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Homocysteine and coronary heart disease in the Caerphilly cohort: a 10 year follow up FREE

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Homocysteine and coronary heart disease - Authors' reply

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Dear Editor

We wish to thank Professor Wald and colleagues for highlighting an error in our paper.[1] We misreported the standard deviation for total plasma homocysteine concentration (tHcy) in table 2 so that this was, as Wald infers, too small. This error occurred because our analyses were based on the log transformed data. The true value of the back-transformed standard deviation is between 3.4 and 4.8 mmol/l (see amended table 2). For the analysis in table 4, one standard deviation in log transformed tHcy is equivalent to 4.3 mmol/l tHcy. None of the effect estimates are changed. This means that our results are not consistent with those of the BUPA cohort study.[2] We fully agree that our data cannot exclude a small positive association between homocysteine and CHD, however it does not support the likelihood that homocysteine is a strong risk factor for CHD within this cohort.

Table 2 Serum total homocyst(e)ine and potential confounding variables for CHD in the control group

	Linear regression	*95% confidence interval (p value)*
	*Beta coefficient**	
Age (per 5 years)	0.033	0.01 to 0.05 (0.001)
Blood pressure		
systolic BP (per 10 mm/Hg)	0.0046	-0.003 to 0.01 (0.2)
diastolic BP (per 10 mm/Hg)	-0.0016	-0.29 to 0.19 (0.8)
Dietary factors		
†alcohol (per SD in ml/day)	-0.044	-0.062 to -0.02 (
folate (per SD in microg/day)	-0.056	-0.07 to- 0.03 (
†B_{12} (per SD in microg/day)	-0.053	-0.07 to -0.03 (
B_6 (per SD in mg/day)	-0.035	-0.05 to -0.01 (
Blood lipids		
total cholesterol (per SD in mmol/l)	-0.021	-0.03 to -0.004 (0.01)
HDL cholesterol (per SD in mmol/l)	-0.019	-0.03 to -0.002 (0.02)
†triglycerides (per SD in mmol/l)	-0.010	-0.05 to 0.01 (0.03)
Clotting factors		
fibrinogen (per SD in g/l)	-0.002	-0.014 to 0.20 (0.7)
Body mass index (10 kg/m^2)	-0.10	-0.15 to -0.06 (
Creatinine (per SD in micromol/l)	0.57	0.03 to 0.07 (

Smoking	*Serum tHcy (microm/l)*	*SD*
never smoked	11.3	3.4
ex smoker	11.7	4.7
current smoker	12.1	4.8
		ANOVA p=0.01
Difference in means	*Serum tHcy (microm/l) (SD)*	*t Test p value*
Hypertensive	11.9 (4.8)	
Normotensive	11.7 (4.7)	0.2
Manual social class	11.9 (4.8)	
Non-manual social class	11.6 (4.6)	0.2
Angina	12.2 (4.9)	
No angina	11.7 (4.7)	0.2
ECG ischaemia	11.9 (3.6)	
Normal ECG	11.8 (4.7)	0.6

*Change in homocysteine (natural log) per unit change in CHD risk factor.

†Log transformed.

ANOVA, analysis of variance; BP, blood pressure; HDL, high density lipoprotein; tHcy, total serum homocyst(e)ine concentration.

Criteria for selecting confounders is controversial. We believe that the choice of confounders should be based on *a priori* knowledge of exposure and disease associations, rather than any arbitrary statistical level or stepwise procedure.[3] Previous studies have documented a strong positive dose response relationship between smoking and tHcy concentration.[4] Smoking leads to 21% attenuation of the association in the BUPA cohort, and given the way in which measurement imprecision dilutes our ability to statistically adjust risk associations[5] this suggests a substantial degree of confounding.

The best evidence regarding homocysteine and CHD risk comes from studies of genetic polymorphisms related to homocysteine metabolism. Individuals homozygous for the thermolabile variant of the methylenetetrahydrofolate reductase (MTHFR) gene (T/T) have homocysteine levels about 2.6 mmol/l higher than those homozygous for the wild type (C/C) gene, and a relative risk of CHD of 1.11 (95% confidence intervals 0.91-1.37)[6]. Thus for a 5 mmol/l higher level of homocysteine the BUPA study yields a relative risk of 1.33 (1.22-1.59), the Caerphilly study 1.12 (0.98-1.27) and the MTHFR studies 1.22 (0.83-1.83). These are all compatible with a small positive association. The MTHFR studies provide, of course, far better evidence than observational studies which have measured homocysteine, such as the BUPA and Caerphilly cohorts. Through "Mendelian randomisation"[7] they test, essentially, the unconfounded association between homocysteine and CHD risk. In the observational studies of measured homocysteine and CHD risk, extensive confounding is possible and indeed probable. This is unlikely with genetic studies, although theoretically possible due to population stratification or the MTHFR polymorphisms being in linkage disequilibrium with other loci influencing disease risk. Conventional epidemiological studies have a limited future[8] and resources should be put into either randomised trials of homocysteine manipulation or further studies utilising Mendelian randomisation.

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References

(1) Fallon UB, Ben Shlomo Y, Elwood P, Ubbink JB, Smith GD. Homocysteine and coronary heart disease in the Caerphilly cohort: a 10 year follow up. *Heart* 2001;**85**:153-8.

(2) Wald NJ, Watt HC, Law MR, Weir DG, McPartlin J, Scott *et al*. Homocysteine and ischemic heart disease: results of a prospective study with implications regarding prevention. *Arch Intern Med* 1998;**158**:862-7.

(3) Rothman KJ, Greenland S. Modern Epidemiology. 2nd ed. USA: Lippincott Williams & Wilkins, 1998.

(4) Nygard O, Vollset SE, Refsum H, Stensvold I, Tverdal A, Nordrehaug JE *et al*. Total plasma homocysteine and cardiovascular risk profile. The Hordaland Homocysteine Study. *JAMA* 1995;**274**:1526-33.

(5) Phillips AN, Smith GD. Bias in relative odds estimation owing to imprecise measurement of correlated exposures. *Stat Med* 1992;**11**:953-61.

(6) Brattstrom L, Wilcken DE, Ohrvik J, Brudin L. Common methylenetetrahydrofolate reductase gene mutation leads to hyperhomocysteinemia but not to vascular disease: the result of a meta-analysis. *Circulation* 1998;**98**:2520-6.

(7) Gray R, Wheatley K. How to avoid bias when comparing bone marrow transplantation with chemotherapy. *Bone Marrow Transplant* 1991;7(Suppl 3):9-12.

(8) Smith GD, Ebrahim S. Epidemiology-is it time to call it a day? *Int J Epidemiol* 2001;**30**:1-11.

Conflict of Interest:
None declared.