2. Hales CN, Barker DJP, Clark PMS et al. (1991) Fetal and infant growth and impaired glucose tolerance at age 64. Br Med J 303: 1019–1022
3. Robinson S, Walton RJ, Clark PM, Barker DJP, Hales CN, Osmond C (1992) The relation of fetal growth to plasma glucose in young men. Diabetologia 35: 444–446
4. Gruenwald P (1970) Environmental influences on twins apparent at birth. A preliminary study. Biol Neonate 15: 79–93
5. Corey LA, Nance WE, Kang KW, Christian JC (1979) Effects of type of placentation on birthweight and its variability in monozygotic and dizygotic twins. Acta Genet Med Gemellol 28: 41–50

Dr. D. I. W. Phillips
Metabolic Programming Group
MRC Environmental Epidemiology Unit
Southampton General Hospital
Tremona Road
Southampton SO9 4XY
UK

Response from the authors

Dear Sir,
We thank Drs. Phillips, Hales and Barker for their comments on our paper [1]. They suggest that fetal nutrition may play a role in the aetiology of Type 2 (non-insulin-dependent) diabetes mellitus. They suggest that as monozygotic (MZ) twins have lower mean birthweight than dizygotic (DZ) twins, an increased concordance for Type 2 diabetes in MZ twins could be due to fetal and not genetic factors. In our study the rate of Type 2 diabetes in MZ twins was not significantly increased compared to DZ twins, and we are not aware of other population-based twin studies finding such differences. Because our data was derived from multiple medical registers, we cannot know at present the true prevalence of Type 2 diabetes in the twin population without testing all twins in the population.

Phillips, Hales and Barker imply that a higher rate of low birthweight among MZ twins would result in greater concordance of Type 2 diabetes. At birth, the pairwise correlation of weight ($r = 0.62$, 95% CI 0.51–0.71) of MZ twins is no greater than that of like-sexed DZ pairs ($r = 0.66$, 95% CI 0.53–0.76) or even opposite sex DZ pairs ($r = 0.68$, 95% CI 0.53–0.79) according to the longitudinal data from the Louisville Twin Study [2]. Only after the age of 6 months is there higher concordance for weight in MZ pairs compared to DZ pairs [2]. In Aberdeen, Fraser and Nylander [3] found little evidence to substantiate the claim that the heavier twins will go on to grow taller than their lighter co-twins. They suggest that the birthweight of a twin is not on its own an indication of the quality of the prenatal environment, but has to be viewed in relation to that of its co-twin [3]. Thus, the special prenatal environment of twins would suggest that birthweights of twins cannot be compared directly to birthweights of singletons.

Should an increased prevalence of Type 2 diabetes in MZ twins compared to DZ twins be observed, this may be due to many other factors than prenatal nutritional factors. MZ twins tend to have more contact with each other than DZ twins in adulthood [4], which may result in greater similarity for behaviour relevant to the aetiology of Type 2 diabetes, for example dietary habits or physical activity patterns. Also, as we have speculated elsewhere [5, 6] a higher prevalence of disease in MZ pairs could be due to infectious mechanisms.

While we acknowledge the importance of the fetal period (maybe not only nutrition) for the development of various diseases, including diabetes, later in life, we would like to stress the strong influence of genetic factors in the aetiology of Type 2 diabetes. Without clustering of susceptibility genes there will be no familial clustering of diabetes. Before having a better understanding about the genetic susceptibility, it may be of little value to argue about the usefulness of different study designs in genetics of diabetes which all have their limitations. We believe that twin studies offer a good potential to sort out the unsolved questions related to genetic-environmental interaction in the development of Type 2 diabetes although the actual birth weights may be more difficult to interpret among twins than singletons.

Sincerely yours,

J Kaprio, J Tuomilehto, M Koskenvuo, K Romanov,
A Reunanen, J Eriksson, J Stengård, and YA Kesäniemi

References

1. Kaprio J, Tuomilehto J, Koskenvuo M, et al. (1992) Concordance for Type 1 (insulin-dependent) and Type 2 (non-insulin-dependent) diabetes mellitus in a population-based cohort of twins in Finland. Diabetologia 35: 1060–1067
2. Wilson RS (1979) Analysis of longitudinal twin data. Basic model and applications to physical growth measures. Acta Genet Med Gemellol (Roma) 28: 93–105
3. Fraser C, Nylander PPS (1988) The relationship of birth weight to later growth and intelligence in twins. In: MacGillivray I, Campbell DM, Thompson B (eds) Twinning and twins. John Wiley & Sons, Chichester, pp 241–252
4. Kaprio J, Koskenvuo M, Langinvainio H, Romanov K, Sarna S, Rose RJ (1987) Genetic influences on use and abuse of alcohol: a study of 5638 adult Finnish twin brothers. Alcohol Clin Exp Res 11: 349–356
5. Järvinen P, Kaprio J, Mäkitalo R, Koskenvuo M, Aho K (1992) Systemic lupus erythematosus and related systemic diseases in a nationwide twin cohort: an increased prevalence of disease in MZ twins and concordance of disease features. J Intern Med 231: 67–72
6. Kinnunen E, Koskenvuo M, Kaprio J, Aho K (1987) Multiple sclerosis in a nationwide series of twins. Neurology 37: 1627–1629

Dr. J. Tuomilehto
Department of Epidemiology
and Health Promotion
National Public Health Institute
Elimäenkatu 25 A, 6th Floor
SF-00510 Helsinki
Finland

In addition to von Willebrand factor and urinary albumin excretion, plasma endothelin is an indicator of endothelial dysfunction in diabetes mellitus

Dear Sir,
Stehouwer et al. [1] demonstrated the increased concentrations of von Willebrand factor (vWF) in patients with Type 1 (insulin-dependent) diabetes mellitus independent of the presence or absence of retinopathy. Recently Stehouwer et al. [2] described in Type 2 (non-insulin-dependent) diabetes that an increase in urinary albumin excretion in patients with an increased baseline level of von

Table 1. Immunoreactive endothelin (ETi) and von Willebrand factor antigen (vWFi) blood concentrations in normal control subjects and in diabetic patients with microvascular complications

Group	n	HbA_{1c} (%)	vWFi (%)	ETi (pg/ml)
Control	10	5.5 ± 0.7	125 ± 35	5.3 ± 1.4
Microalbuminuria	10	8.7 ± 1.0	175 ± 83	5.7 ± 1.3
Macroalbuminuria	8	8.1 ± 1.0	160 ± 70	9.2 ± 1.9[a]
Retinopathy	14	8.1 ± 1.8	147 ± 51	5.3 ± 3.9

[a] $p < 0.05$ vs control group
Results are mean ± SD

Willebrand factor during follow-up is associated with an increased risk of developing cardiovascular disease. We report here some observations about vWF endothelin levels in seven Type 1 and 25 Type 2 diabetic patients, which demonstrate that endothelin may be a more sensitive indicator of endothelial damage than vWF in patients with diabetes.

We measured in 10 control subjects and in 32 patients with diabetes under standardized conditions the urinary albumin excretion, HbA_{1c}, and the plasma levels of vWF and endothelin. The patients are subdivided in three groups: A) 10 with microalbuminuria, B) 8 with macroalbuminuria,C) 14 with diabetic retinopathy, without nephropathy. Six patients in group A and one patient in group B had Type 1, the other 25 patients had Type 2 diabetes. Endothelin appeared significantly elevated in group B patients with diabetic nephropathy. Other parameters such as HbA_{1c} and vWF were not significantly different between the three patient groups (Table 1). Although these data represent results in a small group of patients with no follow-up, we conclude that plasma endothelin should be taken into consideration as a sensitive indicator of endothelial damage in patients with diabetes.

Yours sincerely,

I. Vermes, P. F. M. J. Spooren, E. M. Kalsbeek-Batenburg and C. Haanen

References

1. Stehouwer CDA, Zellenrath P, Polak BCP et al. (1992) von Willebrand factor and early diabetic retinopathy: no evidence for a relationship in patients with type 1 (insulin-dependent) diabetes mellitus and normal urinary albumin excretion. Diabetologia 35: 555–559
2. Stehouwer CDA, Nauta JJP, Zeldenrust GC, Hackeng WHL, Donker AJM, den Ottolander GJH (1992) Urinary albumin excretion, cardiovascular disease and endothelial dysfunction in non-insulin-dependent diabetes mellitus. Diabetologia 35: A170 (Abstract)

Dr. I. Vermes
Medical Spectrum Twente
P.O.Box 50000
NL-7500 KA Enschede
The Netherlands

Response from the Authors

Dear Sir,
We thank Dr. Vermes and colleagues for their interesting data. However, we think that their contention – that endothelin may be a more sensitive indicator of endothelial damage than von Willebrand factor (vWF) – is very speculative at present. First, there is no gold standard for endothelial damage with which either vWF or endothelin can be compared; therefore, estimates of endothelial damage are by necessity indirect. Second, the levels of vWF observed by Vermes et al. in patients with microalbuminuria are in fact similar to those we found, although we found lower levels in patients with normal albumin excretion [1]. Thus, the difference appears to be in the control group rather than the microalbuminuria group.As vWF levels may be influenced by the blood sampling procedure, smoking habits, age, and the presence of atherosclerosis, there are many possible explanations for the difference between our data and those reported by Dr. Vermes. Finally, from the data presented by Dr. Vermes, it appears premature to conclude that plasma endothelin levels may be influenced by gender [2], atherosclerosis and renal function; in addition, it may be relevant to distinguish between Type 1 (insulin-dependent) and Type 2 (non-insulin-dependent) diabetes, as we found endothelin levels to be actually decreased in men with Type 1 diabetes and normal urinary albumin excretion when compared with age-matched healthy control subjects [3].

Such factors should be taken into account when analysing the relationships between urinary albumin excretion and plasma endothelin levels. Nevertheless, we agree that the role of endothelin in the microangiopathy of diabetes needs to be investigated.

On behalf of the authors,
Yours sincerely,

C. D. A. Stehouwer

References

1. Stehouwer CDA, Nauta JJP, Zeldenrust GC, Hackeng WHL, Donker AJM, den Ottolander GJH (1992) Urinary albumin excretion, cardiovascular disease, and endothelial dysfunction in non-insulin-dependent diabetes mellitus. Lancet 340: 319–323
2. Polderman KH, Stehouwer CDA, van Kamp GJ, Dekker GA, Verheugt FWA, Gooren LJG (1993) Influence of sex hormones on plasma levels of endothelin. Ann Intern Med (in press)
3. Smulders RA, Stehouwer CDA, Olthof GC, van Kamp GJ, Donker AJM (1992) Plasma endothelin levels and vascular effects of L-arginine in type 1 (insulin-dependent) diabetes. Diabetologia 35: [Suppl. 1] :A19 (Abstract)

Dr. C. D. A. Stehouwer
Department of Internal Medicine
Free University Hospital
De Boelelaan 1117
NL-1081 HV Amsterdam
The Netherlands