Recent findings that low folate levels are associated with a high body mass index (BMI) have potentially important health implications. The apparent association warrants further investigation to determine whether a causal relationship exists as the current obesity epidemic is a major public health issue, affecting the whole population irrespective of age, gender and ethnic group. Folate supplementation of commonly consumed foods (e.g. flour), currently being considered in the UK (Scientific Advisory Committee on Nutrition. Folate and Disease Prevention, TSO, London, 2006), could be a potential population level intervention to reverse the obesity epidemic if low folate levels are indeed causally related to obesity.

Lower serum folate levels have been found to be strongly associated with increased BMI in women of childbearing age in two waves of the National Health and Nutrition Examination Survey, each 10 kg/m^2 increase in BMI was associated with a 15.6% decrease in serum folate ($P<0.001$), an association that persisted even after controlling for age, ethnicity, folate intake and red blood cell folate. A further large cross-sectional study of women in prenatal care replicated the finding of an association between low serum folate levels and obesity. Also, a small case–control study found much higher plasma homocysteine, a biomarker of low folate levels, among obese children and adolescents compared with non-obese controls. Further, indirect evidence for an association between low folate and obesity is that high pre-pregnancy BMI has been consistently found to be associated with neural tube defects, which are caused by low perinatal folate levels.

It is possible that lower levels of serum folate are observed among heavier women, simply because their requirements are greater. Another plausible explanation for the association between low folate status and obesity could be confounding by dietary habits, since it is likely that those individuals who have a high-energy diet will eat less fruit, vegetables and cereals and thus have a lower folate intake. However, we have observed an association between the *MTHFR C677T TT* genotype, which is associated with reduced folate availability, and obesity in the British Women's Heart and Health Study (BWHHS). Clearly, this genotype could not have been altered by adult BMI, and it is not subject to confounding by lifestyle factors. Thus, our *MTHFR* genotype–obesity findings suggest that folate levels may be causally related to greater BMI and obesity.

A potential mechanism by which folate could influence body mass and obesity is via epigenetic control of gene expression. Methylation of cytosines in CpG dinucleotides is an important epigenetic modification, which affects gene expression and thus cellular function. To a certain extent, methylation patterns can be controlled by environmental factors such as intake of dietary folate, which is an important donor of methyl groups required for methylation. Folate depletion in humans has been observed to diminish genomic DNA methylation. The hypothesis that epigenetic changes including methylation are linked to adult obesity is supported by the observation that in humans several genes have been shown to exhibit changes in expression that correlated closely with BMI and/or waist/hip ratio. Further, obesity is one of the symptoms of Prader–Willi syndrome that is caused by irregular DNA methylation patterns in a given region on chromosome 15q.

Preliminary analysis has shown that the *MTHFR C677T TT* genotype was associated with an ~20% increase in the prevalence of obesity in the BWHHS, although only very small differences

in BMI were observed by genotype. Since initial positive genotype–phenotype associations frequently fail to replicate, we sought to examine the association of *MTHFR C677T* genotype with BMI and obesity in two further population-based cohorts and to present a full analysis in the BWHHS.

The methylenetetrahydrofolate reductase *C677T* genotype and the risk of obesity in three large population-based cohorts

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