Aberrant gene-specific DNA methylation occurs in normal cells and contributes to disease vulnerability. We have investigated the relationships between nutrient intakes/status and gene-specific methylation of panels of genes in normal cells of the colorectal mucosa or in whole blood from healthy subjects participating in two separate studies. The combination of quantitative DNA methylation analysis with novel, multivariate modelling led to the identification of factors contributing significantly to gene-specific methylation. In the colorectal mucosa of 200 subjects shown to be free of colorectal disease, the methylation status of a panel of 11 genes known to influence colorectal cancer risk was significantly associated with levels of folate, selenium and vitamin D in blood. In whole blood from 500 participants in the Cardiovascular Health Study, a multi-site observational cohort investigating cardiovascular disease (CVD) in older adults from 1989-present, intakes of a number of dietary constituents such as types of fat including saturated fat, carotenoids, flavonoids, etc were significantly associated with the methylation status of a panel of genes involved in CVD. In addition, significant relationships between gene-specific methylation and blood lipid status, BMI, hypertension, existing diabetes, and markers of inflammation were identified. Weak associations between gene-specific methylation and future incidence of coronary heart disease, stroke and mortality were also identified. These studies show that nutritional factors influence gene-specific methylation in normal cells with consequences for risk of disease.