Early growth and clotting factors in adult life

SIR,—We disagree with Richard de Courcy-Wheeler and Charles Wolfe,¹ who seem unclear that plasma fibrinogen and factor VII concentrations in adult men are related to the combination of placental weight and birth weight²; overlook the fact that these relations are independent of gestation; and wrongly state that a raised ratio of placental weight to birth weight is associated with a decreased ratio of head circumference to length.

George Davey Smith and Yoar Ben-Shlomo raise the question of whether the strong relations between early growth and adult cardiovascular disease and risk factors result from confounding variables.³ In our recent study men who had had lower weight at 1 year included more cigarette smokers (the smoking history being known for all except three men, not nine as they suggest). The trends in lower fibrinogen concentration with increasing weight at 1 year were independent of smoking. Davey Smith and Ben-Shlomo argue, however, that men who had had different weights at 1 year could also differ in leisure activities, psychosocial characteristics, and other possible confounding variables, known and unknown, measured and unmeasurable. Such arguments can easily be made about any non-randomised study and cannot formally be refuted. The relations of fibrinogen concentration with weight at 1 year and the ratio of placental weight to birth weight, however, were found within each social class. Furthermore, whereas more short men smoked cigarettes, irrespective of their weight as infants, more men who were light during infancy had high plasma fibrinogen and factor VII concentrations irrespective of their adult height.

Davey Smith and Ben-Shlomo also suggest that the relation of raised plasma factor VII concentrations with lower weight at 1 year may have arisen because the men who had low weights at 1 year smoke more and eat more saturated fat and consequently have a raised factor VII concentration. The table shows that this suggestion is incorrect. Men who had low weight at 1 year and now smoke had below average factor VII concentrations.

The relations between early growth and adult cardiovascular risk factors, including haemostatic factors,² blood pressure,⁴ plasma glucose, insulin,⁵ and apolipoprotein B, are not only strong and graded but specific. Different risk factors are associated with different patterns of reduced fetal or infant growth. We now need to know more

about the effects of growth retardation on different organs and systems and hence understand the early processes that "programme" adult disease.

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- 2 Barker DJP, Meade TW, Fall CHD, Lee A, Osmond C, Phipps K, et al. Relation of fetal and infant growth to plasma fibrinogen and factor VII concentrations in adult life. *BMJ* 1992;304:148-52. (18 January.)
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Fetal growth and ratio of placental weight to birth weight

SIR,—Richard de Courcy-Wheeler and Charles Wolfe argue against using the ratio of placental weight to birth weight as a marker of fetal growth because the regression line does not pass through the origin.¹ This is not a valid argument. The regression line is not expected to pass through the origin even when there is a true proportional relation unless the two variables are perfectly correlated. The regression line is the best line for predicting birth weight from placental weight. It is not the best line for describing the true relation between these variables.

The data of de Courcy-Wheeler and Wolfe may be misleading. Inspection of their figure shows two suspicious points: one for a placental weight of about 30 g and birth weight of 2800 g and another for a placental weight of about 100 g and birth weight of 2100 g. These points may exert considerable influence on the regression line and correlation coefficient. Using data from the St George's birth weight study,² for 1492 births we had a minimum placental weight of 190 g, and no subject with a placental weight above 950 g had a birth weight below 3500 g. The correlation between

birth weight and placental weight was $r=0.619$. (This is much greater than the value of $r=0.385$ reported in the text by de Courcy-Wheeler and Wolfe, but in their figure they give $r^2=0.385$, which corresponds to $r=0.620$.) The regression of birth weight on placental weight gave the equation $\text{birth weight}=1784+2.553 \text{ placental weight}$, which is similar to the line reported by de Courcy-Wheeler and Wolfe. But there are two regression lines. We can also calculate the regression of placental weight on birth weight, giving $\text{placental weight}=104.5+0.1503 \text{ birth weight}$. If we rearrange this equation to put birth weight on the left we get $\text{birth weight}=695+6.653 \text{ placental weight}$, with a negative intercept. Thus the two regression lines pass either side of the origin. The true, functional relation between birth weight and placental weight will lie somewhere between them.

Taking the ratio of placental weight to birth weight implies that one is approximately proportional to the other and so the line describing the true relation should go near the origin. Both sets of data seem consistent with this possibility. There may be other grounds to question the appropriateness of looking at placental weight as a proportion of birth weight, but the ratio should not be rejected because of the findings of de Courcy-Wheeler and Wolfe's regression analysis.

The same misconception is common when regression is used in studies comparing methods. Here the two methods measure the same quantity and so the true ratio is around 1 for all subjects. The expected slope and intercept of the regression line, however, are not 1 and 0.³

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SIR,—Richard de Courcy-Wheeler and Charles Wolfe's letter¹ arguing that D J P Barker and colleagues' paper² failed to prove an association between reduced fetal growth and high concentrations of fibrinogen and factor VII raises several interesting issues.

Their argument is based on Barker and colleagues' use of the ratio of placental weight to birth weight as a marker of reduced fetal growth. A regression of birth weight on placental weight for 163 male infants is used as evidence of the difficulties of interpreting such a ratio: the (presumably significant) failure of the fitted line to pass through the origin would mean that the ratio would take different values despite birth weight being appropriate to placental weight. No attempt is made to interpret the intercept—that is, to explain why infants with a placental weight of zero should have a birth weight of about 1750 g.

In an attempt to derive a more feasible model of

Mean plasma factor VII concentration (percentage of standard) in men aged 59 to 70 according to weight at 1 year and smoking habit

Weight at 1 year (lb)	Smoking habit							
	Never smoked		Ex-smoker		Current smoker		All	
	Factor VII (%)	No of men	Factor VII (%)	No of men	Factor VII (%)	No of men	Factor VII (%)	No of men
≤18	122	6	130	19	109	12	122	37
–20	101	11	122	48	101	30	112	89
–22	104	30	105	97	115	48	108	175
–24	105	32	104	93	112	40	106	165
–26	102	17	105	46	114	17	106	80
>26	96	4	104	22	102	7	103	33
All	105	100	109	325	110	154	108	579