Underestimation of the importance of homocysteine as a risk factor for cardiovascular disease in epidemiological studies.

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BACKGROUND: In epidemiological studies, within-person variability in plasma total homocysteine (tHcy) measurements may dilute the association of 'usual' levels of tHcy with risk of cardiovascular disease, referred to as 'regression dilution'. The aim of this report was to estimate the magnitude of regression dilution after varying intervals of follow-up. METHODS: Regression dilution ratios (RDR) for tHcy were calculated using replicate tHcy measurements obtained after 3, 6 and 8 years from the Rotterdam, Hordaland and Framingham studies, respectively, and after 3, 6, 9 and 12 years from the United Kingdom Prospective Study of type 2 Diabetes Mellitus (UKPDS). RESULTS: The RDR for tHcy decreased with increasing interval in the three population-based studies and in the UKPDS. Moreover, the rate of decline of the RDR in the population-based studies was similar to that obtained in the UKPDS. Using linear regression analysis for the population-based studies, these results suggest an RDR of 0.83 at 2 years, 0.71 at 6 years and 0.53 at 12 years. CONCLUSIONS: These results have important implications for the interpretation of prospective studies of tHcy and cardiovascular disease. Failure to correct for increasing regression dilution using lower RDRs for longer follow-up may underestimate the relative risks of cardiovascular disease associated with tHcy by about one-fifth after 2 years and one-half after 10 years.