USE OF "MENDELIAN RANDOMIZATION" FOR TESTING CAUSALITY
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Background and aim: Associations between exposures and disease seen in observational studies can be confounded or be the result of reverse causality. These two biases are theoretically absent when studying associations between genotypes that mimic environmental influences and disease. This is referred to as "Mendelian randomization", the random assignment of genotypes in a population. We evaluated the strengths and limitations of Mendelian randomization to test causality in general, and more specific for the association of total homocysteine (tHcy) with coronary heart disease (CHD).

Methods: Methodological issues to consider are publication bias, sample size - especially with respect to investigating gene-nutrient interactions - population stratification, the fact that polymorphisms may have several phenotypic effects, genotyping errors, and linkage disequilibrium.

Results: Large studies are required to detect effects of genotype on disease. We studied the association between the 677 C→T polymorphism of methylenetetrahydrofolate reductase (MTHFR) and CHD by pooling 11,162 cases and 12,758 controls from observational studies. The relative risk of 1.16 (95% confidence interval, 1.05–1.28) was in line with the predicted effect of tHcy on CHD, and confounding was absent. The other issues described above appeared to be no serious limitation. However, effects of tHcy and folate could not be disentangled. For other polymorphisms, the effect on tHcy is mostly unclear and studies are too small to assess an association with CHD with sufficient statistical power.

Conclusions: Mendelian randomization is useful for testing causality. Data should be pooled whenever possible, as small studies are uninformative and misleading.

COMMON GENE POLYMORPHISMS IN THE METABOLIC FOLATE AND METHYLATION PATHWAY AND THE RISK OF ACUTE LYMPHOBLASTIC LEUKEMIA AND NON-HODGKIN'S LYMPHOMA
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Background and aims: Many studies suggest that folate status modulates carcinogenesis. Anomalous folate levels may alter DNA methylation, synthesis and repairing processes, affecting gene expression and DNA stability. Several gene polymorphisms have been described to influence the activity of the main enzymes of the folate pathway modulating disease susceptibility. In this view, we evaluated if four common polymorphisms in methylenetetrahydrofolate reductase (MTHFR C677T and A1298C), methionine synthase (MS A2756G) and methionine synthase reductase (MTRR A66G) genes may have a role in acute lymphoblastic leukemia (ALL) and non-Hodgkin's lymphoma (NHL) in adults.

Methods: We genotyped by PCR and restriction analysis 120 ALL, 200 NHL and 257 control subjects statistically computing the genotype distributions for the evaluation of the associated OR values. Results: In univariate analysis, MTHFR 677TT cases had OR = 0.28 (95% CI, 0.13–0.60) and MS 2756GG cases had OR = 0.18 (95% CI, 0.02–1.30) yielding a risk reduction of 3.6 and 5.6-fold respectively. In combined results, subjects with MTHFR 677CT/TT and MS 2756AG/GG genotypes revealed a 3.6-fold ALL risk reduction (OR = 0.28; 95% CI, 0.14–0.57). Statistical analysis in NHL group, did not detect any significant difference for all the polymorphisms investigated.

Conclusions: These data suggest that folate and methionine polymorphisms might play different roles in ALL and NHL susceptibility by modulating DNA synthesis and/or DNA methylation processes...