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B-vitamins and their interaction with the *MTHFR* C677 T genotype as determinants of bone health in older adults from the TUDA Ageing cohort study

M. Clarke[1,2], M. Ward[1], L. Hoey[1], J.J. Strain[1], A. Molloy[3], E. Laird[3], M. Healy[4], M.C. Casey[5], C. Cunningham[5], M.T. McCann[1] and H. McNulty[1]

[1]*Northern Ireland Centre for Food and Health, University of Ulster, Coleraine, BT52 1SA,* [2]*UCD Institute of Food and Health, Belfield, University College Dublin, Dublin 4, Ireland,* [3]*School of Medicine, Trinity College Dublin 2, Ireland,* [4]*The Department of Clinical Biochemistry, Central Pathology, St James's Hospital, Dublin, Ireland and* [5]*The Mercers Institute for Research on Ageing, St James's Hospital, Dublin, Ireland*

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Osteoporosis, characterised by reduced bone mineral density (BMD) and a high risk of fragility fracture, is increasingly prevalent in today's ageing society[(1)]. Large observational studies support a protective role for certain B-vitamins integral to 1-carbon metabolism (i.e. folate, vitamins B12, B6 and riboflavin) against osteoporosis[(2)]. A common polymorphism (C677 T) in the folate metabolising enzyme methylenetetrahydrofolate reductase (MTHFR) has also been linked to osteoporosis, with a heightened risk demonstrated in the presence of low B-vitamin status[(2)]. However, previous studies exploring the role of this polymorphism have tended to overlook relevant gene-nutrient interactions[(2)]. The aim of this investigation was to examine the interaction of relevant B-vitamin biomarkers with the *MTHFR* 677TT genotype as determinants of low BMD.

Older adults (*n* 3,127) recruited to the Trinity Ulster Department of Agriculture (TUDA) Ageing cohort study, and with BMD measured by dual energy X-ray absorptiometry scans, were investigated. Low BMD was defined as a combination of osteopenia (T-Score; between −1 and −2·5 SD) and osteoporosis (T-Score; −2·5 SD or less).

Age ($p < 0{\cdot}001$), physical inactivity ($p = 0{\cdot}015$), and parathyroid hormone ($p < 0{\cdot}001$) were associated with an increased risk of low BMD, while increasing body weight ($p < 0{\cdot}001$) reduced the risk. The *MTHFR* C677 T genotype was not found to be a significant predictor of low BMD in either males or females. Females with the *MTHFR* 677TT genotype in combination with low biomarker status of riboflavin or folate had a two-fold increased risk of low BMD compared to those with the *MTHFR* 677CC genotype and optimal B-vitamin status, after adjustment for covariates; these associations were not observed in men (Table).

Table. Predictors of low bone mineral density 'BMD' (osteoporosis and osteopenia combined)

B-vitamin biomarker (*n* 3,127)	OR	95 % CI	P
Males (*n* 1,056)			
MTHFR 677TT genotype	1·047	0·672–1·631	0·841
Low riboflavin**MTHFR* 677TT genotype	0·937	0·476–1·844	0·831
Low folate**MTHFR* 677TT genotype	1·905	0·896–4·049	0·094
Females (*n* 2,071)			
MTHFR 677TT genotype	1·378	0·961–1·976	0·081
Low riboflavin**MTHFR* 677TT genotype	2·314	1·237–4·329	0·009
Low folate**MTHFR* 677TT genotype	2·007	1·106–3·642	0·022

Analysis by binary logistic regression, comparing lowest tertile of vitamin status to the other tertiles combined. Reference category; *MTHFR* 677CC genotype and highest B-vitamin status. Riboflavin was measured using erythrocyte glutathionine reductase activation coefficient 'EGRac'. Folate was measured in red blood cells by microbiological assay.

These findings suggest that there are important gene-nutrient interactions within 1-carbon metabolism that appear to play an important role in maintaining bone health throughout life.

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