25 Rose GA, Blackburn H. Cardiovascular survey methods. In: *WHO Monograph Series No 56*. Geneva: World Health Organisation, 1968.
26 Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972;18:499-502.
27 Robbins DC, Andersen L, Bowsher R, Chance R, Dinesen B, Frank B, et al. Report of the American Diabetes Association's task force on standardization of the insulin assay. *Diabetes* 1996;45:242-56.
28 Mohamed-Ali V, Gould MM, Gillies S, Goubet S, Yudkin JS, Haines AP. Association of proinsulin-like molecules with lipids and fibrinogen in non-diabetic subjects—evidence against a modulating role for insulin. *Diabetologia* 1995;38:1110-6.
29 Office of Population Censuses and Surveys. *Classification of occupations*. London: HMSO, 1980.
30 World Health Organisation Study Group. Report on diabetes mellitus. *WHO Tech Rep Ser* 1985;727:9-12
31 Gould MM, Mohamed-Ali V, Goubet SA, Yudkin JS, Haines AP. Microalbuminuria: associations with height and sex in non-diabetic subjects. *BMJ* 1993;306:240-2.
32 Stein CE, Fall CHD, Kumaran K, Osmond C, Cox V, Barker DJP. Fetal growth and coronary heart disease in South India. *Lancet* 1996; 348:1269-73.
33 Kramer MS, Joseph KS. Enigma of fetal/infant-origins hypothesis. *Lancet* 1996;348:1254-5.
34 Paneth N, Susser M. Early origin of coronary heart disease (the "Barker hypothesis"). *BMJ* 1995;310:423-7.
35 Martyn CN, Barker DJP, Osmond C. Mothers' pelvic size, fetal growth, and death from stroke and coronary heart disease in men in the UK. *Lancet* 1996;348:1264-8.
36 Barker DJP, Gluckman PD, Robinson JS. Conference report: fetal origins of adult disease—report of the first international study group, Sydney, 29-30 October 1994. *Placenta* 1995;16:317-20.
37 Emanuel JI, Filakti H, Alberman E, Evans SJW. Intergenerational studies of human birthweight from the 1958 birth cohort. 1. Evidence for a multigenerational effect. *Br J Obstet Gynaecol* 1992;99:67-74.
38 Marmot MG, Shipley MJ, Rose G. Inequalities in death-specific explanations of a general pattern? *Lancet* 1984;i:103-6.
39 Brown DC, Byrne CD, Clark PM, Cox BD, Day NE, Hales CN, et al. Height and glucose tolerance in adult subjects. *Diabetologia* 1991;34:531-3.
40 Stein Z, Susser M, Saenger G, Marolla F. Famine and human development. The Dutch hunger winter of 1944-1945. New York: Oxford University Press, 1975.
41 Walker M, Shaper AG, Phillips AN, Cook DG. Short stature, lung function and risk of a heart attack. *Int J Epidemiol* 1989;18:602-6.

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Commentary: A hypothesis challenged

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Critics have charged David Barker, champion of the hypothesis that the environment in the uterus programmes the risk of adult disease,[1] with overenthusiastic inductive reasoning as well as inattention to issues of selection bias and confounding.[2] A growing number of independent epidemiologists, however, have confirmed associations between birth weight and hypertension,[3 4] diabetes mellitus,[3 5–7] cardiovascular disease,[8 9] and breast cancer.[10–12] These associations have been observed in various settings and have proved robust to adjustment for socioeconomic and lifestyle factors. Thus increasing attention is being paid to what underlies these observations; Barker himself has invoked "undernutrition" of the fetus to explain the cardiovascular outcomes.[1] Now Stanner and colleagues put this explanation to the test by measuring cardiovascular risk factors among adults who were exposed to severe famine in the siege of Leningrad while in utero or in their first year of life. Their results are resoundingly null. Yet, before proclaiming this study a lethal blow to the hypothesis of in utero programming, consider whether this was a fair test of a clearly delineated hypothesis.

Stanner and colleagues' study is ecological as it lacked data on the exposure status of individuals. Thus the authors were forced to assume that every mother pregnant during the siege was malnourished and that every mother who delivered before the siege was not. The greater the deviation from this assumption, the more a bias to the null would result. At the appalling siege ration of 300 carbohydrate calories/day, however, little cause exists to second guess the extraordinary deprivation experienced by those enduring the siege. Indeed, the mean birth weight of those exposed to the siege in utero was 700 g less than those born before the siege. During the siege 27% of pregnancies delivered in Leningrad's hospitals were stillborn or perished in their first month.[13] The selective survival implied by such a grim mortality might also raise our suspicions of bias. Yet, according to the Barker hypothesis, programming should be most evident among those fetuses who successfully downregulated their growth and survived. Among those who survived infancy during the siege, 64% could not be traced or declined to participate. However, the authors found no evidence for the rather implausible scenario necessary to produce biased results from loss to follow up: that they had inadvertently "over-enrolled" healthy adults who had been exposed to the siege in utero or had "under-enrolled" ill adults who were not exposed in utero.

With some assurance of a fair test, then, what was the hypothesis? As both exposure groups experienced famine during infancy, the study measures the additional impact of having been starved in utero. One interpretation of the null result is that starvation at any point between conception and an infant's first birthday is sufficient to exert programming effects. At the other extreme, perhaps only starvation during a certain period of gestation is relevant, and the exposed group was too broadly defined to detect an effect. Or specific dietary imbalances, rather than sheer starvation, may programme the fetus. Another alternative is that intrauterine programming results from factors other than maternal diet. Finally, these null results could be evidence that intrauterine programming is a chimera of confounding by social class, as rich and poor seem to have been equally starved in the Leningrad siege.

Such broad latitude in interpretation invites new, more specific hypotheses to explain the observed associations between measures of fetal growth and the risk of adult disease. Several recent theories implicate maternal and fetal hormones[14 15] as well as trimester-specific effects of maternal diet.[1] Historical data may prove too blunt to test these increasingly specific hypotheses. Other study designs, including animal experiments and prospective studies of mothers and their offspring, are likely to yield more definitive results. These studies are important to do, because ensuring optimal wellbeing for young women may prove a powerful way to promote the lifelong health of their children.

1 Barker DJP. *Mothers, babies, and disease in later life.* London: BMJ Publishing, 1994.
2 Paneth N, Susser M. Early origin of coronary heart disease (the "Barker hypothesis"). *BMJ* 1995;310:411-2.
3 Valdez R, Athens MA, Thompson GH, Bradshaw BS, Stern MP. Birthweight and adult health outcomes in a biethnic population in the USA. *Diabetologia* 1994;37:624-31.
4 Curhan G, Chertow GM, Willett WC, Spiegelman D, Colditz GA, Manson JAE, et al. Birth weight and adult hypertension and obesity in women. *Circulation* 1996;94:1310-5.
5 McCance DR, Pettitt DJ, Hanson RL, Jacobsson LTH, Knowler WC, Bennett PH. Birth weight and non-insulin dependent diabetes: thrifty genotype, thrifty phenotype, or surviving baby genotype. *BMJ* 1994;308: 945-8.
6 Curhan G, Willett W, Rimm E, Spiegelman D, Ascherio A, Stampfer M. Birth weight and adult hypertension, diabetes mellitus and obesity in US men. *Circulation* 1996;94:3246-50.
7 Rich-Edwards J, Colditz G, Stampfer M, Willett W, Gillman M, Hennekens C, et al. Birthweight and the risk of non-insulin-dependent diabetes mellitus in adult women. *Am J Epidemiol* 1996;143:S39.
8 Frankel S, Elwood P, Sweetnam P, Yarnell J, Smith GD. Birthweight, body-mass index in middle age, and incident coronary heart disease. *Lancet* 1996;348:1478-80.
9 Rich-Edwards JW, Stampfer MJ, Manson JAE, Rosner B, Hankinson SE, Colditz GA, et al. Birth weight and risk of cardiovascular disease in a cohort of women followed up since 1976. *BMJ* 1997;315:396-400.
10 Michels KB, Trichopoulos D, Robins JM, Rosner BA, Manson JE, Hunter DJ, et al. Birthweight as a risk factor for breast cancer. *Lancet* 1996;348:1542-6.
11 Ekbom A, Trichopoulos D, Adami HO, Hsieh CC, Lan SJ. Evidence of prenatal influences on breast cancer risk. *Lancet* 1992;340:1015-9.
12 Sanderson M, Williams MA, Malone KE, Stanford JL, Emanuel I, White E, et al. Perinatal factors and risk of breast cancer. *Epidemiology* 1996;7:34-7.
13 Antonov AN. Children born during the seige of Leningrad in 1942. *J Pediatrics* 1947;30:250-9.
14 Trichopoulos D. Is breast cancer initiated at utero. *Epidemiology* 1990;1:95-6.
15 Swerdlow AJ, Huttly SRA, Smith PG. Prenatal and familial associations of testicular cancer. *Br J Cancer* 1987;55:571-7.

Effectiveness of a regional trauma system in reducing mortality from major trauma: before and after study

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Abstract

Objective: To assess the effect of the development of an experimental trauma centre and regional trauma system on the survival of patients with major trauma.
Design: Controlled before and after study examining outcomes between 1990 and 1993, spanning the introduction of the system in 1991-2.
Setting: Trauma centre in North Staffordshire Royal Infirmary and five associated district general hospitals in the North West Midlands regional trauma system, and two control regions in Lancashire and Humberside.
Subjects: All trauma patients taken by the ambulance services serving the regions or arriving other than by ambulance with injury severity scores >15, whether or not they had vital signs on arrival at hospital.
Main outcome measures: Survival rates standardised for age, severity of injury, and revised trauma score.
Results: In 1990, 33% of major trauma patients in the experimental region were taken to the trauma centre, and by 1993 this had risen to only 39%. Crude death rates changed by the same amount in the control regions (46.5% in 1990-1 to 44.4% in 1992-3) as in the experimental region (44.8% to 41.3%). After standardisation, the estimated change in the probability of dying in the experimental region compared with the control regions was -0.8% per year (95% confidence interval -3.6% to 2.2%); for out of hours care, the change was 1.6% per year (-2.3% to 5.6%), and, for multiply injured patients, the change was -1.6% (-6.1% to 2.6%).
Conclusion: Any reductions in mortality from regionalising major trauma care in shire areas of England would probably be modest compared with reports from the United States.

Introduction

A working party of the Royal College of Surgeons of England found "significant deficiencies in the management of seriously injured patients," most notably that up to 33% of the deaths of 514 patients with major trauma admitted to hospitals' accident and emergency departments could have been avoided.[1] It recommended that accident and emergency services for the care of major trauma patients in Britain should be reorganised so that such patients would be transferred to regional trauma centres conceived along the lines of the American model,[2] which was widely reported as reducing avoidable trauma deaths, particularly for patients with multiple injuries.[3–6] In this model a number of key elements were identified by the American College of Surgeons—such as 24 hour reception in emergency departments by senior staff, all key specialties in the treatment of trauma care on the same site, a high volume of seriously injured patients (about 10-20 a week), and a system to ensure that seriously injured patients would be treated in the trauma centre.[2]

In order to assess whether this concept would transfer cost effectively into the British setting, the Department of Health funded the establishment and evaluation of an experimental regional trauma system in the North West Midlands region based around the North Staffordshire Royal Infirmary. The nascent regional system covered an area of about 6000 km^2 with a catchment population of 1.8 million and was served by five other district general hospitals' accident and emergency departments and three ambulance services (see table 1).

This paper concentrates on the benefits from the system in terms of survival from major trauma. Detailed results on other patient groups, avoidable deaths, outcomes for survivors, and costs will be reported elsewhere.

Methods

Design

We examined changes in outcomes for trauma patients before and after the development of the trauma system. In order to control for secular trends over the four years studied, from January 1990 to December 1993, we compared changes in the experimental

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