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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*

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

3

4

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

6

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26 **Abstract**

27 **Background:** Studies of the effect of vitamin B12 and folate on risk of asthma and hay fever  
28 have shown inconsistent results that may be biased by reverse causation and confounding.

29 We used a Mendelian randomization approach to examine a potential causal effect of vitamin  
30 B12 and folate on hay fever, asthma, and selected biomarkers of allergy by using eleven  
31 vitamin B12-associated single nucleotide polymorphisms (SNPs) and two folate-associated  
32 SNPs as un-confounded markers.

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

36 **Findings:** Using genetic proxies for B12 and folate, instrumental variable analyses did not  
37 show evidence for associations between serum B12 and hay fever: OR=1.02 (95% CI: 0.98,  
38 1.05), asthma: OR=0.99 (95% CI: 0.95, 1.04), allergic sensitization: OR=1.02 (95% CI: 0.74,  
39 1.40), or change in serum IgE: 10.0% (95% CI: -9.6%, 29.6%) per 100 pg/ml B12. Similarly  
40 there was no evidence for association between serum folate and hay fever: OR=0.74 (95%  
41 CI: 0.45, 1.21), asthma: OR=0.80 (95% CI: 0.43, 1.49), allergic sensitization: OR=1.92 (95%  
42 CI: 0.11, 33.45), but there was a statistically significant association with change in serum  
43 IgE: 2.0% (95% CI: 0.43%, 3.58%) per 0.1 ng/ml serum folate.

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

47

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

## 50 **Introduction**

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

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

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

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

78

## 79 **Materials and Methods**

### 80 *Study populations*

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

93

### 94 *Genotype*

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

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

99

#### 100 *Exposure*

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

106

#### 107 *Outcome*

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

114

#### 115 *Statistical analyses*

116 Statistical analyses were performed with SAS, version 9.4 (SAS Institute Inc., Cary, NC,  
117 USA), and STATA, version 12 and 13 (StataCorp, College Station, TX, USA), and R version  
118 3.3.3 (RStudio). Code can be made available on request. The reported P-values are two-  
119 tailed, and statistical significance was defined as  $P < 0.05$ . The included SNPs were  
120 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



145 a study population different from our own (23). Associations of B12-associated SNP-scores  
146 and log<sub>2</sub> transformed serum vitamin B12 and folate in both simple and weighted B12 and  
147 folate SNP-scores were tested including only studies with data on  $\geq 12$  SNPs (SHIP, Inter99,  
148 Health2006, Monica10, and UK Biobank. In addition, we examined the association between  
149 SNP-scores and hay fever and asthma in different samples of the UK Biobank, i.e. genetically  
150 vs. self-reported European ancestry, and in the Bileve sample vs. the rest, when further  
151 adjusted for income, body mass index, alcohol intake, and smoking habits (Table S5-S6 and  
152 figure S1-S6).

153

## 154 **Results**

### 155 *Observational analyses*

156 Descriptive statistics for the study populations are shown in Table 1. In total, we had data on  
157 162,736 participants. Serum vitamin B12 was not associated with higher risk of hay fever:  
158 odds ratio (OR) =1.01 (95% confidence interval [CI]: 0.96, 1.07), asthma: OR=1.01 (95% CI:  
159 0.95, 1.07), or allergic sensitization: OR=1.02 (95% CI: 0.98, 1.03) per 100 pg/ml higher  
160 serum vitamin B12 (Figure 1). Increasing folate was associated with a higher odds of allergic  
161 sensitization: OR=1.09 (95% CI: 1.02, 1.16), but not with risk of hay fever: OR=1.05 (95%  
162 CI: 0.97, 1.13) and asthma: OR=0.99 (95% CI: 0.90, 1.09) per 10 ng/ml higher folate (Figure  
163 2).

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

168 0.10 ng/ml higher serum folate. In general, the heterogeneity between studies was low and  
169 ranged from 0.0-14.6% according to  $I^2$ .

### 170 *Genetic analyses*

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

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

184 Fixed effects meta-analyses of the age- and sex-adjusted associations between  
185 serum vitamin B12 or folate associated SNPs and the outcomes showed no evidence of a  
186 causal effect of B12 on hay fever: OR=1.01 (95% CI: 1.00, 1.01), asthma: OR=1.00 (95% CI:  
187 0.99, 1.00), allergic sensitization: OR=0.99 (95% CI: 0.96, 1.01), and a 1.0% (95% CI: -  
188 1.0%, 2.0%) change in serum total IgE per B12-increasing allele. Results of corresponding  
189 analyses for serum folate were for hay fever: OR=0.99 (95% CI: 0.97, 1.01), asthma:  
190 OR=0.99 (95% CI: 0.97, 1.01), allergic sensitization: OR=1.02 (95% CI: 0.97, 1.08), and a  
191 4.0% (95% CI: 0.4%, 7.0%) change in serum total IgE per folate-increasing allele.

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

197

### 198 *Instrumental variable analyses*

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

210

### 211 **Discussion**

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

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

221           Previous studies have mainly focused on a possible detrimental effect of high  
222 folate levels and folate supplementation in pregnancy on offspring risk of allergy and asthma  
223 (28-35). In a systematic review of prospective cohort studies, Brown et al. concluded that the  
224 investigations of the association between maternal folate levels and risk of childhood asthma  
225 and allergic disease reported conflicting results (36). Some of the studies found that higher  
226 maternal levels of serum folate levels associated with a slightly increased risk of allergic  
227 disease, while most of the included studies found no association (36). Another systematic  
228 review that also included a meta-analysis, Crider et al. found no association between maternal  
229 folic acid supplementation before and in the first trimester of pregnancy and risk of asthma in  
230 the offspring (32).

231           In a birth cohort of 2001 children, Van der Valk et al. found that folate and  
232 vitamin B12 levels at birth did not affect asthma- and eczema-associated outcomes up to the  
233 age of 6 years (33). Matsui et al. found that serum folate levels were inversely associated with  
234 atopy, wheeze and high total IgE levels in a cross-sectional study of 8,083 children two years  
235 of age and older (37). In a high-risk birth cohort, Okupa et al. found that higher serum folate  
236 levels in the early childhood were significantly associated with higher incidence of both food  
237 and aeroallergen sensitization (38). Blatter et al. found that folate deficiency was associated  
238 with higher risk of atopy and severe asthma exacerbations in 582 Puerto Rican children aged  
239 6-14 years (39). In comparison, in a population-based study of 6,784 adults aged 30-60 years,

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

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

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

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

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

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

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

290

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300

### 301 **Declaration of interests**

302 None

303

304 Supplementary Information accompanies the paper on the EJCN website

305 (<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
<b>Allergy98</b>	1,169	45.8 (536)	26.5 (310)	11.0 (128)	37.9 (443)	38 (29, 51)	-	-	37.2 (12.2, 106)
<b>Monica10</b>	2,079	49.6 (1,031)	11.1 (231)	6.7 (139)	18.3 (381)	52 (42, 62)	-	-	-
<b>Health2006</b>	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)	-
<b>Health2008</b>	622	44.7 (278)	21.2 (132)	12.2 (76)	27.6 (172)	47 (40, 54)	544 (447, 663)	4.1 (3, 6)	-
<b>Inter99</b>	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)
<b>The 1936 Cohort</b>	593	47.4 (281)	9.8 (58)	6.8 (40)	14.3 (85)	60 (60, 61)	-	-	-
<b>UK Biobank</b>	146,072	47.0 (68,662)	22.4 (32,752)	12.3 (18,010)	-	58 (51, 63)	-	-	-
<b>SHIP</b>	4,291	49.1 (2,107)	7.9 (341)	0.9 (38)	-	50 (36, 63)	-	-	36.4 (16.7, 103)*
<b>SHIP TREND</b>	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)**

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

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







