950, 1960, and 1970 selected for the determination of both homocysteine, MTHFR(C677T) genotype, and IgE. A total of 3480 persons were eligible for invitation and 48.0% (n = 1671) participated.

Assessment of atopy

Measurement of atopy was performed by using the ADVIA Centaur® Allergy Screen (AS) assay (Bayer HealthCare Diagnostics division, Tarrytown, NY).[14,15] The AS assay is a multiallergen assay for the qualitative detection of IgE antibodies specific to common inhalant allergens in serum. The test encompasses the 19 most commonly encountered inhalant allergens: two house dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), three animal danders (horse, cat, and dog), two grasses (*Phleum pratense* and *Cynodon dactylon*), three moulds (*Cladosporium herbarium*, *Aspergillus fumigatus*, and *Alternaria alternata*), four trees (*Betula verucosa*, *Quercus alba*, *Olea europae* and *Cryptomeria japonica*), four weeds (*Amrosia*

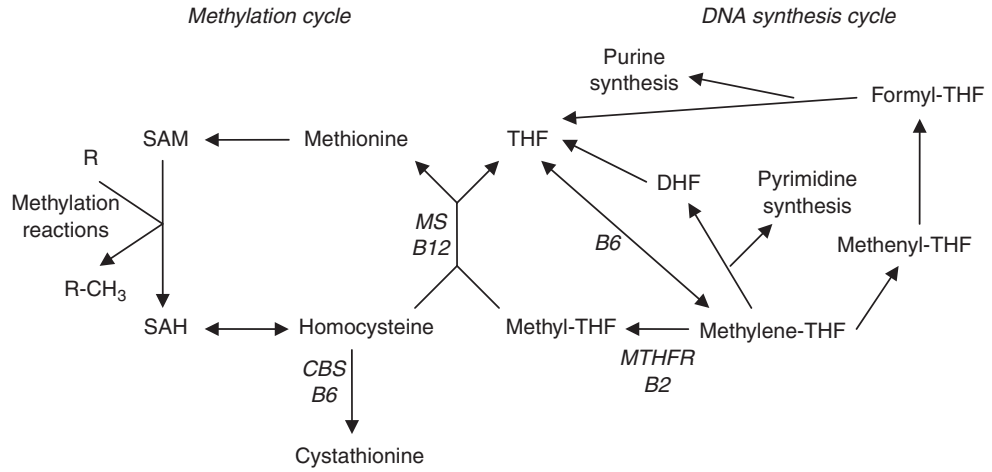

Figure 1 Simplified diagram of folate metabolism. *Abbreviations:* SAM S-adenosylmethionine, SAH S-adenosylhomocysteine, R biological molecule, R–CH_3 methylated biological molecule, THF tetrahydrofolate, DHF dihydrofolate, *MS* methionine synthase, *MTHFR* methylenetetrahydrofolate reductase, *CBS* Cystathionine-β-synthase

artemisifolia, *Artemisia vulgaris*, *Plantago lanceolata*, and *Parietaria officinalis*), and finally one insect (*Blattella germanica*). Atopy was defined as a positive result of the dichotomized AS assay test output. The AS assay has previously been validated in our background population and proved to be a valid measure of allergic respiratory disease and skin prick test reactivity, the gold standard for measuring atopy.[15] A total of 78 (4.6%) participants had missing data on atopy.

Determination of MTHFR(C677T) genotype

DNA was extracted from blood leukocytes, and the presence of the MTHFR(C677T) mutation was determined by PCR followed by RFLP (restriction fragment length polymorphism) analyses as described previously.[16,17] A total of 179 (10.7%) participants had missing data on MTHFR genotype.

Homocysteine measurement

Homocysteine was determined in fasting blood samples using Abbott's Imx FPIA (Fluorescent Polarization Immuno Assay) (Abbott Laboratories, Abbott Park, IL) as described previously.[16] A total of 152 (9.1%) participants had missing data on total homocysteine.

Assessment of dietary vitamin intake

The dietary vitamin intake was assessed using an extensive food frequency questionnaire (FFQ) covering 198 food items and beverages. The FFQ was based on FFQs previously used and validated in the Diet, Cancer and Health study and The Danish National Birth Cohort,[18,19] but the questionnaire was modified to improve estimates of fatty acids, cholesterol, and complex carbohydrates. The extensive FFQ has been described previously.[20] Briefly, participants were asked to report their average intake of different foods and beverages of the last month, choosing between 7 and 11 possible responses, ranging from never to eight or more times per day. The questionnaire also included questions about the types of bread, spread, and fat used for cooking. The food consumption quantity was obtained by multiplying the frequency of consumption of each unit of food by standard portion sizes.[21,22] To translate food consumption into energy intake and daily nutrient intake all food items were linked to food items in the Danish Food Composition Databank[23] and the software program FoodCalc version 1.3[24] was used for the calculations. A total of 90 (5.4%) participants did not complete the 198 item FFQ or clearly misunderstood the questionnaire.

Self-administered questionnaire

The self-administered questionnaire provided information on potential confounders such as socioeconomic factors, smoking status, and alcohol consumption.

Social class was defined on the basis of questions regarding number of years of vocational training and employment status and categorized into five classes as described previously.[12] For the statistical analyses the lowest and highest social classes were combined with the neighbouring categories to give the categories: lower (1 + 2), middle (3), and upper (4 + 5) social class.

Smoking status was defined in five categories: never smokers, ex-smokers, occasional smokers (<1 g of tobacco per day), light smokers (<15 g/day), and heavy smokers (≥15 g/day). The amount and type of alcoholic beverages were recorded as mean number of bottles/glasses per week in the last 12 months. The number of units of ethanol (1 unit = 1.5 cl/12 g) was calculated.

Statistical analyses

Statistics were computed with the statistical program SAS, version 9.1 (SAS Institute Inc. Cary, NC, USA). Comparisons between atopic and non-atopic individuals as well as between MTHFR(C677T) genotypes were done by the Wilcoxon two-sample test/the Kruskall–Wallis test for continuous outcome variables and the chi-squared test for frequency outcomes. Logistic regressions models were used to evaluate whether the various markers of impaired folate metabolism [MTHFR(C677T) genotype, plasma total homocysteine, and dietary intakes of methionine, folates, B12, B6, and B2, respectively] were associated with the prevalence of atopy . All models were adjusted for sex, age, and smoking status. Models including dietary variables were adjusted for total energy intake. Additionally, potential confounders (alcohol consumption, physical activity, social class) were included if statistically significant and/or influencing effect estimates. Continuous variables were tested for linear associations by including the squared terms of the variables in the respective models. Interaction effects between MTHFR(C677T) genotype and dietary factors influencing folate metabolism were assessed by evaluating the effect estimates and *P*-values of the relevant interactions in the multiple adjusted regression models. Since the C677T mutation is a recessive mutation, the CC and CT genotype groups were combined to increase the statistical power in the interaction analyses.

Results

General characteristics of the Inter99 study population has been described in detail elsewhere.[13,16] The current study population consisted of 797 men and 874 women aged 30, 40, 50, and 60 years. The prevalence of atopy was 25.4%. The prevalence of the three MTHFR(C677T) genotypes was 50.0% (CC homozygotes), 41.6% (CT heterozygotes), and 8.4% (TT homozygotes). The overall frequency of the T allele was 29.2%. The observed genotype distribution did not deviate significantly from Hardy–Weinberg equilibrium.

Distributions of plasma total homocysteine and dietary intakes of methionine, folates, and vitamins B12, B6, and B2 did not differ between persons with and without atopy (Table 1). Neither did the prevalence of alcohol consumption, physical activity, overall dietary habits, and social class differ between persons with and without atopy. However, atopic persons were more likely to be non-smokers and of younger age (Table 1). In addition, the prevalence of TT genotype was significantly higher among atopic persons compared with non-atopic persons (Table 1). Accordingly, the prevalence of atopy was also higher among TT individuals compared with CC and CT individuals (Table 2).

The age and sex distributions did not differ between MTHFR(C677T) genotypes (Table 2). Neither did dietary

Table 1 Characteristics of the study population according to the presence of atopy

	Total	Atopy		*P*-value[a]
		No	Yes	
MTHFR TT genotype[b]	8.5 (126)	7.3 (78)	12.4 (46)	0.0027
Homocysteine (μmol/l)[c]	8.08 (4.62–17.84)	8.06 (4.62–17.68)	8.20 (4.75–20.58)	0.22
Total energy intake (MJ/day)[c]	9.30 (4.43–18.23)	9.29 (4.57–18.23)	9.42 (4.40–18.20)	0.98
Methionine intake (g/day)[c]	1.55 (0.69–2.95)	1.55 (0.70–2.88)	1.59 (0.69–3.09)	0.54
Folate intake (μg/day)[c]	357 (156–790)	357 (159–825)	353 (148–728)	0.36
Vitamin B12 intake (μg/day)[c]	5.23 (1.65–14.89)	5.28 (1.65–15.63)	4.96 (1.58–13.94)	0.32
Vitamin B6 intake (mg/day)[c]	1.40 (0.61–2.56)	1.41 (0.62–2.52)	1.40 (0.61–2.76)	0.98
Vitamin B2 intake (mg/day)[c]	1.65 (0.72–3.53)	1.68 (0.72–3.52)	1.60 (0.71–3.53)	0.42
Age (years)[c]	50 (30–60)	50 (30–60)	40 (30–60)	0.0003
Males[b]	47.7 (797)	47.5 (564)	51.6 (209)	0.15
Current smokers (>1 g/day)[b]	33.6 (558)	35.5 (420)	26.7 (108)	0.0012
Alcohol (units/week)[c]	6 (0–38)	6 (0–40)	6 (0–35)	0.43
Low physical activity[b]	21.8 (357)	21.5 (250)	21.5 (86)	1.00
Unhealthy dietary habits[b]	15.7 (256)	15.7 (181)	15.8 (63)	0.97
Lower social class[b]	12.5 (191)	13.0 (141)	10.9 (41)	0.31

[a] Differences between groups were tested using Wilcoxon two-sample test for continuous data, and chi-square test for frequency data.
[b] % (*n*) of total with non–missing data on the particular covariates.
[c] Median (2.5th–97.5th percentiles).

Table 2 Characteristics of the study population according to MTHFR(C677T) genotype

	MTHFR(C677T) genotype			*P*-value[a]
	CC	CT	TT	
Atopy[b]	25.7 (185)	23.7 (141)	37.1 (46)	0.0079
Homocysteine (μmol/l)[c]	7.81 (4.40–14.53)	8.16 (4.79–18.17)	9.84 (5.06–37.29)	<0.0001
Total energy intake (MJ/day)[c]	9.22 (4.63–18.30)	9.17 (4.37–18.24)	9.60 (4.38–18.34)	0.45
Methionine intake (g/day)[c]	1.55 (0.72–2.91)	1.54 (0.66–2.91)	1.61 (0.66–3.40)	0.29
Folate intake (μg/day)[c]	353 (159–838)	355 (148–777)	374 (156–865)	0.90
Vitamin B12 intake (μg/day)[c]	5.28 (1.70–15.01)	5.15 (1.46–14.59)	5.53 (1.86–14.30)	0.91
Vitamin B6 intake (mg/day)[c]	1.40 (0.64–2.56)	1.40 (0.59–2.47)	1.44 (0.64–2.98)	0.28
Vitamin B2 intake (mg/day)[c]	1.67 (0.74–3.53)	1.61 (0.66–3.37)	1.82 (0.65–4.06)	0.16
Age (years)[c]	50 (30–60)	50 (30–60)	50 (30–60)	0.91
Males[b]	48.1 (359)	46.5 (288)	50.0 (63)	0.70
Current smokers (>1 g/day)[b]	32.1 (239)	35.9 (221)	27.8 (35)	0.13
Alcohol (units/week)[c]	6 (0–40)	6 (0–37)	6 (0–29)	0.88
Low physical activity[b]	22.1 (162)	21.6 (131)	25.0 (31)	0.70
Unhealthy dietary habits[b]	15.7 (115)	15.5 (93)	20.2 (25)	0.41
Lower social class[b]	13.2 (90)	11.3 (64)	10.7 (12)	0.53

[a] Differences between MTHFR(C677T) genotypes were tested using Kruskal–Wallis test for continuous data, and chi-square test for frequency data.
[b] % (*n*) of total with non-missing data on the particular covariates.
[c] Median (2.5th–97.5th percentiles).

vitamin intakes nor the prevalence of potential lifestyle confounders (Table 2), although persons with the TT genotype had significantly higher plasma total homocysteine than persons with the CT and CC genotypes (Table 2).

In logistic regression models the MTHFR(C677T) polymorphism was associated with the risk of atopy ($P = 0.019$). TT individuals had a significantly higher risk compared with CC [odds ratio 1.70, 95% confidence interval (95% CI) 1.13–1.56, $P = 0.010$] and CT (odds ratio 1.83, 95% CI 1.20–2.78, $P = 0.0046$) individuals (Table 3). Since CT individuals did not differ from CC individuals with respect to atopy (odds ratio 0.93, 95% CI 0.72–1.20, $P = 0.59$), these genotypes were combined (Table 3). Elevated plasma total homocysteine was not associated with higher risk of atopy (Table 3). Neither were dietary intakes of methionine and vitamins B12, B6, and B2 (Table 3). A tendency towards a lower risk of atopy was

Table 3 Risk of atopy associated with markers of folate metabolism in relation to MTHFR(C677T) genotype

	Risk of atopy [OR (95% CI)][a]		
Markers of folate metabolism	Overall	MTHFR CC/CT	MTHFR TT
MTHFR (C677T) genotype (TT vs CC/CT)	1.76 (1.19–2.60)	Not applicable	Nor applicable
	$P = 0.0058$	Not applicable	
Plasma total homocysteine (per 5 µmol/l)	1.12 (0.98–1.29)	Not applicable	Not applicable
	$P = 0.11$	Not applicable	
Methionine intake (per 1 g/day)	1.13 (0.81–1.59)	1.22 (0.84–1.76)	0.57 (0.27–1.20)
	$P = 0.47$	$P_{interaction} = 0.033$	
Folate intake (per 100 µg/day)	0.91 (0.82–1.01)	0.94 (0.84–1.06)	0.67 (0.49–0.91)
	$P = 0.07$	$P_{interaction} = 0.017$	
Vitamin B12 intake (per 1 µg/day)	0.98 (0.95–1.02)	0.99 (0.95–1.03)	0.86 (0.74–1.00)
	$P = 0.41$	$P_{interaction} = 0.048$	
Vitamin B6 intake (per 1 mg/day)	0.99 (0.65–1.51)	1.09 (0.70–1.72)	0.51 (0.21–1.24)
	$P = 0.95$	$P_{interaction} = 0.072$	
Vitamin B2 intake (per 1 mg/day)	0.90 (0.72–1.14)	0.97 (0.75–1.26)	0.54 (0.30–0.96)
	$P = 0.40$	$P_{interaction} = 0.037$	

[a] Risk of atopy was estimated by logistic regression analyses. *P*-values are likelihood ratio tests. All models were adjusted for sex, age, and smoking status. Models including dietary intake variables were also adjusted for total energy intake. Effect modification by MTHFR(C677T) genotype was assessed by evaluating the effect estimates and *P*-values of the relevant interaction terms in the regression models. Inclusion of additional potential confounders did not alter the results.

observed with increasing dietary intake of folates (Table 3). Significant interaction effects were observed between MTHFR(C677T) genotype and dietary intakes of methionine, folates, B12, B6 (borderline) as well as B2 (Table 3). Thus dietary intakes of these vitamins were negatively associated with risk of atopy in genetically predisposed persons with the MTHFR TT genotype. Adjustment for additional potential lifestyle confounders did not affect the results.

Owing to multicollinearity between dietary variables (Table 4), it was not possible to include these variables in the same model and, thus, separate the individual effects from one another.

Discussion

In this study we examined the associations between various markers of impaired folate metabolism and the prevalence of atopy. MTHFR TT individuals had a significantly higher risk of atopy compared with CC and CT individuals. In addition, low dietary intakes of methionine, folates, and additional B vitamins were associated with high risk of atopy in persons with the MTHFR TT genotype predisposing to an impaired folate metabolism.

Table 4 Correlations[a] among dietary factors

Dietary factors	Methionine	Folate	Vitamin B12	Vitamin B6	Vitamin B2
Methionine	1	0.62	0.75	0.80	0.85
Folate	0.62	1	0.58	0.81	0.68
Vitamin B12	0.75	0.58	1	0.62	0.80
Vitamin B6	0.80	0.81	0.62	1	0.76
Vitamin B2	0.85	0.68	0.80	0.76	1

[a] Spearman correlation coefficients, all *P*-values <0.0001.

To our knowledge, this is the first study reporting the association between the MTHFR(C677T) genotype and atopy.

Since MTHFR is a crucial enzyme in folate metabolism, our results suggest that an impaired folate metabolism may be causally related to the development of atopy. The finding of gene–nutrient interaction effects supports this hypothesis.

The MTHFR C677T polymorphism has been shown to affect folate metabolism in several ways. Specifically, the methylation cycle seems to be impaired in TT individuals. The TT genotype has been associated with reduced enzyme activity and decreased remethylation of homocysteine to methionine leading to elevated total homocysteine and reduced *de novo* methyl group supply for transmethylation reactions.[25]

The C677T transition in the MTHFR gene causes an amino acid change (ala222val) in the catalytic domain of the enzyme that results in enhanced dissociation of the vitamin B2 cofactor and inactivation of the enzyme.[26,27] An optimal folate supply has been shown to prevent the loss of B2 binding and to suppress the inactivation of the enzyme.[26,27] Accordingly, gene–nutrient interaction effects between folate and the MTHFR(C677T) polymorphism have been reported.[28,29]

In addition, the distribution of the different forms of folate is altered in TT individuals.[30] The red blood cells of TT individuals have diminished proportions of methylated tetrahydrofolates and increased amounts of formylated folates.[30] Conversely, cells from CC individuals contain only methylated folate derivatives.[30] These data suggest that the TT genotype is associated with an impairment to convert formylated forms to methylated folate derivatives.

Finally, the MTHFR TT genotype has been associated with lower overall blood concentrations of folates compared with CC and CT individuals, which could not be attributed to differences in dietary intakes of folates between genotypes.[31]

Thus, persons with the TT genotype have an increased folate demand compared with persons with CC and CT genotypes indicating that an inadequate folate supply may contribute to the development of atopy.

One potential mechanism by which MTHFR(C677T) genotype and inadequate folate status may be related to development of atopic allergy comprises an altered th1/th2 balance resulting from inhibition of the remethylation cycle.

Although a strict counterbalance between th1- and th2-type immune responses is probably too simplistic,[32] *in vitro* and *in vivo* studies have shown a cross-regulatory influence between th1- and th2-type immune responses, down-regulating each other when activated.[33] Because of this cross-regulatory interplay, the susceptibility for allergic diseases may increase

when th2-type cytokines are overproduced as well as when th1-type cytokines are suppressed.

During a non-allergic th1-type proliferative immune response, folates are necessary for the essential methyl-group transfer reactions in proliferating cells. Thus in TT individuals, an allergic th2-type immune response may be favoured over a th1-type immune response at low folate status as a result of the increased folate demand associated with the TT genotype.

This hypothesis may also explain why oxidative stress has been related to enhanced allergic inflammation. Immune activation is associated with oxidative stress, which in turn causes oxidation of antioxidant substances and afterwards the oxidation of other antioxidant substances such as 5-MTHF. Low antioxidant capacity might cause a shift towards th2-type immune response through impairment of folate metabolism. On the other hand, a recent review hypothesized that excessive antioxidants may increase the probability of developing allergic diseases and asthma.[34] However, the authors did not address the role of folates and other B vitamins.

Alternatively, the development of atopy may also be a direct effect of elevated homocysteine or some of its metabolites, which appears to exert a number of diverse effects on immune function.[35] In addition, total homocysteine has been shown to increase in response to immune activation and cell proliferation during a non-allergic th1-type immune response.[36] Nevertheless, total homocysteine was not associated with prevalence of atopy in the current study, suggesting that homocysteine is not the causal factor and that atopic persons do not have elevated homocysteine. The finding that MTHFR genotype but not homocysteine was associated with atopy may seem contradictory. However, residual confounding or changes in homocysteine over time may have attenuated the association toward the null value.

An impaired folate metabolism may also inhibit the DNA biosynthesis cycle. Low folate has been associated with uracil misincorporation during DNA synthesis. However, it has been reported that the MTHFR TT genotype is not associated with uracil misincorporation and DNA strand breaks.[37] The TT genotype may even be protective against some cancer forms by favouring purine and pyrimidine synthesis.[38–40] Thus impairment of the DNA synthesis cycle is probably not involved in the development of atopy.

Since this was an observational study, the observed MTHFR-atopy association could be caused by potential methodological problems. According to the principle of Mendelian randomization (based on Mendel's second law—the law of independent assortment of alleles) the observed association was probably not due to confounding by environmental factors.[41–43] Nevertheless, the association could theoretically be caused by unidentified pleiotropic effects of the MTHFR gene or by a polymorphism in another gene in linkage disequilibrium with the MTHFR gene.[41–43] In addition, the fact that this is the first study reporting on a relationship between MTHFR(C677T) genotype and atopy may result from publication bias. Thus a type I error, i.e. false positive finding caused by chance, cannot be excluded, and confirmation in other studies is required.

In contrast, the effect of vitamin status may even have been underestimated, since vitamin intake may have changed considerably from the time when the primary sensitization took place. In addition, no information on vitamin supplement use was available, which may have caused a non-differential misclassification of vitamin intake and attenuated the associations towards the null value. Another explanation could be that the association between these variables and atopy was confounded by unknown atopy determinants not adjusted for in the analyses.

In conclusion, in this general population study, the prevalence of atopy was associated with MTHFR(C677T) genotype. This finding, if confirmed, suggests that impaired folate metabolism may be causally related to the development of atopy.

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KEY MESSAGES

- The prevalence of atopy was associated with the MTHFR(C677T) polymorphism.
- TT individuals had a significantly higher risk of atopy compared with CC and CT individuals.
- An interaction effect between MTHFR genotype and dietary factors influencing folate metabolism was observed.
- Impaired folate metabolism may be causally related to the development of atopy.

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