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Associations of genetic determinants of serum vitamin B12 and folate concentrations with hay fever and asthma: a Mendelian randomization meta-analysis

Short title: B12, folate, hay fever, allergic sensitization and asthma

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Abstract

Background: Studies of the effect of vitamin B12 and folate on risk of asthma and hay fever have shown inconsistent results that may be biased by reverse causation and confounding. We used a Mendelian randomization approach to examine a potential causal effect of vitamin B12 and folate on hay fever, asthma, and selected biomarkers of allergy by using eleven vitamin B12-associated single nucleotide polymorphisms (SNPs) and two folate-associated SNPs as un-confounded markers.

Methods: We included 162,736 participants from nine population-based studies including the UK Biobank. Results were combined in instrumental variable and meta-analyses and effects expressed as odds ratios (ORs) or estimates with 95% confidence interval (CI).

Findings: Using genetic proxies for B12 and folate, instrumental variable analyses did not show evidence for associations between serum B12 and hay fever: OR=1.02 (95% CI: 0.98, 1.05), asthma: OR=0.99 (95% CI: 0.95, 1.04), allergic sensitization: OR=1.02 (95% CI: 0.74, 1.40), or change in serum IgE: 10.0% (95% CI: -9.6%, 29.6%) per 100 pg/ml B12. Similarly there was no evidence for association between serum folate and hay fever: OR=0.74 (95% CI: 0.45, 1.21), asthma: OR=0.80 (95% CI: 0.43, 1.49), allergic sensitization: OR=1.92 (95% CI: 0.11, 33.45), but there was a statistically significant association with change in serum IgE: 2.0% (95% CI: 0.43%, 3.58%) per 0.1 ng/ml serum folate.

Conclusions: Our results did not support the hypothesis that levels of vitamin B12 and folate are causally related to hay fever, asthma, or biomarkers of allergy, but we found evidence of a positive association between serum folate and serum total IgE.

Keywords: allergic disease, serum specific IgE, hay fever, rhinitis, asthma, allergic sensitization.

Introduction

Changes in dietary intake of micronutrients such as vitamin B12 and folate have been suggested to play a role in the increase in allergic respiratory diseases (1-4). Low intake and low serum levels of folate are common, particularly in countries without food fortification with folic acid (5). Folate deficiency changes the cell-mediated immune response (6) and increases the susceptibility to infections (7), and folate deficiency might also directly contribute to the development of atopy by inhibiting the re-methylation cycle in humans (4). On the other hand, in mice, a diet enriched with folate was shown to increase allergic responses, likely through epigenetic changes (8).

Inferring causal relationships in observational studies may be hampered by reverse causation and confounding. Mendelian randomization is a method to examine possible causal relationships where genetic variants with known effects on an exposure are used as proxies for that exposure (9). It is based on an assumption that alleles are randomly allocated from parent to child, thus mimicking a randomized controlled trial potentially free from confounding and reverse causation (10,11).

There are different designs for Mendelian randomization studies (12). Some provide evidence on whether a causal association exists. Others allow the magnitude of the causal effect to be estimated; for example, in the two-sample approach the SNP-exposure associations are estimated in non-overlapping samples (12). In this study we used available serum B12- and folate-associated single nucleotide polymorphisms (SNPs), e.g., a SNP in the methylene-tetrahydrofolate reductase (MTHFR) that affects serum levels of folate (13,14). If the assumptions of Mendelian randomization analysis are met, these genetic proxies for B12 and folate levels unlike serum B12 and folate levels should not be associated with the confounders that may distort the associations. Our primary aim was to test the causal nature

of the association of vitamin B12 and folate with hay fever, asthma, allergic sensitization, and serum total IgE, by performing a Mendelian randomization analysis of the effect of eleven vitamin B12-associated SNPs and two folate-associated SNPs. We also aimed to quantify any such effects in a two-sample instrumental variable analysis.

Materials and Methods

Study populations

We used data on 162,736 participants of European ancestry from the following nine population-based studies: the Allergy98 Cohort (15), the Danish Monitoring of trends and determinants in Cardiovascular Diseases study (the Monica10 study) (16), Health2006 (17), Health2008 (15), Inter99 (18), the 1936 Cohort (19), the Study of Health in Pomerania (SHIP) (20), and SHIP-TREND (21), and the UK Biobank (22) (see Supplementary Material). The studies were approved by local Ethics Committees, and participants gave their informed consent. Prior to the study, we performed a number of power calculations. For example, for the B12-associated SNP-score, a sample of approximately 142,600 persons of which approximately 1 in 7 have hay fever would allow us to detect a causal effect odds ratio of 0.93 for hay fever per standard deviation higher B12 with a power of 0.80 and a significance level of 0.05. This corresponds to an odds ratio of 0.94 per 100 pmol/l higher vitamin B12.

Genotype

We included the B12- and folate-associated SNPs listed in Table 2 (23) (more information in Supplementary Material). The selection was based on a previous study that found eight novel

loci associating with levels of B12 and folate and confirmed another seven loci for these traits (23). The SNPs were classified according to the number of B12/folate increasing alleles.

Exposure

Serum vitamin B12 and folate were measured in the SHIP-TREND, Health2006, and Health2008 Study by chemiluminescent immunoassay (Dimension Vista platform, Siemens Healthcare Diagnostics GmbH, Eschborn in Germany), in the Inter99 by competitive chemiluminescent enzyme immunoassays (IMMULITE 2000 System, Siemens Healthcare Diagnostics, Deerfield, IL, USA).

Outcome

Information on asthma and hay fever was based on self-report (Table S4). Allergic sensitization was defined as specific IgE positivity (specific IgE $\geq$0.35 kU/l) to at least one of a number of relevant inhalant allergens (Table S4). Serum total IgE was measured with IMMULITE 2000 Allergy Immunoassay System in the Allergy98 and Inter99 Study, and by the Latex IgE test on the BN II Nephelometer (Dade Behring Marburg GmbH, Marburg, Germany) in the SHIP Study (24) (Supplementary Material).

Statistical analyses

Statistical analyses were performed with SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA), and STATA, version 12 and 13 (StataCorp, College Station, TX, USA), and R version 3.3.3 (RStudio). Code can be made available on request. The reported P-values are two-tailed, and statistical significance was defined as $P<0.05$. The included SNPs were preselected. We combined the 13 included single-SNP estimates in meta-analyses across

121 study populations and across SNPs in the main analyses rather than using a SNP-score. To
122 comply with requirements of normality, serum total IgE was log-transformed in the
123 regression analyses.

124 All reported regression analyses were adjusted for sex and age. Observational
125 analyses of the associations of vitamin B12 and folate and hay fever, asthma, allergic
126 sensitization, and serum total IgE were assessed by logistic and linear regression analyses.
127 The associations of each of the 13 SNPs with vitamin B12 and folate and with hay fever,
128 asthma, allergic sensitization, and serum total IgE were assessed using linear and logistic
129 regression. For each SNP, the single SNP estimates from each study were meta-analyzed
130 using the 'metan' command in Stata. The meta-analyzed single SNP estimates were then
131 combined in instrumental variable and fixed-effects meta-analyses. Heterogeneity was
132 examined by the I^2.

133 In the two-sample IV analysis, the SNP-exposure estimates were calculated in
134 the four studies that had data on B12 and folate. SNP-outcome estimates were performed in
135 the five studies with no data on B12 and folate. We used the inverse-variance weighted (ivw)
136 estimator for the B12- and folate-analyses with the "mregger" command in Stata, and the
137 "mr_ivw" package in R (25), respectively. To make the IV analyses of the binary outcomes
138 comparable with the observational analyses, the estimates and CIs were expressed per 100
139 pg/ml change in B12 and per 10 ng/ml change in folate. For the binary B12-analyses, we also
140 performed MR Egger regression analyses to test for pleiotropy (12).

141 In sensitivity analyses, we investigated the associations of the B12- and folate-
142 associated SNPs excluding SNPs with low SNP-exposure F-value which is an indicator of
143 power in MR studies (data not shown) (26). In further analyses, we assessed unweighted,
144 weighted, and standardized SNP-scores (Table 2). The individual weights were derived from

a study population different from our own (23). Associations of B12-associated SNP-scores and log2 transformed serum vitamin B12 and folate in both simple and weighted B12 and folate SNP-scores were tested including only studies with data on ≥12 SNPs (SHIP, Inter99, Health2006, Monica10, and UK Biobank. In addition, we examined the association between SNP-scores and hay fever and asthma in different samples of the UK Biobank, i.e. genetically vs. self-reported European ancestry, and in the Bileve sample vs. the rest, when further adjusted for income, body mass index, alcohol intake, and smoking habits (Table S5-S6 and figure S1-S6).

Results

Observational analyses

Descriptive statistics for the study populations are shown in Table 1. In total, we had data on 162,736 participants. Serum vitamin B12 was not associated with higher risk of hay fever: odds ratio (OR) =1.01 (95% confidence interval [CI]: 0.96, 1.07), asthma: OR=1.01 (95% CI: 0.95, 1.07), or allergic sensitization: OR=1.02 (95% CI: 0.98, 1.03) per 100 pg/ml higher serum vitamin B12 (Figure 1). Increasing folate was associated with a higher odds of allergic sensitization: OR=1.09 (95% CI: 1.02, 1.16), but not with risk of hay fever: OR=1.05 (95% CI: 0.97, 1.13) and asthma: OR=0.99 (95% CI: 0.90, 1.09) per 10 ng/ml higher folate (Figure 2).

Vitamin B12 was positively and significantly associated with serum total IgE with a 4.0% (95% CI: 0.2%, 8.0%, p=0.041) change in total IgE per 100 pg/ml higher serum vitamin B12 (Figure 3). There was no clear evidence for an association between serum folate and serum total IgE with a 0.04% (95% CI: -0.05%, 0.14%) change in serum total IgE per

0.10 ng/ml higher serum folate. In general, the heterogeneity between studies was low and ranged from 0.0-14.6% according to I^2.

Genetic analyses

All SNPs were independent and did not deviate from Hardy-Weinberg equilibrium (Bonferroni-adjusted significance level 0.0005). Our results confirmed that the vitamin B12 and folate-associated alleles were associated with an increase in serum levels of vitamin B12 and folate (except for rs652197). We kept this SNP, since the SNP was preselected because it was confirmed as an instrument for folate in a previous study (23).

F-values for the associations between each serum B12- or folate-associated SNP and serum vitamin B12 and folate, respectively, are shown in Supplementary Table S3. The F-values were reasonably strong and well above ten for the most part. However, for the rs778805, rs1047891, and rs652197 SNPs, the F-values were quite low, and they were excluded in sensitivity analyses (explained below). In UK Biobank, the associations between the genetic B12 and folate scores and hay fever and asthma were largely similar when they were adjusted for age, sex, BMI, household income, alcohol intake, and smoking status as opposed to just age and sex.

Fixed effects meta-analyses of the age- and sex-adjusted associations between serum vitamin B12 or folate associated SNPs and the outcomes showed no evidence of a causal effect of B12 on hay fever: OR=1.01 (95% CI: 1.00, 1.01), asthma: OR=1.00 (95% CI: 0.99, 1.00), allergic sensitization: OR=0.99 (95% CI: 0.96, 1.01), and a 1.0% (95% CI: -1.0%, 2.0%) change in serum total IgE per B12-increasing allele. Results of corresponding analyses for serum folate were for hay fever: OR=0.99 (95% CI: 0.97, 1.01), asthma: OR=0.99 (95% CI: 0.97, 1.01), allergic sensitization: OR=1.02 (95% CI: 0.97, 1.08), and a 4.0% (95% CI: 0.4%, 7.0%) change in serum total IgE per folate-increasing allele.

Mendelian randomization analyses of the associations of scores of the B12- or folate associated SNPs excluding SNPs with low F-values left the estimates almost unchanged. Simple and weighted B12 and folate SNP-scores were similar when including only studies with data on ≥12 SNPs. Genetic analyses in different UK Biobank samples showed no substantial differences.

Instrumental variable analyses

Instrumental variable analyses showed no evidence for associations between B12 and hay fever: OR=1.02 (95% CI: 0.98, 1.05), asthma: OR=0.99 (95% CI: 0.95, 1.04), allergic sensitization: OR=1.02 (95% CI: 0.74, 1.40), and a 10.0% (95% CI: -9.6%, 29.6%) change in serum IgE per 100 pg/ml B12. Similarly there was no evidence for association between folate and hay fever: OR=0.74 (95% CI: 0.45, 1.21), asthma: OR=0.80 (95% CI: 0.43, 1.49), allergic sensitization: OR=1.92 (95% CI: 0.11, 33.45). There was evidence of a positive association between folate and serum IgE with a 2.00% (95% CI: 0.43%, 3.58%) change in serum IgE per 0.1 ng/ml serum folate. We found no evidence of pleiotropy for B12 and binary outcomes, as indicated by the MR Egger intercept test. However, the MR Egger analyses were underpowered which was reflected by the large confidence intervals for the odds ratios (27).

Discussion

In a Mendelian randomization meta-analysis of nine population-based studies, we found that genetically determined higher serum vitamin B12 and folate levels were not associated with hay fever, asthma, or allergic sensitization. In contrast, a genetically determined higher folate level was positively associated with changes in total serum total IgE. Thus, beside a possible

causal role of folate level on serum total IgE, our results do not support the conclusion that high or low vitamin B12 and folate status are causally related to the examined allergy and asthma phenotypes. MR-studies in general need large sample sized. Of note in the current study, the analyses of allergic sensitization and serum total IgE included substantially fewer participants than the other outcomes and may have been underpowered.

Previous studies have mainly focused on a possible detrimental effect of high folate levels and folate supplementation in pregnancy on offspring risk of allergy and asthma (28-35). In a systematic review of prospective cohort studies, Brown et al. concluded that the investigations of the association between maternal folate levels and risk of childhood asthma and allergic disease reported conflicting results (36). Some of the studies found that higher maternal levels of serum folate levels associated with a slightly increased risk of allergic disease, while most of the included studies found no association (36). Another systematic review that also included a meta-analysis, Crider et al. found no association between maternal folic acid supplementation before and in the first trimester of pregnancy and risk of asthma in the offspring (32).

In a birth cohort of 2001 children, Van der Valk et al. found that folate and vitamin B12 levels at birth did not affect asthma- and eczema-associated outcomes up to the age of 6 years (33). Matsui et al. found that serum folate levels were inversely associated with atopy, wheeze and high total IgE levels in a cross-sectional study of 8,083 children two years of age and older (37). In a high-risk birth cohort, Okupa et al. found that higher serum folate levels in the early childhood were significantly associated with higher incidence of both food and aeroallergen sensitization (38). Blatter et al. found that folate deficiency was associated with higher risk of atopy and severe asthma exacerbations in 582 Puerto Rican children aged 6-14 years (39). In comparison, in a population-based study of 6,784 adults aged 30-60 years,

Thuesen et al. found that folate deficiency was associated with self-reported asthma and attacks of shortness of breath but not allergic sensitization. Folate deficiency at baseline was not associated with changes in these outcomes over a five-year follow-up period (24).

The validity of an IV is dependent on three assumptions referred to as 'relevance', 'independence', and 'exclusion' where the first can be verified but the two latter can only be falsified (12). The assumptions behind the approach of estimating the magnitude of the causal effect are even more stringent compared to methods to investigate whether a causal association exists (12). Regarding relevance, the IVs were constructed by SNPs with previously published associations (in populations different from those included here) with B12 or folate. In general, the strengths of the instruments in our samples were acceptable, and in additional analyses, the exclusion of the few SNPs with less favourable F-values led to similar results. The risk of violation of this assumption is also reduced when using biologically plausible SNPs (23).

Testing the independence assumption, we performed MR Egger tests on B12 and binary outcomes to remove the bias due to pleiotropy where the genetic marker has diverse biological functions (40). In addition, Grarup et al. have evaluated possible pleiotropic effects of the included B_{12} and folate associated SNPs by screening their phenotype database that holds data on most of the common diseases and risk factors (23). The *FUT2* SNP was strongly associated with serum levels of alkaline phosphatase and psoriasis as previously reported (23). Also, they found an association between the *FUT6* variant and abdominal aortic aneurysm and between the folate-associated variant in *MTHFR* and thoracic aortic aneurysm (23). However, these associations are not likely to affect the risk of allergic disease. Grarup et al. also tested that the SNPs were not in linkage disequilibrium.

The minimal impact on the results of adjusting for potential confounders suggests that the exclusion assumption was not violated. Further substantiating the results in general, a number of supplementary analyses in different samples (e.g., in UK Biobank sub-samples), adjusting for other possible confounders, using different scores and weighting, and in studies with ≥12 SNPs or with F-values ≥10, left the results largely unchanged.

The proportion of participants with hay fever, asthma, and allergic sensitization varied across studies, and this is likely to reflect true differences in disease prevalence for different age groups, period of examination, and methodology. The techniques and assays used for B12, folate and IgE measurements varied across the studies and may have influence the associations described. Serum levels of vitamin B12 and folate were only measured in four out of the nine studies included which is why we could only verify the SNP/biomarker associations in these studies. In addition, due to the smaller study sample with data on B12 and folate, the IV-estimates had less precision resulting in wider 95% CIs for the estimated effects sizes. Similarly we had much less data on allergic sensitization compared to hay fever and asthma resulting in lower precision for effects on allergic sensitization. Of note, the use of the two-sample MR approach in the instrumental variable analyses caused a substantial loss of power because we needed two samples with no overlap, thereby reducing the sample sizes in the SNP-exposure and SNP outcome analyses (12).

In conclusion, we found that known genetic markers of serum vitamin B12 and folate concentrations were not associated with hay fever, asthma, and allergic sensitization (specific IgE to inhalant allergens). Genetic markers of serum folate level were positively associated with levels of serum total IgE. However, serum total IgE is a less specific biomarker of allergic respiratory disease than serum specific IgE. Hence, results of this Mendelian randomization meta-analysis do not support that high or low serum vitamin B12

and folate concentrations are causally related to the risk of hay fever, asthma, or allergic sensitization in adults.

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Declaration of interests

None

Supplementary Information accompanies the paper on the EJCN website (http://www.nature.com/ejcn)

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Figure Legends

Figure 1. Meta-analyses of age- and sex-adjusted associations between measured and genetically determined higher levels of vitamin B12 and hay fever, asthma and allergic sensitization according to ordinary least square (OLS), instrumental variable and Egger regression analysis.
N is the total number participants in each analysis. The studies providing data for each analysis were for OLS: hay fever (Health2006, Health2008, and SHIP TREND), asthma (Health2006, Health2008, Inter99, and SHIP TREND), and allergic sensitization (Health2006, Health2008, and Inter99), and for IV and Egger regression: hay fever (all nine), asthma (all nine) and allergic sensitization (all but SHIP and UK Biobank).

Figure 2. Meta-analyses of age- and sex-adjusted associations between measured and genetically determined higher serum level of folate and hay fever, asthma and allergic sensitization according to ordinary least square and instrumental variable analysis.
N is the total number participants in each analysis. The studies providing data for each analysis were for the observational analyses: hay fever (Health2006, Health2008, and SHIP TREND), asthma (Health2006, Health2008, Inter99, and SHIP TREND), and allergic sensitization (Health2006, Health2008, and Inter99), and for instrumental variable analyses: hay fever (all nine), asthma (all nine) and allergic sensitization (all but SHIP and UK Biobank).

Figure 3. Meta-analyses of age- and sex-adjusted associations between measured and genetically determined higher serum levels of B12 and folate, and changes in serum total IgE level in % according to ordinary least square and instrumental variable analysis.
N is the total number participants in each analysis. The studies providing data for each analysis were for both B12 and folate: OLS (Inter99) and IV (all but Monica10 and UK Biobank).

Table 1. Descriptive statistics of the study populations.

	N	% (N)				Median (IQR)			
	Total	**Males**	**Hay fever**	**Asthma**	**Allergic sensitization**	**Age, years**	**Vitamin B12, pg/ml**	**Folate, ng/ml**	**Serum total IgE, IU/ml**
Allergy98	1,169	45.8 (536)	26.5 (310)	11.0 (128)	37.9 (443)	38 (29, 51)	-	-	37.2 (12.2, 106)
Monica10	2,079	49.6 (1,031)	11.1 (231)	6.7 (139)	18.3 (381)	52 (42, 62)	-	-	-
Health2006	2,362	46.1 (1,088)	17.8 (420)	10.2 (242)	23.6 (558)	50 (40, 60)	382 (309, 467)	15.4 (10.7, 26.1)	-
Health2008	622	44.7 (278)	21.2 (132)	12.2 (76)	27.6 (172)	47 (40, 54)	544 (447, 663)	4.1 (3, 6)	-
Inter99	4,565	48.4 (2,209)	-	8.4 (383)	33.6 (1,535)	45 (40, 50)	291 (239, 359)	7.3 (5.9, 10.0)	28.2 (10.6, 76.8)
The 1936 Cohort	593	47.4 (281)	9.8 (58)	6.8 (40)	14.3 (85)	60 (60, 61)	-	-	-
UK Biobank	146,072	47.0 (68,662)	22.4 (32,752)	12.3 (18,010)	-	58 (51, 63)	-	-	-
SHIP	4,291	49.1 (2,107)	7.9 (341)	0.9 (38)	-	50 (36, 63)	-	-	36.4 (16.7, 103)*
SHIP TREND	983	43.7 (430)	14.3 (141)	4.2 (41)	-	50 (40,61)	435 (332, 551)	9.4 (6.5, 13.2)	-

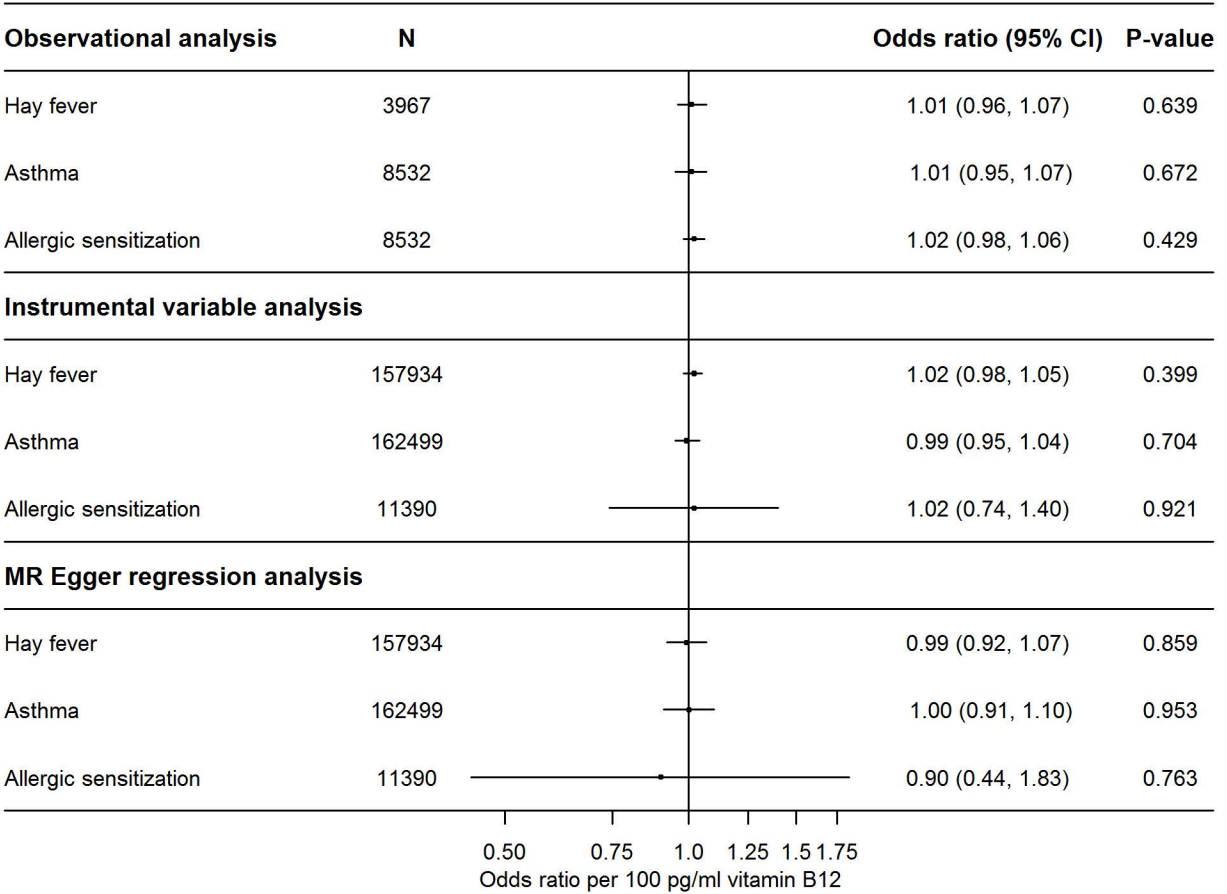
Abbreviations: Inter99, Intervention 1999; IgE, immunoglobulin E; IQR, interquartile range; Monica, Monitoring of trends and determinants in Cardiovascular Diseases; SHIP, Study of Health in Pomerania; UK Biobank, United Kingdom Biobank.

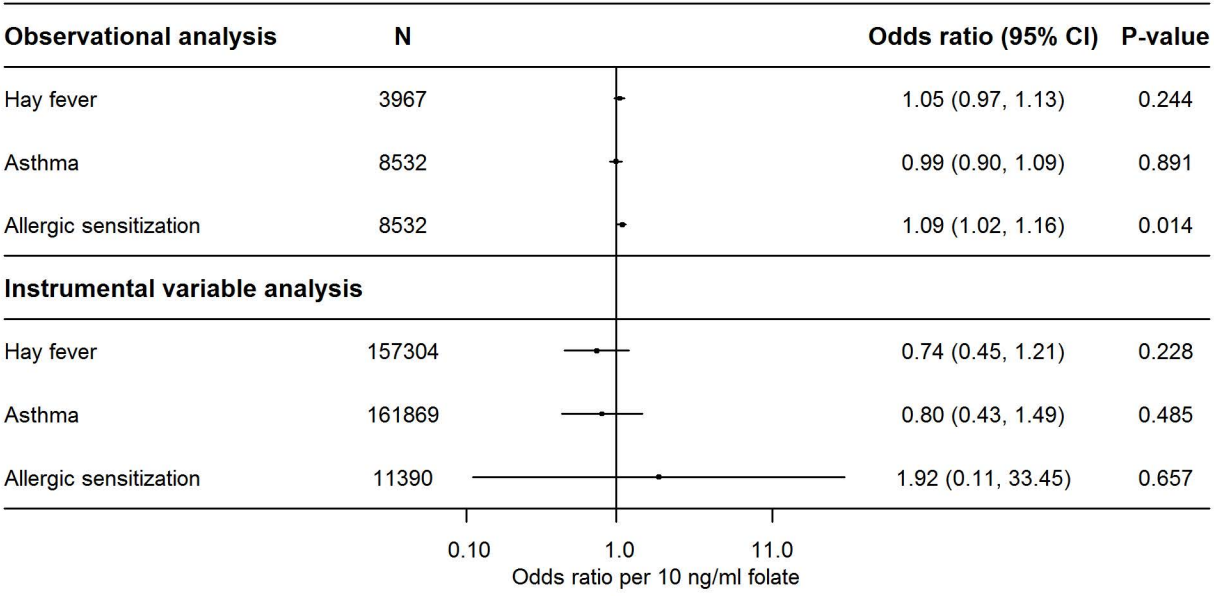
* Only measured in 3,450 persons.

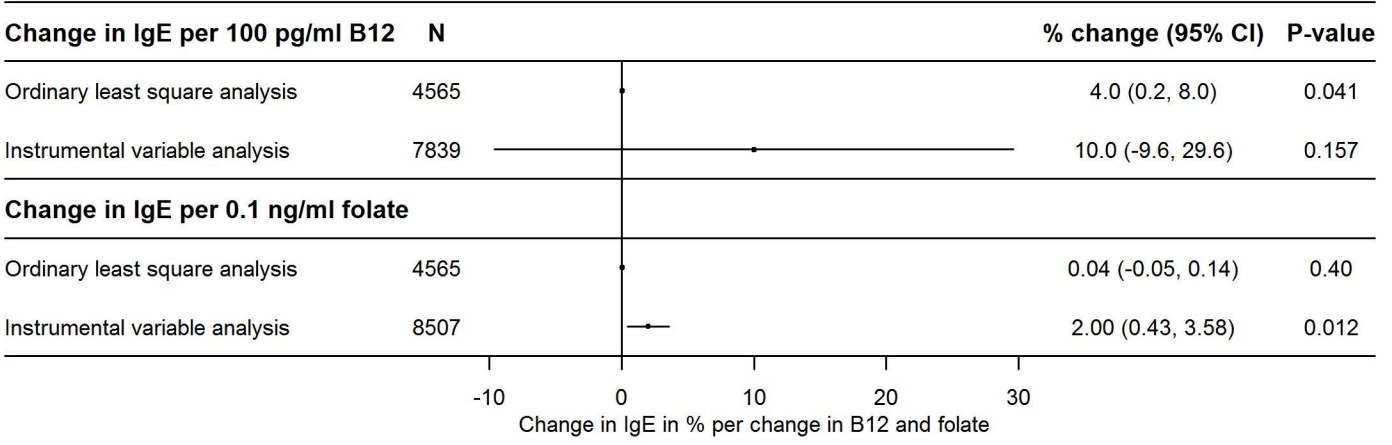
Table 2. Individual SNPs associated with serum levels of vitamin B12 or folate (14)

SNP	**Alleles**[*](effect/other)	**Effect allele frequency**	**Weights**[**]	**Location/nearest gene**
B12-associated				
rs3742801	T/C	0.294	0.045	*ABCD4*
rs602662	A/G	0.596	0.16	*FUT2*
rs2336573	T/C	0.031	0.32	*CD320*
rs1131603	C/T	0.055	0.19	*TCN2*
rs1801222	G/A	0.593	0.11	*CUBN*
rs34324219	C/A	0.881	0.21	*TCN1*
rs41281112	C/T	0.948	0.17	*CLYBL*
rs2270655	G/C	0.941	0.066	*MMAA*
rs1141321[***]	C/T	0.627	0.061	*MUT*
rs778805	A/G	0.254	0.046	*FUT6*
rs1047891	C/A	0.038	0.038	*CPS1*
Folate-associated				
rs1801133	G/A	0.668	0.096	*MTHFR*
rs652197	C/T	0.179	0.069	*FOLR3*

[*] The effect allele is the allele associated with increased serum B12 or folate levels, respectively. The numbers are from previously published data. [**]From an Icelandic sample (14). [***]rs4267943 is proxy.


Observational analysis
N
Odds ratio (95% CI)
P-value
Hay fever
3967
1.01 (0.96, 1.07)
0.639
Asthma
8532
1.01 (0.95, 1.07)
0.672
Allergic sensitization
8532
1.02 (0.98, 1.06)
0.429
Instrumental variable analysis
Hay fever
157934
1.02 (0.98, 1.05)
0.399
Asthma
162499
0.99 (0.95, 1.04)
0.704
Allergic sensitization
11390
1.02 (0.74, 1.40)
0.921
MR Egger regression analysis
Hay fever
157934
0.99 (0.92, 1.07)
0.859
Asthma
162499
1.00 (0.91, 1.10)
0.953
Allergic sensitization
11390
0.90 (0.44, 1.83)
0.763
0.50
0.75
1.0
1.25
1.5
1.75
Odds ratio per 100 pg/ml vitamin B12


Observational analysis
N
Odds ratio (95% CI)
P-value
Hay fever
3967
1.05 (0.97, 1.13)
0.244
Asthma
8532
0.99 (0.90, 1.09)
0.891
Allergic sensitization
8532
1.09 (1.02, 1.16)
0.014
Instrumental variable analysis
Hay fever
157304
0.74 (0.45, 1.21)
0.228
Asthma
161869
0.80 (0.43, 1.49)
0.485
Allergic sensitization
11390
1.92 (0.11, 33.45)
0.657
0.10
1.0
11.0
Odds ratio per 10 ng/ml folate


Change in IgE per 100 pg/ml B12
N
% change (95% CI)
P-value
Ordinary least square analysis
4565
4.0 (0.2, 8.0)
0.041
Instrumental variable analysis
7839
10.0 (-9.6, 29.6)
0.157
Change in IgE per 0.1 ng/ml folate
Ordinary least square analysis
4565
0.04 (-0.05, 0.14)
0.40
Instrumental variable analysis
8507
2.00 (0.43, 3.58)
0.012
-10
0
10
20
30
Change in IgE in % per change in B12 and folate