Corticosteroids in acute traumatic brain injury: systematic review of randomised controlled trials

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Abstract

Objective: To quantify the effectiveness and safety of corticosteroids in the treatment of acute traumatic brain injury.
Design: Systematic review of randomised controlled trials of corticosteroids in acute traumatic brain injury. Summary odds ratios were estimated as an inverse variance weighted average of the odds ratios for each study.
Setting: Randomised trials available by March 1996.
Subjects: The included trials with outcome data comprised 2073 randomised participants.
Results: The effect of corticosteroids on the risk of death was reported in 13 included trials. The pooled odds ratio for the 13 trials was 0.91 (95% confidence interval 0.74 to 1.12). Pooled absolute risk reduction was 1.8% (– 2.5% to 5.7%). For the 10 trials that reported death or disability the pooled odds ratio was 0.90 (0.72 to 1.11). For infections of any type the pooled odds ratio was 0.92 (0.69 to 1.23) and for the seven trials reporting gastrointestinal bleeding it was 1.05 (0.44 to 2.52). With only those trials with the best quality of concealment of allocation, the pooled odds ratio estimates for death and death or disability became closer to unity.
Conclusions: This systematic review of randomised controlled trials of corticosteroids in acute traumatic brain injury shows that there remains considerable uncertainty over their effects. Neither moderate benefits nor moderate harmful effects can be excluded. The widely practicable nature of the drugs and the importance of the health problem suggest that large simple trials are feasible and worth while to establish whether there are any benefits from use of corticosteroids in this setting.

Introduction

Traumatic brain injury is a leading cause of premature death and disability. Motor vehicle accidents account for most fatal head injuries.[1] Although road death rates are falling in most industrialised countries, in the rapidly motorising Asian countries they are rising and will almost certainly continue to do so. Road death rates per head in China are already similar to those in the United States, even though there are only five vehicles per 1000 population in China compared with 770 vehicles per 1000 population in the United States.[2] Overall, about 75% of the estimated 850 000 deaths due to road accidents each year occur in the developing world.[3]

In the United States the incidence of disability related to brain injury is estimated to be 33 new cases per 100 000 people per year.[4] As this often occurs in young people and is long term, disability related to traumatic brain injury is a major cause of ill health worldwide. In 1961 Galicich and French reported rapid and significant improvement in response to corticosteroids in 28 of 34 people with cerebral oedema either due to brain tumours or postoperatively.[5] This led to their use in other intracranial problems characterised by raised intracranial pressure and in severe head injury.[6] Eighty per cent of patients with fatal head injuries show evidence of increased intracranial pressure at necropsy.[7]

For a problem as common as brain injury, even a moderate reduction in mortality or disability from an intervention as widely practicable as corticosteroids would be important. There have been several randomised controlled trials of corticosteroids in head injury with apparently conflicting findings. Continuing uncertainty about the effects of corticosteroids for this indication is reflected in substantial variation in their use. A recent study in the United Kingdom found that corticosteroids were used in just under half of the intensive care units surveyed.[8] We reviewed the randomised trials that have examined the effects of corticosteroids in acute traumatic brain injury on subsequent death and disability.

Methods

Inclusion criteria

We included studies in the review if they met the following criteria. Firstly, study participants had to have a clinically diagnosed acute traumatic brain injury of any severity. Secondly, the experimental intervention was corticosteroids (those steroids with predominantly glucocorticoid effects—namely, prednisolone, betamethasone, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisone, and triamcinolone) administered in any dose by any route for any duration started within seven days of the injury. Thirdly, study participants were randomly assigned to treatment or control groups. Studies that used quasi-random methods of allocation, such as alternation, were excluded.

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Identification of relevant trials

We searched Medline for 1966 to December 1995 using a combination of the March 1996 update of the optimally sensitive search strategy for trials from the Cochrane Collaboration (earlier version published as referenced[9]) with the MeSH headings "head injuries," "intracranial pressure," "brain edema," and "brain-concussion" including all subheadings. The resulting citations were examined on screen to identify possibly relevant trials and those thus identified were retrieved in full and compared with the inclusion criteria. A search of Embase, years 1974-1996 (performed in March 1996) was done by using a similar approach to that for Medline.

We searched the Cochrane Library in August 1996 using each of the text terms "head," "brain," "dexamet*," and "steroids."[10] We asked the Ottawa Stroke Trials Registry and the United Kingdom based Intensive Care National Audit and Research Centre to search their databases, which contain the results of hand searching many neurological, neurosurgical, intensive care, and emergency medicine journals. Several other journals were also hand searched for this review. All the journals from these sources are listed in an appendix, which is available on the internet at www.bmj.com.

The reference lists of all trials found were searched for additional trials. We attempted to contact all the trialists identified, asking them to identify any further published or unpublished trials. No language restrictions were used.

Data extraction and study appraisal

We each extracted the following information independently from each trial: strategy for concealment of allocation, number of randomised patients, duration of follow up, and number lost to follow up. The major outcome data sought were numbers of deaths and numbers of people disabled at the end of the study period. All but one study (see Faupel et al[18]) used the Glasgow outcome scale[11] to assess neurological outcome; the categories for persistent vegetative state, severe disability, and moderate disability were combined into "disability" for this review. This enabled inclusion of the one trial that did not use the Glasgow outcome scale but used a similar ordinal categorisation of function. Where there was more than one steroid group in a trial (for example, low dose and high dose) those groups were combined. We also extracted data on side effects or complications when they were reported by using the authors' definitions of these.

As there is evidence that the quality of concealment of allocation particularly affects the results of studies, each of us scored this quality on the scale used by Schulz et al as shown below, assigning 1 to poorest quality and 3 to best quality[12]: 1 = trials in which concealment was inadequate (such as alternation or reference to case record numbers or to dates of birth); 2 = trials in which the authors either did not report an allocation concealment approach at all or reported an approach that did not fall into one of the other categories; and, 3 = trials deemed to have taken adequate measures to conceal allocation (for instance, central randomisation; numbered or coded bottles or containers; drugs prepared by the pharmacy; serially numbered, opaque, sealed envelopes; or other description that contained elements convincing of concealment).

When the method used to conceal allocation was not clearly reported the author was contacted, if possible, for clarification. We then compared the scores allocated and resolved differences by discussion.

Statistical methods

Summary odds ratios were calculated in RevMan 3.0 software[13] with the Mantel-Haenszel method. We tested for heterogeneity using a χ^2 test.

Results

The combined search strategies identified 18 reports of trials that satisfied the inclusion criteria.[14-31] Two were reports of the same trial[28 29]: this trial was excluded after contact with the first author showed that concealment of allocation had been inadequate. Contact with one trialist showed that allocation had been concealed by using a third party to prepare and supply the drug and placebo preparations.[26] The trial by Hernesniemi and Troupp was published as an abstract with no results, but the first author, when contacted, was able to provide full outcome data for the 169 randomised participants.[20] Contact with Pitts revealed a further unpublished randomised trial of 279 participants,[21] and the author was also able to provide complete outcome data for death and disability. The trial with 100 participants by Tahara et al was reported as an abstract in 1972 with no usable outcome data.[17] The authors were contacted but were unable to locate the trial data. Similarly, the abstract published by Hoyt et al of a trial on 16 patients provided insufficient detail of outcomes.[15] We were unable to contact the author.

A total of 2073 participants were randomised in 14 included trials. Table 1 describes the participants, intervention, period of follow up, numbers of participants, and quality of concealment of allocation for each trial assessed. The rate of exclusions or losses to follow up was highest in the trial by Cooper because the trial was reported before all patients had been evaluated.[19] Table 2 shows the numbers of deaths, numbers disabled, and complication rates for the trials.

Summary odds ratios

Figures 1 and 2 present summary odds ratio charts for the two main outcomes for all trials in chronological order. For death the odds ratio was 0.91 (95% confidence interval 0.74 to 1.12), and when the categories of death and disability were summed for analysis it was 0.90 (0.72 to 1.11). The summary odds ratio was 0.92 (0.69 to 1.23) for infections and 1.05 (0.44 to 2.52) for gastrointestinal bleeds.

Subgroup analysis—For the two main outcomes—death and death or disability—we performed a subgroup analysis by analysing the trials with only the highest quality of concealment of allocation. This was not done for the other two outcomes because of the small numbers of events involved. For death, the summary odds ratio was 1.04 (0.83 to 1.30) and for death and disability 0.97 (0.77 to 1.23).

Table 1 Summary of participants, interventions, follow up period, size of trial, and quality of concealment of allocation

Study	Details of participants	Intervention	Follow up period	No randomised (No excluded or lost to follow up)	Quality of concealment of allocation
Alexander 1972[14]	Patients admitted to hospital with acute non-missile head injuries who responded to painful stimuli by withdrawal or rigidity but who would not respond to voice command	(1) Dexamethasone 10 mg IV, then 4 mg IM every 6 hours for 10 days (2) No steroid, no mention of placebo	Not stated	110	2
Hoyt 1972[15]	Cranial trauma	(1) Dexamethasone, dose not stated (2) Triamcinolone, dose not stated (3) Placebo	Not reported	16	2
Ransohoff 1972[16]	Critically ill acute closed head injury without evidence of angiographic shift or significant clots but with documented increase in intracranial pressure. Age not stated	(1) Methylprednisolone 125 mg IV every 6 hours for 4 days, starting within 24 hours of admission (2) Placebo	Not stated	35	2
Tahara 1972[17]	Seriously head injured	(1) Prednisolone 2680 mg over 2 weeks (2) Prednisolone 160 mg on first day, tapering over 2 weeks, total dose 1000 mg (3) No steroid	—	100	2
Faupel 1976[18]	All adults with severe (not defined) closed head injury. Exclusions: children (age cut off not given), impression fractures, missile injuries, imminent brain death, and open head injuries. After randomisation, 3 patients considered brain stem dead on angiography, 1 given steroids outside the trial, and 1 who died of other injuries were excluded	(1) Dexamethasone, initial dose 100 mg IV, then 100 mg IM after 6 hours, then 4 mg IM every 6 hours for 8 days, then tapered off by daily reduction of 4 mg (2) Dexamethasone, initial dose 12 mg IV, then 4 mg IM every 6 hours for 8 days, then tapered off by daily reduction of 4 mg (3) Placebo	"At discharge"	100 (5)	2
Cooper 1979[19]	All patients with head injury admitted with a Grady coma grade of 3, 4, or 5. Glasgow coma scale also measured and in all except two patients was ⩽ 8. Patients excluded due to inability to obtain informed consent, previous administration of steroids, or arrival at hospital > 6 hours after injury	(1) High dose dexamethasone phosphate 60 mg initial dose, 24 mg every 6 hours thereafter for 6 days (2) Low dose dexamethasone phosphate 10 mg initial dose, 4 mg every 6 hours thereafter for 6 days (3) Placebo (water, sodium bisulphite, methylparaben, propylparaben)	6 Months	76 (21)	3
Hernesniemi 1979[20]	Age 15 or above with severe closed brain injury. 5 exclusions: 3 not head injury, 1 aged 14 years, 1 imminent death	(1) Betamethasone 100 mg IV on admission, then 80 mg/day IV for 7 days, then tapering off over further 7 days (2) Placebo	6 or 12 Months	169 (5)	3
Pitts 1980[21]	Head injured adults admitted to hospital who were comatose on admission or who lapsed into coma ⩾ 6 hours	(1) Dexamethasone: initially 24 mg IV per day, for a maximum of 7 days, tapering off for the last 5 (2) Dexamethasone, initially 16 mg IV daily, for a maximum of 7 days, tapering off for the last 5 (3) Placebo	6 Months	279 (4)	3
Saul 1981[22]	Patients admitted with craniocerebral trauma within 6 hours of injury. No other body systems injured, Glasgow coma scale ⩽ 7 on admission. Average age 31 years	(1) Methylprednisolone 250 mg IV initially, then 125 mg every 6 hours (2) Some in steroid group received dexamethasone in equivalent dose (3) No steroid, no placebo	6 Months	100	2
Braakman 1983[23]	Any age with severe non-missile related head injury in coma on admission to hospital. Coma defined as no eye opening, no spoken response to painful stimuli, and not obeying commands. Exclusions: those already brain stem dead (apnoea, flaccidity, dilated pupils not reacting to light, absence of reflex eye movements) or expected to become so within 1 hour; those who regained consciousness during initial examination; those who had already been given steroids; and those with diabetes mellitus or history of peptic ulcer	(1) Dexamethasone phosphate, initial dose 100 mg IV (< 6 hours after injury), 100 mg/day IV days 1 to 4, 16 mg/day IV or IM days 5 to 7, 12 mg IV/IM day 8, 8 mg IV/IM day 9, 4 mg IV/IM day 10 (2) Placebo	6 Months	164 (3)	3
Giannotta 1984[24]	Blunt head trauma and Glasgow coma scale ⩽ 8, 6 hours after injury. Exclusions: history of peptic ulcer; undiagnosed or untreated medical condition; taking steroids during 2 weeks before injury; penetrating brain injuries; other injuries expected to cause rapid death; and pregnancy	(1) Methylprednisolone 30 mg/kg IV every 6 hours for 2 doses, then 250 mg IV every 6 hours for 8 doses, then tapering off over the next 8 days (2) Methylprednisolone 1.5 mg/kg IV every 6 hours for 2 doses, then 25 mg IV every 6 hours for 8 doses, then tapering off over 8 days (3) Placebo (Patients randomised in 2:2:1 ratio for these groups)	6 Months	88	3
Braun 1986[25]	Head trauma victims admitted from emergency room to adult neurosurgical intensive care unit	(1) Dexamethasone 6 mg/kg IV in the emergency room; then 6 mg/kg IV 6 hourly for 1 day, then 1 mg/kg IV 6 hourly for 4 days followed by a tapering dose (2) Dexamethasone 6 mg/kg IV in the emergency room; then 0.1 mg/kg IV 6 hourly for 5 days followed by a tapering dose (3) Dexamethasone 6 mg/kg IV in the emergency room: single dose only (4) No steroids, no mention of placebo	Until death, diagnosis of pneumonia, discontinuation of mechanical ventilation, or completion of 14 days of mechanical ventilation	70	2
Dearden 1986[26]	All ages, severe head injury (Glasgow coma scale < 9, no eye opening after resuscitation). Exclusions: incorrect administration of steroid or placebo during trial; receiving steroids before admission	(1) Dexamethasone, initial dose 50 mg IV (0.75 mg/kg for children), 100 mg/day IV days 1,2,3, 50 mg/day IV day 4, 25mg/day IV day 5 (2) Placebo	6 Months	142 (12)	3
Zagara 1987[27]	Average age 29. Severe isolated head trauma with mean (SD) Glasgow coma scale 5.7 (1.2) in one group and 5.8 (1.2) in other	(1) Dexamethasone 0.36 mg/kg/day IV for 9 days (2) No steroid, no placebo mentioned	3 Months	24	3
Kloti 1987[28]; Fanconi 1988[29]	Children aged 1.4 to 15.8 years with severe head injury (Glasgow coma scale < 8)	(1) Dexamethasone, initial dose 1 mg/kg followed by 1 mg/kg/day for 3 days. Route not stated (2) No steroid, no placebo mentioned	6 Months	25	1
Gaab 1994[30]	Age 15 to 55 with moderate central nervous system injury (two or more of disturbed consciousness, eye opening to stimulation, no adequate verbal response, disorientation in time and place) or severe central nervous system injury (comatose on injury and/or on admission to hospital, no eye opening to painful stimuli). Patients also required to have obvious neurological symptoms (for example, hemiparesis or hemiplegia) or computed tomography evidence of lesions requiring surgical intervention or hypodense area(s) in brain. Reasons for exclusion: time to treatment > 3 hours; already had steroids; penetrating head injury; primary bulbar symptoms present; prognosis considered hopeless; known malignancy; peptic ulcer; tuberculosis; Cushing's syndrome; non-traumatic neurological or psychiatric disease; spinal injury; suspected coagulation defects	(1) Dexamethasone, initial dose 200 mg IV, then 300mg over next 3 hours, then 200 mg 3 hours later, then 200 mg 6 hourly for 8 doses (2) Placebo	10 to 14 Months	299 (30)	3
Grumme 1995[31]	All ages admitted with head injury. Exclusions: contraindication to steroids (not specified); impaired consciousness not due to trauma; absence of relevant brain damage (not specified)	(1) Triamcinolone acetonide, 200 mg IV, then 40 mg 8 hourly for 4 days, then 20 mg 8 hourly for 4 days (2) Placebo	About 1 year	396 (26)	3

IM=intramuscularly; IV=intravenously.

Table 2 Summary of outcome data. In some trials, denominators vary between outcomes: this is assumed to be effects of time on loss to follow up

	No (%) who died		No (%) with disability		No (%) of all infections*		No (%) with "major" or "significant" gastrointestinal bleed	
Trial	Steroid	Control	Steroid	Control	Steroid	Control	Steroid	Control
Alexander 1972[14]	16/55 (29.1)	22/55 (40.0)	—	—	—	—	1/55 (1.8)	0/55 (0.0)
Ransohoff 1972[16]	9/17 (52.9)	13/18 (72.2)	—	—	—	—	—	—
Faupel 1976[18]	16/67 (23.9)	16/28 (57.1)	42/67 (62.7)	11/28 (39.3)	—	—	—	—
Cooper 1979[19]	26/49 (53.1)	13/27 (48.1)	16/49 (32.7)	7/27 (25.9)	28/49 (57.1)	11/27 (40.7)	0/49 (0.0)	1/27 (3.47)
Hernesniemi 1979[20]	35/81 (43.2)	36/83 (43.4)	24/81 (29.6)	21/83 (25.3)	23/81 (28.4)	27/83 (32.5)	3/81 (3.7)	1/83 (1.2)
Saul 1981[22]	8/50 (16.0)	9/50 (18.0)	19/50 (38.0)	28/50 (56.0)	—	—	—	—
Braakman 1983[23]	44/81 (54.3)	47/80 (58.8)	23/81 (28.4)	21/80 (26.3)	—	—	1/81 (1.2)	1/80 (1.3)
Giannotta 1984[24]	34/72 (47.2)	7/16 (43.8)	26/72 (36.1)	5/16 (31.3)	—	—	1/72 (1.4)	0/16 (0.0)
Braun 1986[25]	—	—	—	—	—	—	—	—
Dearden 1986[26]	33/68 (48.5)	21/62 (33.9)	13/68 (19.1)	19/62 (30.6)	—	—	—	—
Zagara 1987[27]	4/12 (33.3)	4/12 (33.3)	—	—	—	—	—	—
Gaab 1994[30]	19/133 (14.3)	21/136 (15.4)	32/133 (24.1)	37/136 (27.2)	37/130 (28.5)	36/141 (25.5)	3/147 (2.0)	2/151 (1.3)
Grumme 1995[31]	38/175 (21.7)	49/195 (25.1)	34/175 (19.4)	43/195 (22.1)	38/187 (20.3)	57/209 (27.3)	1/187 (0.5)	3/209 (1.4)

* Trials that reported overall infection rates; excludes reports of one type of infection only and reports of more than one infection for which a pooled rate could not be calculated.
— Means not reported or the report stated "no significant difference."

Discussion

This systematic review summarises the evidence from randomised controlled trials of corticosteroids in acute traumatic brain injury.

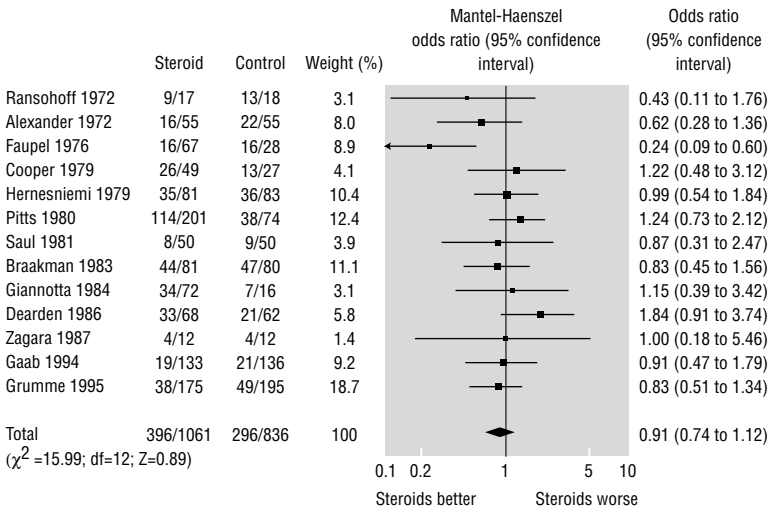

Fig 1 Summary odds ratio for death at end of study

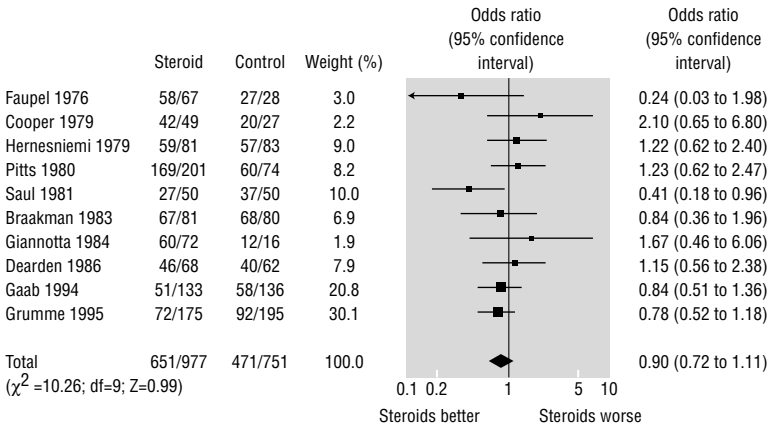

Fig 2 Summary odds ratio for death or disability at end of study

Methodological issues

The inclusion of an Embase search identified one study not found on Medline.[17] Contact with trialists enabled us to include data from two large unpublished studies[20 21] but not from others.[15 17 21]

Numbers of events were small for infections and gastrointestinal bleeds, resulting in wide confidence intervals around the estimate of effect.

None of the tests for heterogeneity yielded significant results. When death was the outcome, however, the upper limit of the 95% confidence interval in the trial by Faupel et al[18] did not overlap with the lower limit in the trial by Dearden et al.[26] In Faupel's trial the outcome was assessed "at discharge," yet overall 19% of the participants were classified as "unconscious stabilised." The apparently short follow up period may account for the incongruous result.

Other sources of variation may include severity and pathology of the head injury, variations in corticosteroid regimens (for example, drug, dose, route), and temporal trends in the use of other interventions. The use of corticosteroids in spinal cord injury suggests that the timing of administration is important,[32] so this is another possible source of variation.

When we excluded trials with less than the highest quality of concealment of allocation the differences between experimental and control groups was reduced for both death and death or disability. This is consistent with the evidence that inadequate concealment of allocation results in overestimates of the effect of treatment,[12] but it could also be due to random variation. There were several trials in which the true quality of concealment was not known, which makes interpretation difficult.

Implications

Despite 25 years of randomised controlled trials of the use of corticosteroids in patients with head injury, their effects are still not clear. In this review the risk of death in those given corticosteroids was 1.8% less than in the control groups (95% confidence interval 5.7% less to 2.5% more) when we used the trials' average control death rate of 35.4% as the background rate.

Key messages

- Traumatic brain injury is an important global cause of death and disability
- Corticosteroids are a widely practicable intervention
- This systematic review shows continued uncertainty over the effects of steroids
- The estimate of absolute risk reduction for death is 1.8% (95% confidence interval −2.5 to 5.7)
- Further large scale randomised controlled trials are needed

The recent guidelines from the Brain Trauma Foundation on the management of severe head injury include a standard (a recommendation made with a "high degree of clinical certainty") that "the use of glucocorticoids is not recommended."[33] These guidelines reviewed six of the randomised trials used in this systematic review and did not attempt a quantitive overview of them. Even with 14 trials, as in this systematic review, considerable uncertainty remains over the effects of corticosteroids.

Can this uncertainty be resolved? To do so would require large randomised trials. For example, a trial with 90% power to detect a 2.6% reduction in risk of death from 35.4% (the total control mortality in this review) to 32.8% at the 0.01 level of significance would require about 20 000 participants.[34] Such large trials to detect effects of this size can be justified when the health problem is important and the treatment widely practicable.[35] Corticosteroids for acute traumatic head injury meet these criteria. Without such a trial clinicians and patients and their families are being forced to make important decisions on the basis of inadequate evidence.

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Endpiece

Two modes of thought

There is a line among the fragments of the Greek poet Archilochus which says, "The fox knows many things, but the hedgehog knows one big thing." Scholars have differed about the correct interpretation of these dark words, which may mean no more than that the fox, for all his cunning, is defeated by the hedgehog's one defence. But, taken figuratively, the words can be made to yield a sense in which they mark one of the deepest differences which divide writers and thinkers, and, it may be, human beings in general.

Isaiah Berlin, *The Hedgehog and the Fox* (1953)

Prospective study of effect of switching from cigarettes to pipes or cigars on mortality from three smoking related diseases

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Abstract

Objective: To estimate the extent to which cigarette smokers who switch to cigars or pipes alter their risk of dying of three smoking related diseases—lung cancer, ischaemic heart disease, and chronic obstructive lung disease.
Design: A prospective study of 21 520 men aged 35-64 years when recruited in 1975-82 with detailed history of smoking and measurement of carboxyhaemoglobin.
Main outcome measures: Notification of deaths (to 1993) classified by cause.
Results: Pipe and cigar smokers who had switched from cigarettes over 20 years before entry to the study smoked less tobacco than cigarette smokers (8.1 g/day *v* 20 g/day), but they had the same consumption as pipe and cigar smokers who had never smoked cigarettes (8.1 g) and had higher carboxyhaemoglobin saturations (1.2% *v* 1.0%, $P < 0.001$), indicating that they inhaled tobacco smoke to a greater extent. They had a 51% higher risk of dying of the three smoking related diseases than pipe or cigar smokers who had never smoked cigarettes (relative risk 1.51; 95% confidence interval 0.96 to 2.38), a 68% higher risk than lifelong non-smokers (1.68; 1.16 to 2.45), a 57% higher risk than former cigarette smokers who gave up smoking over 20 years before entry (1.57; 1.04 to 2.38), and a 46% lower risk than continuing cigarette smokers (0.54; 0.38 to 0.77).
Conclusion: Cigarette smokers who have difficulty in giving up smoking altogether are better off changing to cigars or pipes than continuing to smoke cigarettes. Much of the effect is due to the reduction in the quantity of tobacco smoked, and some is due to inhaling less. Men who switch do not, however, achieve the lower risk of pipe and cigar smokers who have never smoked cigarettes. All pipe and cigar smokers have a greater risk of lung cancer than lifelong non-smokers or former smokers.

Introduction

It is recognised that cigarette smokers inhale tobacco smoke while men who smoke only pipes or cigars tend not to. Pipe and cigar smokers are at lower risk of the main smoking related diseases, probably in part because of this difference in inhaling habit[1] and because they may smoke less tobacco. There is evidence that smokers who switch from cigarettes to pipes or cigars tend to maintain their acquired inhaling habits.[2-7] The extent to which this occurs and the extent to which it negates the potential health benefits associated with smoking cigars or pipes rather than cigarettes is uncertain. We used data from the British United Provident Association (BUPA) study to examine these points in greater detail in relation to three diseases caused by smoking—namely, lung cancer, ischaemic heart disease, and chronic obstructive lung disease. In particular, we assessed the merits of switching from smoking cigarettes to smoking pipes and cigars.

Subjects and methods

The BUPA study, a prospective study of 21 520 professional and business men aged 35-64 years who attended the BUPA Medical Centre in London for a routine health examination between 1975 and 1982, has been described previously.[8] At the time of each examination, which included a blood pressure measurement, a detailed history of smoking was obtained, including self reported inhaling habits classified into four categories (nil, slight, moderate, deep). A blood sample was collected, carboxyhaemoglobin saturation and various other factors (including serum cholesterol) measured, and serum samples stored at −40°C. The study was restricted to men with NHS numbers so that their NHS records could be flagged and the Office of Population Censuses and Surveys could inform us of all deaths and their certified causes. Further information was then sought from the doctor who certified death. Eight hundred and twenty nine men were lost to follow up because they emigrated. The average follow up time was 14 years and 4 months. This report is based on the deaths that occurred in the study up to October 1993. The codes of ICD-9 (international classification of diseases, ninth revision) used to classify the three specified smoking related diseases were 162 for lung cancer, 410-414 for ischaemic heart disease, and 416, 491, 492, 496, and 519 for chronic obstructive lung disease.

To assess the benefits of switching from cigarettes to cigars or pipes, or both, we compared mortality from the three smoking related diseases in current pipe or cigar smokers who had switched (switchers) from smoking cigarettes at least 20 years before entry to the study (that is, 20 years before 1975-82) with that in pipe or cigar smokers who were current smokers at entry and had never smoked cigarettes (non-switchers). The 20 year interval between switching and the date of the examination was selected to avoid the excess health hazards attributable to past cigarette smoking. We verified this by showing that men who had stopped smoking cigarettes for at least 20 years before entry to the study and had not switched to pipes or cigars had death rates from the three specified diseases that were similar to those in lifelong non-smokers. We also compared death rates in the switchers with those in cigarette smokers who did not smoke cigars or pipes, with those in former smokers, and with those in lifelong non-smokers.

Consumption of tobacco was estimated on the basis of one cigarette containing 1 g of tobacco, one small cigar (cheroot) containing 2 g, and one large cigar containing 5 g. The weight of tobacco used by pipe smokers

was recorded directly on the questionnaire. Carboxyhaemoglobin saturations were measured (taking the mean of two measurements) with an IL182 co-oximeter, as described in detail previously, for all men at the time they attended the medical centre.[9] Risks of mortality from the three specified diseases were compared by using Cox's proportional hazards survival analysis adjusted for age at entry to the study. We used survival analysis to take account of the differing lengths of follow up, which were mainly attributable to the eight year recruitment period. The results were also analysed by logistic regression (results not shown), which gave virtually identical results. The association between carboxyhaemoglobin measurements and self described inhaling category was examined by analysis of variance.

Results

Table 1 shows the data collected in 1975-82 on median tobacco consumption and carboxyhaemoglobin saturations according to smoking group: men who currently smoked cigars or pipes and had never smoked cigarettes, men who currently smoked cigars and pipes but smoked cigarettes at least 20 years previously, and men who smoked only cigarettes. Tobacco consumption was similar in the two groups of pipe and cigar smokers (switchers and non-switchers) (table 1), but the median carboxyhaemoglobin saturation was higher in the switchers (1.2% *v* 1.0%, $P < 0.0001$ by the Wilcoxon rank sum test). The mean carboxyhaemoglobin saturations in both groups of pipe and cigar smokers were much lower than in current cigarette smokers (table 1). In lifelong non-smokers and in former smokers the median carboxyhaemoglobin saturation (reflecting endogenous production and exposure to atmospheric carbon monoxide) was 0.7% (10th-90th centile 0.4-1.1).

Table 2 shows self described inhaling category according to smoking group. One third of the switchers, and about half of the non-switchers said that they inhaled, and 95% of current cigarette smokers said that they inhaled; this indicates clear differences between the three groups.

Table 2 also shows an increasing trend in carboxyhaemoglobin saturation with deeper self described inhaling; cigarette smokers had higher saturations than other smokers except for men in the lightest category of smoking. This was also the case after we allowed for type of product smoked and weight of tobacco smoked ($P < 0.0001$ by analysis of variance). In the pipe and cigar smokers there was no material difference in carboxyhaemoglobin saturations within each inhaling category between switchers and non-switchers; self described inhaling therefore accounted for the difference in carboxyhaemoglobin saturations shown in table 1.

Table 3 shows the mortality and the number of deaths by 1993 from the three smoking related diseases and from all causes for the three groups of current smokers and for former smokers relative to lifelong non-smokers. The combined risk of the three diseases in current cigarette smokers was 3.18 times higher (95% confidence interval 2.55 to 3.84) than in lifelong non-smokers; individual relative risk estimates were 2.27 for ischaemic heart disease, 16.4 for lung cancer, and 29.5 for chronic obstructive lung disease. Having given up smoking cigarettes 20 or more years before entry to the study reduced the risk to about that of a lifelong non-smoker (rows 1 and 2 in

Table 1 Numbers of pipes, cigars, and cigarettes smoked each day, weight of tobacco smoked each day, and carboxyhaemoglobin saturations according to smoking group. Figures are medians (10th-90th centiles)

Smoking group	No of men	No of pipes, cigars, and cigarettes	Weight of tobacco (g)	Observed carboxyhaemoglobin saturation (%)
Pipe/cigar smoker, never smoked cigarettes (non-switchers):				
Pipes only	472	6 (2-16)	12.1 (4.0-20.3)	1.4 (0.7-3.6)
Cigars only	651	2 (0.4-6)	4.7 (2.0-17.8)	0.9 (0.5-2.4)
Both	186	4 (2-12)	11.5 (5.5-24.9)	1.0 (0.5-2.6)
Either or both	1309	3 (0.9-11)	8.1 (2.1-20.3)	1.0 (0.6-3.2)
Pipe/cigar smoker, switched from cigarettes over 20 years ago (switchers):				
Pipes only	187	7 (3-16)	12.1 (4.0-20.3)	1.9 (0.7-4.8)
Cigars only	272	2 (0.6-6)	5.0 (2.0-17.4)	1.0 (0.6-4.2)
Both	63	5 (2-13)	10.8 (6.0-22.4)	1.2 (0.6-3.6)
Either or both	522	4 (1-12)	8.1 (2.0-20.3)	1.2 (0.6-4.5)
Current cigarette smokers (cigarettes/day):				
1-14	947	8 (3-12)	8.0 (3.0-12.0)	1.8 (0.8-4.6)
15-24	1387	20 (15-20)	20.0 (15.0-20.0)	4.4 (2.0-7.0)
25-34	1133	30 (25-30)	30.0 (25.0-30.0)	5.7 (3.2-8.7)
⩾35	717	40 (35-50)	40.0 (35.0-50.0)	6.2 (3.6-9.6)
All amounts	4184	20 (7-40)	20.0 (7.0-40.0)	4.6 (1.4-8.0)

Table 2 Self described inhaling status and median carboxyhaemoglobin saturations by smoking group and inhaling category

	Self described inhaling category (% men in each smoking group)				Median carboxyhaemoglobin saturation by inhaling category (%)			
Smoking group	Nil	Slight	Moderate	Deep	Nil	Slight	Moderate	Deep
Pipe/cigar smoker, never smoked cigarettes (non-switchers):								
Pipes only	61	23	13	3	1.2	2.0	2.8	3.9
Cigars only	69	20	9	2	0.8	0.9	2.0	3.6
Both	52	22	21	5	1.1	1.8	3.2	2.2
Either or both	67	21	10	2	0.9	1.3	2.6	3.7
Pipe/cigar smoker, switched from cigarettes over 20 years ago (switchers):								
Pipes only	40	33	23	5	1.3	2.0	2.6	4.7
Cigars only	55	26	14	5	0.9	1.0	2.3	1.4
Both	74	17	8	1	1.0	2.1	2.4	4.3
Either or both	49	28	18	5	0.9	1.4	2.6	3.8
Currently cigarette smoker (cigarettes/day):								
1-14	7	23	55	15	1.3	1.5	2.0	2.1
15-24	5	11	61	23	3.7	3.7	4.4	4.9
25-34	3	8	56	32	5.2	5.2	5.7	5.8
⩾35	4	9	42	44	5.0	5.9	6.2	6.4
All amounts	5	13	55	27	3.2	3.4	4.6	5.4

Table 3 Relative mortality (with 95% confidence intervals) according to smoking group for the three specified diseases compared with mortality among lifelong non-smokers

Smoking group at entry	Total No of men	Ischaemic heart disease		Lung cancer		Chronic obstructive lung disease		All three diseases		All cause mortality	
		Relative mortality	No of deaths	Relative mortality	No of deaths	Relative mortality	No of deaths	Relative mortality	No of deaths	Relative mortality	No of deaths
Lifelong non-smoker	6539	1.00	125	1.00	7	1.00	1	1.00	133	1.00	346
Former cigarette smoker, stopped smoking over 20 years before entry	1465	1.05 (0.77 to 1.45)	59	1.01 (0.26 to 3.91)	3	†	1	1.07 (0.79 to 1.45)	63	1.11 (0.92 to 1.34)	162
Pipe/cigar smoker, never smoked cigarettes (non-switchers)	1309	0.98 (0.67 to 1.44)	33	3.19* (1.07 to 9.50)	6	†	1	1.11 (0.78 to 1.59)	40	1.23 (0.99 to 1.75)	113
Pipe/cigar smoker, switched from cigarettes over 20 years before entry (switchers)	522	1.29 (0.88 to 1.99)	25	8.64* (3.19 to 23.3)	9	†	1	1.68* (1.16 to 2.45)	35	1.33 (1.03 to 1.73)	69
Current cigarette smoker	4182	2.27* (1.81 to 2.84)	193	16.4* (7.55 to 44.2)	77	29.5* (3.96 to 220)	20	3.13* (2.55 to 3.84)	290	2.26 (1.97 to 2.58)	540

*P<0.05 compared with mortality in lifelong non-smokers.
†Too few deaths to give reliable estimate.

Table 4 Mortality from three specified diseases (ischaemic heart disease, lung cancer, and chronic obstructive lung disease) in men who switched from smoking cigarettes to smoking pipes or cigars, or both, 20 or more years before entry to study, relative to mortality in four reference groups

Reference group*	Mortality (95% CI) relative to reference group
Lifelong non-smokers	1.68 (1.16 to 2.45)
Former cigarette smokers, stopped smoking over 20 years ago (switchers)	1.57 (1.04 to 2.38)
Pipe/cigar smokers, never smoked cigarettes (non-switchers)	1.51 (0.96 to 2.38)
Current cigarette smokers	0.54 (0.38 to 0.77)

*Risk in reference group set at 1.00. Relative mortality estimate can be derived by selecting entry in column in table 3 headed "All three diseases" relating to pipe/cigar smoker, switched from cigarettes over 20 years before entry (switchers) and dividing this by entry for smoking group taken to be reference group.

table 3). The risk in switchers was much less than among continuing cigarette smokers (rows 4 and 5, $P<0.001$) but somewhat higher than the risk in lifelong pipe and cigar smokers (rows 3 and 4, $P=0.07$). Mortality from all causes was also graded as expected. The rates were lower in non-smokers; successively higher in former smokers, pipe and cigar smokers who had never smoked cigarettes, and pipe and cigar smokers who had previously smoked cigarettes; and substantially higher in cigarette smokers. The relative risks of ischaemic heart disease were not materially changed after we allowed for serum cholesterol concentration and blood pressure. They were 0.97 (95% confidence interval 0.71 to 1.33) for former smokers, 1.00 (0.68 to 1.47) for pipe and cigar smokers who never smoked cigarettes, 1.31 (0.85 to 2.03) for those who had switched from cigarettes, and 2.18 (1.74 to 2.73) for cigarette smokers.

Table 4 shows the risk of the three smoking related diseases in the switchers compared with other groups. The risk of all three diseases combined was 46% lower in switchers than in continuing cigarette smokers (relative risk 0.54) and 68% higher than in lifelong non-smokers. It was 51% higher than in pipe or cigar smokers who had not switched from cigarettes.

Discussion

Interpretation of results

Our results indicate that current pipe or cigar smokers who switched from cigarettes smoke about the same amount of tobacco as pipe and cigar smokers who never smoked cigarettes but that they tend to inhale more. Most of the reduction in the risk of dying from ischaemic heart disease, lung cancer, and chronic obstructive lung disease combined compared with that in continuing cigarette smokers is attributable to the fact that pipe and cigar smokers smoke less tobacco than the cigarette smokers (median 8.1 g a day compared with 20 g a day). The risk of dying from the three diseases combined in these switchers was less (24% less; 95% confidence interval 55% less to 27% more) than in light cigarette smokers who smoked the same amount of tobacco—that is, those who smoked between one and 14 cigarettes a day with a median of 8 g tobacco a day—so the reduction may also be explained in part by reduced inhaling. There may be other differences in lifestyle between the switchers and non-switchers, though this is probably unlikely because adjustment for serum cholesterol concentration and systolic blood pressure made no difference to the risk estimates.

Our results indicate a specific adverse effect among pipe smokers who switched from cigarettes that is not due to former cigarette smoking. The carboxyhaemoglobin saturations shown in table 1 suggest this is due to increased inhaling. For example, the mean carboxyhaemoglobin saturation in pipe smokers who never smoked cigarettes was about twice the background level (1.4 v 0.7); it was nearly three times the background level in those who switched from cigarettes (1.9 v 0.7). An interesting result, though one that is not directly relevant to the question we sought to answer, was that carboxyhaemoglobin saturation was related to the risk of the three specified smoking related diseases independently of smoking category or amount smoked. Indeed, after adjustment for carboxyhaemoglobin saturations, smoking was no longer significantly related to risk. We estimated that regardless of smoking category, the risk of dying of the three specified diseases increased by 22% per 1% increase in carboxyhaemoglobin saturation.

Previous studies

Two previous studies have compared mortality in pipe and cigar smokers who switched from smoking cigarettes with those who never smoked cigarettes, but neither yielded conclusive results. The paper by Kaufman et al was a case-control study of cigar and pipe smoking in relation to myocardial infarction in

young men (aged 40-54 years).[10] The group of men who stopped smoking cigarettes and switched to pipes or cigars included men who could have switched as recently as two years previously, so that any excess risk could have been associated with the residual effect of cigarette smoking rather than the effect of pipe or cigar smoking. The Whitehall study showed that pipe or cigar smokers who previously smoked cigarettes had a higher mortality than pipe or cigar smokers who did not previously smoke cigarettes,[11] though again this result could have been due to the residual effects of cigarette smoking in the former cigarette smokers. The study did show that cigarette smokers who switched to smoking pipes (but not to smoking cigars) had a higher mortality from all causes than former cigarette smokers (relative risk 1.17; 1.03 to 1.34), with a significant increase in risk of ischaemic heart disease. The difference was explained by the pipe smokers' previous cigarette smoking habits.

Public health implications

Our results have public health implications. Cigarette smokers may be able to stop smoking when they receive advice and support and by using aids such as nicotine chewing gum.[12] Some, however, may still have difficulty in giving up smoking altogether, and these smokers would be better off changing to cigars or pipes instead of continuing to smoke cigarettes. Much of the effect is due to the reduction in the quantity of tobacco smoked; the rest may be attributable to reduced inhalation. Cigarette smokers may find it easier to reduce consumption by changing to smoking cigars or pipes rather than by smoking fewer cigarettes. The risk of the three specified smoking related diseases, none the less, is still higher than in men who only ever smoked pipes or cigars, higher than in those who gave up smoking altogether—and, of course, higher than in men who never smoked at all.

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Conflict of interest: None.

Key messages

- The health risks from smoking pipes or cigars are less than those from smoking cigarettes, but there is little direct evidence on these risks in cigarette smokers who switch to pipes or cigars
- This prospective study shows that smokers who switch from cigarettes to pipes or cigars halve their combined risk of dying of lung cancer, ischaemic heart disease, or chronic obstructive lung disease compared with continuing smokers, but their risk was still about 50% higher than that of lifelong non-smokers
- Some of this reduction in risk was due to reduced inhaling, but most of it was due to a reduction in the amount of tobacco smoked
- The best option is either not to smoke or to give up altogether; failing that, switching to pipes or cigars is better than continuing to smoke cigarettes

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A memorable patient

When all else fails examine the patient

It was an extremely busy receiving night on the surgical service, which in retrospect is my only inadequate excuse for what occurred. As the senior registrar, I was coping with most of the 15 or 16 emergencies admitted through the night, including patients with perforated ulcers, acute appendicitis, ischiorectal abscess, blunt abdominal trauma, upper gastrointestinal haemorrhage, acute pancreatitis, and acute urinary retention. In between cases in the operating theatre I examined an elderly lady on the ward at about 3 00 am who had been admitted with a short history of cramping abdominal pain. The abdomen was slightly distended, with no signs of peritoneal irritation, rectal examination was normal, and the findings on abdominal radiography were consistent with early small bowel obstruction. After my hurried examination I ordered drip and suction while I rushed back to the long list of emergency operations already scheduled.

Eventually, the operating list was completed and there was just time for a bath and some breakfast before rounds began with the chief and the entire entourage of students, house staff, registrars, and consultants. As we circled the old Florence Nightingale ward, I described with some self satisfaction the salient features of each case and how it had been handled, while the chief paused here and there to examine an abdomen, check an incision, make a management suggestion, or teach on a point of special interest. When we came to the bedside of the lady described above, I explained the history and findings, and how I had decided to treat her with intravenous fluids and nasogastric suction pending a more definitive diagnosis. With a sonorous "hrrumph," the chief threw the bed covers down in order to examine the abdomen. To my horror, I and everyone else in the assembled multitude immediately saw a lump of approximately 3 cm diameter low in the right groin. After a pregnant pause, every moment adding to my extreme discomforture, he said "I suppose Dr Wright will now give us an erudite dissertation on the non-operative treatment of strangulated femoral hernia." I never needed to be reminded thereafter that adequate abdominal examination includes "nipples to knees."

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Prospective cohort study of factors influencing the relative weights of the placenta and the newborn infant

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Abstract

Objectives: To determine the demographic, environmental, and medical factors that influence the relative weights of the newborn infant and the placenta and compare this ratio with other factors known to predispose to adult ill health.

Design: Prospective cohort study.

Setting: The tertiary referral centre for perinatal care in Perth, Western Australia.

Subjects: 2507 pregnant women who delivered a single live infant at term.

Main outcome measures: Placental weight, birth weight, and the ratio of placental weight to birth weight.

Results: By multiple regression analysis the placental weight to birthweight ratio was significantly and positively associated with gestational age, female sex, Asian parentage, increasing maternal body mass index, increased maternal weight at booking, lower socioeconomic status, maternal anaemia, and increasing number of cigarettes smoked daily. There were no consistent relations between the placental weight to birthweight ratio and measures of newborn size.

Conclusions: The ratio of placental weight to birth weight is not an accurate marker of fetal growth. In its role as a predictor of adult disease the ratio may be acting as a surrogate for other factors which are already known to influence health and may act before or after birth. Determining the role that relative growth rates of the fetus and placenta have in predisposing to adult disease requires prospective study to account for the many confounding variables which complicate this hypothesis.

Introduction

Evidence from large British cohort studies suggests that the combination of a large placenta and low birth weight is a strong independent risk factor for cardiovascular disease in adulthood.[1-3] This important finding adds to the epidemiological evidence that intrauterine influences are relevant in the development of adult disease.[4-6] Hypertension is the most important known risk factor for coronary artery disease. Hypertension is significantly more common in people whose history includes a placenta disproportionately large for their birth weight—that is, those who had a high placental weight to birthweight ratio.[1]

Barker and colleagues formed a broad hypothesis that maternal undernutrition before and during pregnancy influences the relative growth rates of the fetus and the placenta,[1-6] programming fetal metabolism and predisposing the person to hypertension in adulthood. Animal studies support this hypothesis.[7] In human pregnancy both small maternal pelvic diameter (a possible marker of poor nutrition during development) and shortness of babies in relation to head circumference and birth weight (possibly indicating mid-pregnancy nutrient deprivation) are associated with significantly raised placental weight to birthweight ratios.[1] Debate has focused on whether these findings represent a true relation or are due to the effects of the many measurable or concealed confounders that are inherent in analyses of this type.[8 9]

We set out to determine the factors that influence the relative weights of the placenta and the newborn infant and to examine the relation between this ratio and measures of newborn size in order to further evaluate the relevance of this variable as a marker of intrauterine events.

Subjects and methods

The design of the study has been detailed elsewhere.[10] Briefly, beginning in 1989 data were collected by questionnaire from 2900 pregnant women and their partners at about 18 weeks of gestation and again at 34 weeks. The study was conducted in Perth, Western Australia, in the sole tertiary level perinatal centre for the state. The potential for introducing bias by using a tertiary referral centre population was minimised by enrolling only women who booked for antenatal care before 18 weeks of gestation, so excluding those referred with complications. Gestational age was ascertained by menstrual dates and ultrasound measurements.

The study was approved by the institutional ethics committee and written consent obtained from each woman at the time of enrolment. Data from the 2507 singleton pregnancies delivered after 37 completed weeks were used in the analysis. Tables 2-4 list the variables included. Social class was calculated from a composite score based on the occupation, income, and

Table 1 Gestational age estimation by menstrual dates and ultrasound measurements at 18 weeks' gestation

Last menstrual period	Last menstrual period agrees with 18 weeks by ultrasonography	Last menstrual period differs from ultrasonography by >7 days	Last menstrual period overestimates estimated date of delivery	Last menstrual period underestimates estimated date of delivery	Total (%)
No (%) certain†	1517 (76.1)	476 (23.9)	209 (10.5)	267 (13.4)	1993 (79.5)
No (%) uncertain	245 (47.7)	269 (52.3)	207 (40.3)	62 (12.1)	514 (20.5)
Total (%)	1762 (70.3)	745 (29.7)	416 (16.6)	329 (13.1)	2507 (100.0)

†"Certain" denotes date of last menstrual period recalled to within one week.

highest level of education attained by the woman and her partner. Racial groupings[11] were categorised by the women and their partners at enrolment. Maternal anaemia was defined as a haemoglobin concentration below 110 g/l at any time in the pregnancy.

Table 1 shows the rate of discordance of gestational age estimation between menstrual dates and ultrasound measurements at 18 weeks. Gestational age was based on the date of the last menstrual period unless there was discordance of more than seven days with ultrasound measurements on or before 18 weeks; in that case the ultrasonic estimate of gestation was used (745 cases; 29.7%). Placental weights were recorded wet without trimming the membranes or cord. Techniques for measurements in newborn infants were as described.[12]

All data were computerised in an SAS format (SAS, Cary, North Carolina). The relations between birth weight, placental weight, and the placental weight to birthweight ratio and various predictor variables were identified by multivariate analysis and logistic regression. To allow for the large number of comparisons probability values of less than 0.01 were considered significant.

Results

Table 2 shows the characteristics of the study population. The mean gestational age at delivery was 39.2 (SD 1.3) weeks. A total of 1205 (48.1%) women were nulliparous and 1434 (57.2%) were in social class I or II. Over a quarter of the population (665 women; 26.5%) smoked during pregnancy, 277 (11.0%) women smoking more than 10 cigarettes a day. Most of the study population was of European origin, the remainder (302 women; 12.0%) being of Asian (predominantly Chinese or Vietnamese), Australian Aboriginal, or Indian origin.

Figure 1 plots placental weight against birth weight. As expected, placental weight and birth weight were highly correlated ($r=0.63$). The 90% confidence intervals for the individual predicted values showed that in general infants with a higher than average placental weight to birthweight ratio had birth weights and placental weights which spanned the range for typical births.

Table 3 lists the factors which by multiple regression analysis influenced the three outcome variables—that is, birth weight, placental weight, and the placental weight to birthweight ratio. Factors that were significantly and positively associated with the placental weight to birthweight ratio were gestational age at delivery, Asian parentage, female infant, maternal anaemia, a higher maternal weight and body mass index at booking, lower socioeconomic score, and increasing number of cigarettes smoked daily during pregnancy. Maternal prepregnancy weight and maternal height do not act independently of maternal body mass index, and therefore these relations were determined by separate regression analyses.

Table 4 shows the relations between measures of newborn size and placental weight, birth weight, and the placental weight to birthweight ratio. Placental weight and birth weight were significantly greater with larger newborn dimensions and higher ponderal index. However, there were no significant associations between the placental weight to birthweight ratio and length, skinfold thickness, or ponderal index when controlled for gestational age, sex of infant, racial origin, maternal smoking, and maternal body mass index. Ratios of abdominal circumference to head circumference and of length to head circumference were used as indicators of the relative amounts of soft tissue and skeletal growth respectively. Birth weight was strongly and positively correlated with both these measures whereas placental weight was also positively correlated with the abdominal circumference to head circumference ratio but was unrelated to changes in the length to head circumference ratio. The placental weight to birthweight ratio was weakly, positively associated with the ratio of abdominal circumference to

Table 2 Characteristics of study population (n=2507)

	No (%) of subjects	Mean (SD)
Age (years):		
Maternal		28 (5.9)
Paternal		30 (6.7)
Socioeconomic score:		
High (I or II)	1434 (57.2)	
Mid (III)	886 (35.3)	
Low (IV or V)	187 (7.5)	
Maternal measurements:		
Prepregnancy weight (kg)		59.8 (12.3)
Height (m)		1.64 (0.07)
Body mass index (kg/m^2)		22 (4)
Parity:		
0	1205 (48.1)	
1	736 (29.4)	
⩾2	566 (22.5)	
Smoking at 18 weeks' gestation:		
Nil	1842 (73.5)	
1-10 cigarettes daily	388 (15.5)	
11-20 cigarettes daily	221 (8.8)	
>20 cigarettes daily	56 (2.2)	
Antenatal complications:		
Maternal anaemia	715 (28.5)	
Hypertension:		
Essential	62 (2.5)	
Pregnancy induced	390 (15.6)	
Pre-eclampsia	43 (1.7)	
Antepartum haemorrhage	180 (7.2)	
Gestational diabetes	88 (3.5)	
Congenital abnormalities	212 (8.5)	
Maternal weight gain at 18-34 weeks (kg)		8.8 (3.7)
Gestational age at delivery (weeks)		39.2 (1.3)
Sex of infant:		
Male	1273 (50.8)	
Birth weight (g)		3423 (465)
Birthweight ratio†		1.0 (0.1)
Placental weight (g)		605.6 (120.8)
Placental weight to birthweight ratio		0.177 (0.027)
Racial origin:		
Maternal:		
European	2205 (88.0)	
Australian Aboriginal	59 (2.4)	
Asian	116 (4.6)	
Indian	65 (2.6)	
Other	62 (2.5)	
Paternal:		
European	2185 (87.2)	
Australian Aboriginal	70 (2.8)	
Asian	79 (3.2)	
Indian	68 (2.7)	
Other	105 (4.2)	

†Birthweight ratio is ratio of actual birth weight to that predicted after controlling for gestational age, maternal height, parity, race, and sex of infant.

Table 3 Multivariate analyses of modelling of birth weight, placental weight, and their ratio in terms of demographic, environmental, and medical factors. Point estimates† are shown with 95% confidence intervals in parentheses

	Birth weight (g)	Placental weight (g)	Placental weight to birthweight ratio (x1000)
Socioeconomic score	NS‡	NS	2.3 (0.9 to 3.7)
Maternal prepregnancy weight (kg)§	6.4 (5.0 to 7.8)	1.6 (1.2 to 1.8)	0.1 (0.01 to 0.19)
Maternal height (m)§	8.3 (5.7 to 10.9)	1.0 (0.1 to 1.8)	NS
Maternal body mass index (kg/m^2)§	164.0 (127.0 to 201.0)	42.1 (30.9 to 53.3)	3.6 (1.0 to 6.2)
Parity (per birth)	66.6 (45.0 to 88.2)	11.5 (4.9 to 18.1)	NS
Smoking	–58.5 (–71.3 to –45.7)	NS	2.1 (1.3 to 2.9)
Anaemia	96.8 (61.8 to 131.8)	28.0 (17.4 to 38.6)	2.6 (0.2 to 5.0)
Hypertension	NS	NS	NS
Diabetes	329.4 (239.2 to 419.6)	67.7 (40.7 to 94.7)	NS
Iron supplements	NS	NS	NS
Weight gain	378.3 (305.7 to 450.9)	59.9 (38.5 to 81.3)	NS
Gestational age (days)	247.8 (147.4 to 348.2)	27.7 (–2.9 to 58.3)	–0.5 (–0.6 to –0.4)
Female sex	–140.0 (–170.5 to –109.5)	–9.35 (–18.9 to 0.2)	4.4 (2.2 to 6.6)
Parental racial origin compared with European:			
Asian	–65.2 (–168.0 to 37.6)	44.4 (14.4 to 74.4)	17.2 (8.6 to 25.8)
Australian Aboriginal	–95.6 (–246.4 to 55.2)	–56.8 (–106.8 to –6.8)	–11.9 (–23.5 to –0.3)

†Point estimates represent magnitude of change in birth weight, placental weight, and placental weight to birthweight ratio for each variable acting independently—for example, for each kg change in maternal prepregnancy weight birth weight is increased by 6.3 g.
‡NS = P > 0.2.
§ Results shown are from separate regression models.

head circumference while also being weakly, negatively correlated with the ratio of length to head circumference.

Discussion

Barker and coworkers together with various other investigators have proposed that poor nutrition before and during pregnancy is a main factor determining the birth weight relative to placental weight and altering fetal metabolism such that there is a predisposition to hypertension in adult life.[1 7 13] Sheep fed on poor pastures in mid-pregnancy respond by initially increasing placental growth before any change in fetal growth.[7] In human pregnancy a higher placental weight to birthweight ratio has been found in association with women who have lower external conjugate pelvic diameters (indicating possible poor nutrition during development)[1] and anaemia (possibly indicating current poor nutritional status).[14 15] Placental weight and birth weight are widely available measures with records dating back to at least the early twentieth century. The ratio of these two variables has the potential to be a most useful marker of fetal nutrition and uteroplacental function.

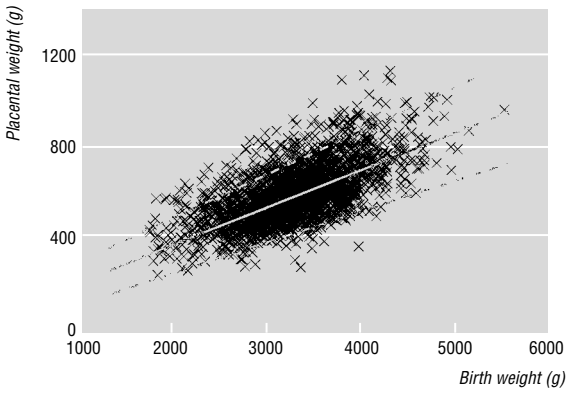

Fig 1 Plot of individual placental weights by birth weights. Solid line represents quadratic regression fit. Dashed lines represent 90% confidence intervals

Table 4 Correlation of measurements of newborn size with placental weight, birth weight, and placental weight to birthweight ratio after controlling for covariates†

	Birth weight	Placental weight	Placental weight to birthweight ratio
Abdominal circumference	0.698 (P=0.0001)	0.466 (P=0.0001)	0.057 (P=0.0013)
Length	0.675 (P=0.0001)	0.414 (P=0.0001)	NS
Head circumference	0.627 (P=0.0001)	0.429 (P=0.0001)	0.060 (P=0.0032)
Skinfold thickness ‡	0.556 (P=0.0001)	0.368 (P=0.0001)	NS
Ponderal index	0.463 (P=0.0001)	0.300 (P=0.0001)	NS
Abdominal circumference/ head circumference	0.426 (P=0.0001)	0.278 (P=0.0001)	0.029 (P=0.0447)
Length to head circumference	0.082 (P=0.0008)	NS	–0.045 (P=0.0197)

†Table 3 lists covariates for placental weight, birth weight, and placental weight to birthweight ratio.
‡Skinfold thicknesses examined were from parascapular, infrascapular, and triceps regions.
NS denotes no significant relation (P < 0.15).

Some of the significant predictors of an increased placental weight to birthweight ratio that we have identified are also environmental risk factors for adult hypertension. Lower socioeconomic status, though not in itself a risk factor for hypertension, is an indicator of lifestyle variables that are risk factors for hypertension—for example, excess alcohol intake and poor dietary patterns. Possibly a high placental weight to birthweight ratio is acting as a surrogate for factors in the maternal environment related to social status to which the growing child may be exposed. We observed that maternal smoking was associated with a significant reduction in birth weight but not placental weight. The effect on birth weight is dose dependent, resulting in an increase in the placental weight to birthweight ratio with the numbers of cigarettes smoked. Other workers who have not found an association between maternal smoking and the placental weight to birthweight ratio did not quantify the numbers of cigarettes smoked.[16] Maternal obesity at booking was also positively correlated with the placental weight to birthweight ratio. This suggests that the ratio may be a surrogate for already well recognised risk factors for hypertensive disease related to a family

history of obesity and poor dietary patterns. In addition, environmental factors associated with alterations in the placental weight to birthweight ratio may not exert their effects exclusively in the antenatal period.

As expected, placental weight and birth weight were highly correlated. An increased placental weight to birthweight ratio could not be predicted by birth weight or placental weight alone. In particular, a high placental weight to birthweight ratio did not imply an infant small for gestational age. We observed no consistent correlation between the placental weight to birthweight ratio and measures of newborn size. Opposing relations were also found between this ratio and indicators of soft tissue and skeletal growth. The ratio of length to head circumference was weakly and negatively correlated with the placental weight to birthweight ratio, possibly suggesting that a relative reduction in skeletal growth during mid-pregnancy could be associated with an increased risk of hypertensive disease in adulthood. However, the ratio of abdominal circumference to head circumference was weakly and positively correlated with the placental weight to birthweight ratio. If the same reasoning is used this would suggest that poor growth in late pregnancy may be associated with a reduction in the placental weight to birthweight ratio and a possible reduced risk of hypertensive disease in adulthood. In addition to these inconsistencies, there was no significant correlation with ponderal index or length. The pattern which has emerged in these analyses is that associations between the placental weight to birthweight ratio and our measures of newborn size do not present an unequivocal, unidirectional relation. The potential role of this ratio as a marker of fetal growth is thus diminished.

Key messages

- Retrospective analyses have identified an association between a raised placental weight to birthweight ratio and hypertension in adulthood
- Accurate estimation of gestational age is crucial when interpreting the placental weight to birthweight ratio
- Environmental factors associated with alterations in the placental weight to birthweight ratio may not exert their effects exclusively in the antenatal period
- As a marker of fetal growth the potential usefulness of the placental weight to birthweight ratio is diminished because the ratio is influenced by a multiplicity of factors
- Prospective study is required to clarify the role of intrauterine programming in the genesis of adult disease

Dangers of extrapolation

We have identified various constitutional and obstetric factors in pregnant women which must be considered when interpreting results of analyses including the placental weight to birthweight ratio. Gestational age has a large influence on the ratio, even within the range of term deliveries. In retrospective studies using old birth records only menstrual dates would have been available, rendering a proportion of the population as unrecognised preterm births. We also observed that girl infants had significantly lower birth weights than boys and only a small trend to lower placental weights, resulting in higher placental weight to birthweight ratios. This highlights that fetal factors are important determinants of fetal growth independent of the placenta. Parental racial origin was also associated with significant differences in weights of newborn infants and their placentas. When both parents were of Asian descent birth weight was significantly lower than that of European offspring, though placental weights were significantly greater. The underlying reason for the increased placental weights in this subgroup is unclear. Analysis of a larger population is required to determine whether this effect is genetic or results from local environmental factors such as diet. This finding may have important implications when extrapolating results from the racially homogeneous population of the United Kingdom at the beginning of this century to the racially heterogeneous population of today.

Extrapolation of findings from populations born at the beginning of this century to those born today is subject to difficulties highlighted by comparison of our cohort with the Preston cohort.[1,2] In the 50 years separating the birth dates of the populations birth weights and placental weights significantly increased. Multiple factors probably contributed, including improved maternal nutrition. In addition, the socioeconomic status of our cohort was likely to be higher than that of the Preston cohort because the study required early attendance for antenatal care and because of the comparative affluence of the population of Perth.

The relation between a raised placental weight to birthweight ratio and adult hypertension needs validation for modern births. Potentially modifiable factors have been identified in this analysis. No clear relation, however, has emerged between measures of newborn size and the placental weight to birthweight ratio. From these results we speculate that a raised placental weight to birthweight ratio is acting as a surrogate for other factors already known to influence the development of cardiovascular disease in adult life. Prospective studies in which fetal growth and placental function are measured directly are needed in this exciting topic to determine the role of intrauterine development as an antecedent of adult disease. There is great potential for preventive medicine if a link between modifiable antenatal factors and adult hypertension can be proved. The children in this cohort remain under long term surveillance and their ongoing participation will provide valuable information on the role of intrauterine programming in predisposing to adult disease.

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Diabetes in institutionalised elderly people: a forgotten population?

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Diabetes mellitus is one of the commonest chronic diseases of elderly people. Nevertheless, this section of the diabetic population has long been neglected,[1] which was emphasised again more recently.[2] We report what we believe to be one of the first large studies of the patterns of care and levels of complications and resource usage of diabetic residents in residential or nursing homes. These people are possibly the most vulnerable section of the aged population.

Subjects, methods, and results

One hundred and nine residents with known diabetes mellitus were randomly selected from 19 nursing, 16 residential, six elderly mentally infirm, and three dual registered homes in the catchment area of one hospital in north west England. Controls were sex and nearest age matched non-diabetic residents in the same homes. All residents were interviewed by a research nurse, who completed a comprehensive questionnaire and examined each subject during six months from January 1995. Hospital and general practice records were subsequently reviewed.

Of all 1611 residents in the 44 homes, 159 (9.9%) had diabetes. There were no significant differences between the 109 diabetic subjects studied and the controls in age (mean 80.9 (SD 7.6) *v* 81.7 (7.0) years), sex (male to female ratio 34:75 *v* 31:76), or durations of stay in the homes (median 2.0 (range 0.3-17.0) *v* 2.0 (0.1-10.0) years). In the diabetic group 45 (41%) subjects were treated by diet, 42 (39%) with oral hypoglycaemic agents, and 22 (20%) with insulin. Monitoring of diabetic control in the homes was done by urine analysis in 11 (10%) cases, home blood glucose monitoring in 21 (19%) cases, and both methods in 48 (44%) cases. Twenty nine patients (27% of the group) were not being monitored for diabetic control. One third of these subjects were in nursing homes. Seventy eight (72%) diabetic residents were regularly weighed. There was a significantly greater prevalence of lower limb amputation, past or present foot ulceration, foot deformity, peripheral vascular disease, and catheterised subjects in the diabetic group than among controls (table 1).

Fifteen (14%) diabetic residents received diabetic care solely from their general practitioner and 27 (25%) received care from a hospital clinic. Seventy (64%) patients had no record of anyone being medically responsible for diabetes review and management the previous year. Diabetic residents in elderly mentally infirm homes were significantly less likely to be receiving formal diabetic care than residents in any of the other three types of home ($P<0.05$). Within the previous year 78 (72%) diabetic residents had seen an optician or had their eyes examined at a medical clinic, 20 (18%) had their feet medically examined, 36 (33%) had their glycated haemoglobin concentration and 31 (28%) their renal function checked, and 32 (29%) had their blood pressure measured. Within the previous four months 97 (89%) diabetic residents had seen a chiropodist (non-state registered in a quarter of cases), though payment for this was made by 68 (62%).

Within the previous year significantly more of the diabetic group had been admitted to hospital for any reason (47/109 subjects *v* 27/107; $P<0.01$) and the

Table 1 Levels of complications for the two groups

Complication	No (%) of diabetic residents (n=109)	No (%) of controls (n=107)	P value	95% CI of difference (%)
Peripheral vascular disease	36 (33)	17 (16)	<0.01	5.9 to 28.4
Foot deformity	104 (95)	92 (86)	<0.05	0.7 to 16.4
Past or present foot ulcer	13 (12)	4 (4)	<0.05	1.1 to 15.3
Amputation	7 (6)	1 (1)	<0.05	0.5 to 10.4
Cerebrovascular disease	23 (21)	19 (18)	NS	−7.2 to 13.9
Visual impairment	82 (75)	67 (63)	NS	0.4 to 24.8
Catheterised	11 (10)	1 (1)	<0.01	3.2 to 15.1

total number of admissions was greater (median 0 (range 0-2) *v* 0 (0-1); $P < 0.01$) than among controls. Diabetic residents had also been seen by their general practitioner significantly more often than controls (3 (0-16) occasions *v* 1 (0-11); $P < 0.05$).

Comment

The provision of care for this vulnerable group of diabetic residents was inadequate despite their high morbidity levels and greater use of health service resources. Many residents had no medical team responsible for their diabetic care and had not been assessed for the presence or risk of diabetic complications.[3] Improved staff training, closer cooperation between primary and secondary care in the management of institutionalised diabetic residents, and individual care plans for these residents are needed. The role of a diabetes specialist nurse with particular responsibility for elderly patients requires evaluation. At a district level guidelines and standards for the management of residents with diabetes are urgently needed.

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Drug points

Drug induced psychosis with doxazosin

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Although fatigue, asthenia, somnolence, and nausea are known side effects of doxazosin, we know of no reports of psychiatric complications and psychiatric side effects are not listed in the *British National Formulary*. Doxazosin is an α adrenoceptor antagonist, reported to have similar properties to prazosin.[1] *Martindale* lists depression and hallucinations for prazosin,[2] and a report of neuropsychiatric complications related to the use of prazosin was published in the *BMJ* in 1986.[3] A search by our drug information department found no specific reference to possible psychogenic effects of doxazosin. We report the case of a patient with an acute psychosis who recovered fully when the drug was withdrawn.

An urgent home visit was requested by the general practitioner of a 71 year old woman. She was assessed as needing formal admission to our psychogeriatric ward. She reported hearing noises coming from the walls of her house, and this had changed over time to hearing videos being played loudly at all hours of the day and night. The content of the videos was violent and unpleasant, and she had called the police and environmental health officers several times to complain. In the previous few weeks she had begun to hear voices, which she believed to be those of her neighbours discussing her, and these were, on occasion, very threatening. In the 24 hours leading to her admission she had had no sleep and believed that she could hear boxes and other items being dragged across the floor of her bedroom and also her son (who was in America) being tortured.

She had a history of non-insulin dependent diabetes, which was controlled by diet, and hypertension, which was controlled with doxazosin (Cardura). The psychotic phenomena started within 1-2 weeks of the dose of doxazosin being increased from 8 mg a day to 16 mg a day about nine months previously. On admission she was taking doxazosin 16 mg daily, nizatidine 150 mg twice daily, and nitrazepam 5 mg at night. Nizatidine and nitrazepam were long term prescriptions and were continued. Sulpiride l00 mg twice daily was prescribed and enalapril was chosen as an alternative treatment for the hypertension. Doxazosin was gradually reduced in 4 mg increments, with concurrent titration of enalapril in 2.5 mg increments. Blood pressure was monitored twice a day, and nifedipine was prescribed as required in the event that diastolic blood pressure exceeded 100 mm Hg.

She responded rapidly to this treatment regimen, and by the time doxazosin had been reduced to 8 mg a day the psychotic experiences were much less evident and much less distressing. By then she had insight into her condition and was able to accept the explanation of a drug induced psychosis. Her blood pressure had been well controlled with doxazosin and was similarly well controlled with enalapril 10 mg a day. Doxazosin treatment was finally stopped 14 days after admission: the voices had then stopped completely and she was comfortable. There was some concern that there might be some recurrence of symptoms when she returned home, but after two uneventful periods of leave she was successfully discharged with no further sequelae. Continued prescription of sulpiride was not considered to be necessary, and the drug was withdrawn in 50 mg decrements soon after discharge.

Although this episode had persisted for some time, the patient made a complete recovery when doxazosin was withdrawn. The case was reported to the Committee on Safety of Medicines. Only 4% of reports of adverse effects of doxazosin are psychiatric symptoms. None have been of psychosis. Reactions reported include depression, agitation, aggression, and depersonalisation (personal communication). Psychotic phenomena seem to be a rare side effect of doxazosin treatment and are not documented in standard reference books. Doctors should be aware that antihypertensive drugs may have a range of psychiatric side effects, and these should always be considered when deciding on appropriate treatment.

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