Phenome-wide association study of genetically determined B vitamins and homocysteine biomarkers with multiple healthand disease outcomes: analysis of the UK Biobank

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Background

- The B vitamins have been investigated in a large number of epidemiological studies in relation to many health and disease outcomes, such as cardiovascular diseases, metabolic and neurological disorders, pregnancy outcomes and cancers. [1]
- Genetic polymorphisms account for 56%, 59% and 66% of the heritability for folate, vitamin B12 and homocysteine, respectively. [2]
- By linking large biorepositories containing human DNA samples and Electronic Health records (EHRs), we can comprehensively evaluate associations between genetically predicted biomarkers and these phenotypes using the phenome-wide association study design (PheWAS). [3]

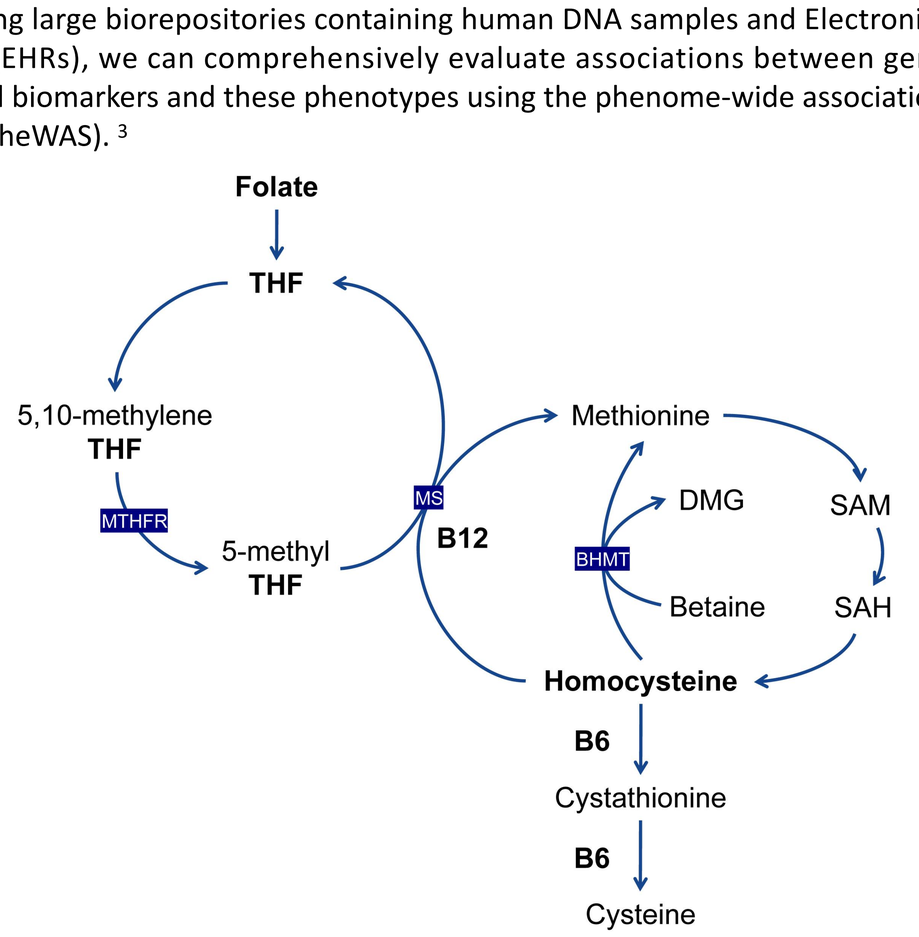

Figure 1 Interrelation between folate, vitamin B6, B12 and homocysteine metabolism

Study design

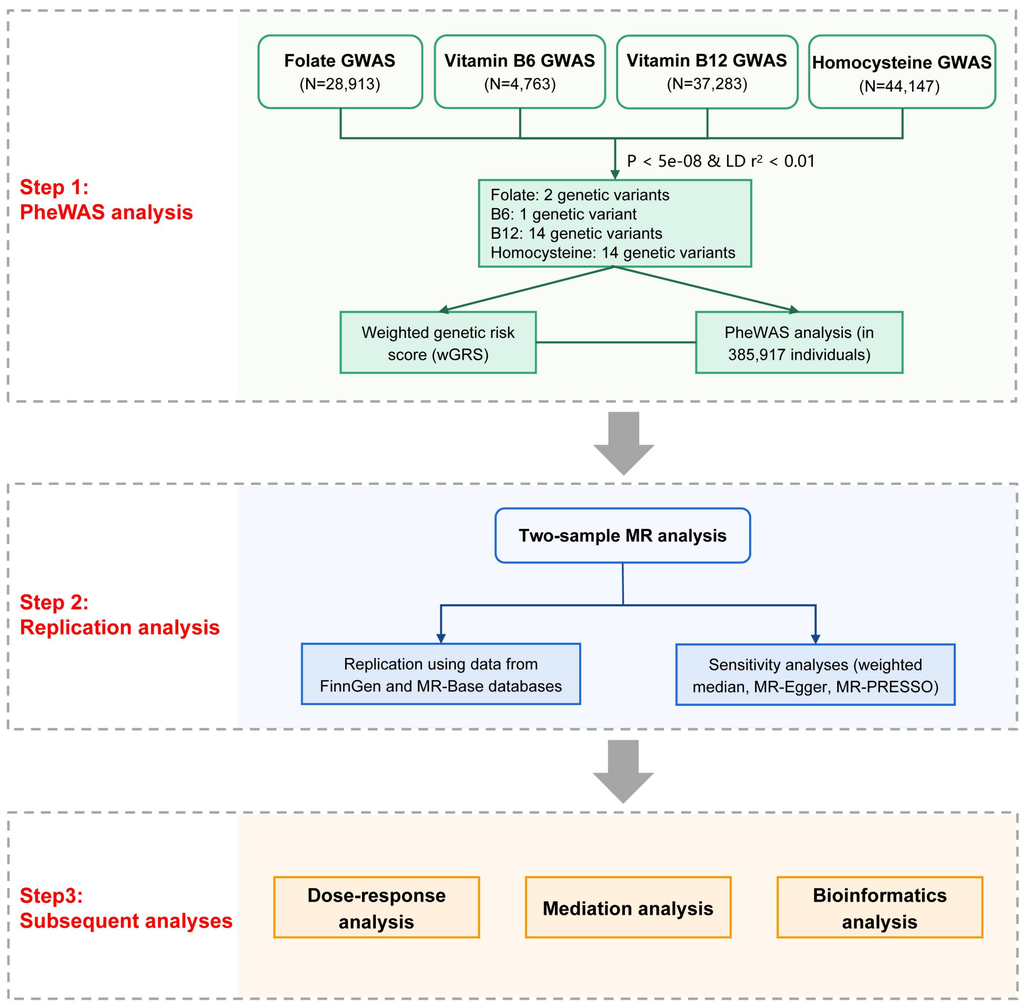

Figure 2 Flowchart for the study design

Statistical methods

- PheWAS analysis was used to test associations between weighted GRSs and phecodes with adjustment for multiple covariates including sex, age, body mass index (BMI), assessment center, and the first 10 genetic principal components (PCs).
- Mendelian randomization approach was used to perform replication analysis and detect causality.
- Dose-response analysis was conducted to examine the potential linear or non-linear trend of the identified associations.
- Bioinformatics analysis was carried out to illustrate potential biological mechanisms based on several publicly available databases.

Results

- A total of **11**, **2**, **10** and **12** pairs of genotype-phenotype associations were identified for folate, vitamin B6, vitamin B12 and homocysteine, respectively.
- Six of the identified associations were further validated, including associations of higher plasma vitamin B6 with lower risk of calculus of kidney; higher serum vitamin B12 with higher risk of hypertension, essential hypertension, and colorectal cancer; higher homocysteine concentration with higher risk of hypercholesterolemia and chronic kidney disease.
- Homocysteine-associated genetic instruments were significantly associated with the expression of *PRDX1*, *MTHFR* and *MMUT*, which may play important roles in the development of hyperlipidemia and chronic kidney disease.

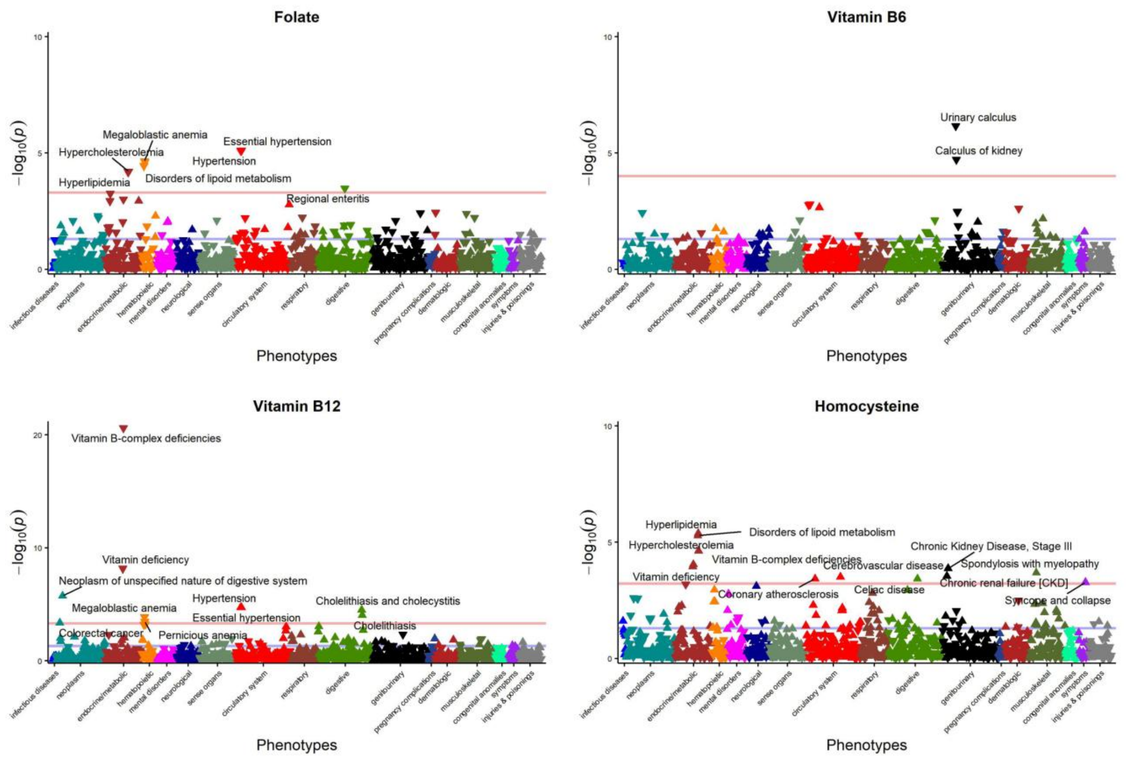

Figure 3 Plots for PheWAS associations of folate, vitamin B6, B12 and homocysteine

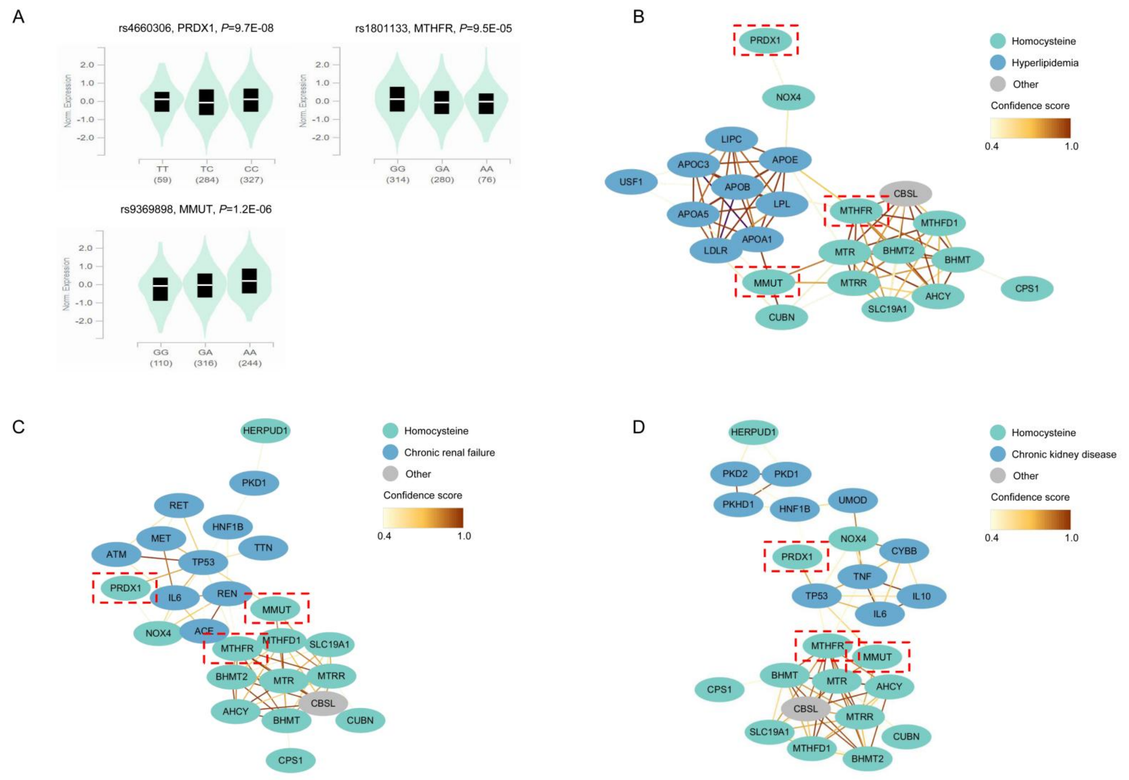

Figure 4 Bioinformatics analysis for homocysteine-associated instrumental variants

Conclusions

- We identified a total of **33** phenotypes significantly associated with folate, vitamin B6, vitamin B12 and homocysteine.
- The effects of B vitamins and homocysteine on calculus, hypercholesterolemia, colorectal cancer, hypertension and chronic kidney disease were further validated in other independent European populations.
- Potential mechanisms may be related to the effects of biomarker-associated genetic variants on the expression of genes that play important role in the development of the outcomes.
- Our findings provide evidence for further investigation on the clinical relevance of B vitamins and homocysteine with the identified disease outcomes.

1. Green R, Allen LH, Bjorke-Monsen AL, Brito A, Gueant JL, Miller JW, Molloy AM, Nexo E, Stabler S, Toh BH, et al. Vitamin B12 deficiency. Nat Rev Dis Primers 2017;3:17040. doi: 10.1038/nrdp.2017.40.
2. Nilsson SE, Read S, Berg S, Johansson B. Heritabilities for fifteen routine biochemical values: findings in 215 Swedish twin pairs 82 years of age or older. Scand J Clin Lab Invest 2009;69(5):562-9. doi: 10.1080/00365510902814646.
3. Bush WS, Oetjens MT, Crawford DC. Unravelling the human genome-phenome relationship using phenome-wide association studies. Nat Rev Genet 2016;17(3):129-45. doi: 10.1038/nrg.2015.36.