III—Analysis of data from trials of salt reduction

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Abstract

Objective—To determine whether the reduction in blood pressure achieved in trials of dietary salt reduction is quantitatively consistent with estimates derived from blood pressure and sodium intake in different populations, and, if so, to estimate the impact of reducing dietary salt on mortality from stroke and ischaemic heart disease.

Design—Analysis of the results of 68 crossover trials and 10 randomised controlled trials of dietary salt reduction.

Main outcome measure—Comparison of observed reductions in systolic blood pressure for each trial with predicted values calculated from between population analysis.

Results-In the 45 trials in which salt reduction lasted four weeks or less the observed reductions in blood pressure were less than those predicted, with the difference between observed and predicted reductions being greatest in the trials of shortest duration. In the 33 trials lasting five weeks or longer the predicted reductions in individual trials closely matched a wide range of observed reductions. This applied for all age groups and for people with both high and normal levels of blood pressure. In people aged 50-59 years a reduction in daily sodium intake of 50 mmol (about 3 g of salt), attainable by moderate dietary salt reduction would, after a few weeks, lower systolic blood pressure by an average of 5 mm Hg, and by 7 mm Hg in those with high blood pressure (170 mm Hg); diastolic blood pressure would be lowered by about half as much. It is estimated that such a reduction in salt intake by a whole Western population would reduce the incidence of stroke by 26% and of ischaemic heart disease by 15%.

Conclusions—The results from the trials support the estimates from the observational data in the accompanying two papers. The effect of universal moderate dietary salt reduction on mortality from stroke and ischaemic heart disease would be substantial—larger, indeed, than could be achieved by fully implementing recommended policy for treating high blood pressure with drugs. However, reduction also in the amount of salt added to processed foods would lower blood pressure by at least twice as much and prevent some 70 000 deaths a year in Britain as well as much disability.

Introduction

Our analyses of between population and within population observational data yielded similar estimates for the magnitude of the association between blood pressure and sodium intake (pp 811 and 815).¹² Dietary sodium in Western countries comes mainly from salt (sodium chloride), and many clinical trials have tested the effect of reduction in dietary salt on blood pressure. Almost all report a reduction in blood pressure, typically greater (in absolute terms) among people with high initial blood pressure and smaller (and often not significant) in those with normal blood pressure. In this paper we examine the results of these trials to determine whether the association between blood pressure and sodium intake shown by our analyses of observational data applies quantitatively when salt intake in subjects is reduced. We used the results of our between population analysis' to calculate a predicted fall in blood pressure for each trial and compared this with the observed fall.

Methods

TRIALS INCLUDED

We identified 70 published studies that recorded the effect of salt restriction on blood pressure.3-72 We subdivided the data from studies that recruited both subjects with high blood pressure and subjects with normal blood pressure^{4 7 11 25 26 43} to allow separate assessment of the effect of salt restriction for each category, making 78 "trials" in total. To avoid bias we included only trials with a crossover design (n=68)or a randomised parallel control group (n=10). We excluded trials that combined salt restriction with another intervention, trials in which patients were taking antihypertensive drugs, and trials in which low and high sodium intake were not both measured in at least one 24 hour urine collection. In 54 trials the low and high salt diets were not otherwise identical, although the potassium content seemed similar (as estimated by 24 hour urinary excretion). In the other 24 trials the same low salt diet was taken throughout but supplemented by salt tablets in one period. Salt reduction was tested in people with a wide range of blood pressures: average values in the 78 trials ranged from 103 to 187 mm Hg (systolic) and from 61 to 118 mm Hg (diastolic). The authors recruited subjects whom they considered to have normal blood pressure in 21 trials and those considered to have high blood pressure in 57 trials. In people with high blood pressure secondary causes of high blood pressure were generally excluded and a run in period of a few weeks before the start of the trial was used to minimise the fall in blood pressure through regression to the mean.

For each trial we recorded the average age (range 16-63 years), 24 hour urinary sodium on the high salt diet (range 130-249 mmol/24 h) and on the low salt diet, blood pressure (supine if available, otherwise sitting) on the low and high salt diets, and number of subjects (5-143). Unpublished changes in blood pressure in four trials^{1112,7172} and separate data for subjects not taking antihypertensive drugs in two trials⁶⁷⁷¹ were provided by the investigators.

STATISTICAL ANALYSIS

We calculated a predicted reduction in blood pressure for each trial by using the results from our between population analysis in which we estimated age specific and blood pressure specific reductions in blood pressure for a given degree of sodium reduction.¹ The average centile for age specific blood pressure for the subjects in each trial was determined from their average sodium intake and blood pressure when taking the high salt diet by using the regression equations for mean blood pressure and for standard deviation of blood pressure given in the appendix of our first paper.¹ With reduction in sodium intake we proposed that the blood pressure of the subjects would move down this centile line, the slope of which can be calculated from the same regression equations. For

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BMJ 1991;302:819-24

example, if point X in figure 1 specifies the average sodium intake and blood pressure in people on the high salt diet in a trial of people aged 60-69 years with high blood pressure the subjects would lie, on average, on the 90th centile. If the sodium intake in the same people on the low salt diet then declined to point X¹ (as in figure) on the same centile the predicted fall in blood pressure would be the vertical distance between X and X^{1} . (The centiles in figure 1 are appropriate for single blood pressure measurements, but for clinical trials in which the average of several readings of each person's blood pressure was taken the same blood pressure would correspond to a more extreme centile. Point X in figure 1, for example, would correspond to the 96th centile, not the 90th, if a large number of readings had been taken. However, the regression slopes-the reduction in blood pressure for a given reduction in sodium intake-would be similar.)

To obtain summary estimates of change in blood pressure in trials according to duration of treatment in five categories (fig 2), we used the method of Der-

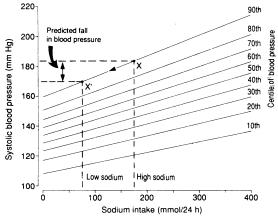
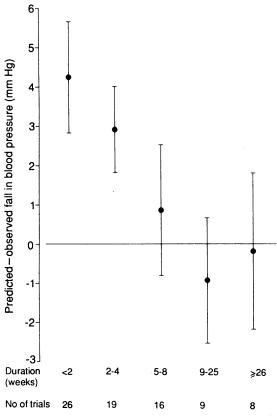
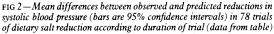


FIG 1-Use of between population analysis of observational data' to calculate predicted blood pressure reductions in 78 trials of salt restriction





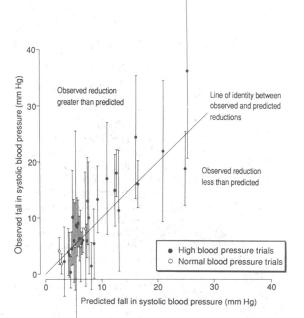


FIG 3—Comparison of observed reductions in systolic blood pressure (vertical lines are 95% confidence intervals) with predicted reductions for individual trials of dietary salt reduction lasting \geq 5 weeks

Simonian and Laird to combine the differences between observed and predicted reductions in blood pressure.⁷³ Combining the different studies required the standard error of the observed fall in blood pressure in each trial. This was available directly for 27 trials. For the other 51 it was estimated from the standard errors (SE) of blood pressure in people on a high salt diet (H) and of those on low salt diet (L) by the equation⁷⁴: SE (H-L)²=SE (H)²+SE (L)²-2r SE (H) SE (L), where r is the correlation coefficient between blood pressure in people on the high and low salt diets. Published data from 24 trials allowed this to be estimated, and the average value of r=0.7 was used.

Results

The table shows the observed and predicted changes in systolic blood pressure for the 78 trials listed in increasing order of duration. In trials of short duration the observed reductions in blood pressure were, on average, less than predicted, but the difference diminished as the duration of salt reduction increased (fig 2). For the 33 trials lasting five weeks or longer the observed reductions in blood pressure were similar to the predicted values and, with three exceptions, the 95% confidence intervals included the predicted value (fig 3). The results were similar for diastolic blood pressure.

The similarity between the observed and predicted falls in blood pressure was not influenced by whether the low salt diet was taken first in crossover trials (indicating that regression to the mean was not a problem in these trials); whether the low and high salt diets were otherwise identical; or whether the trial was double blind.

Discussion

EFFECT ON BLOOD PRESSURE

In the salt restriction trials that lasted five weeks or longer the reductions in blood pressure were similar to those that were predicted from our between population analysis of observational data.¹ The similarity was striking considering the wide range of predicted values (3-25 mm Hg). The similarity applied to trials comprising people with high and normal blood pressure (average initial systolic blood pressure range 107-186 mm Hg), trials with small and large degrees of salt reduction (confirming the continuous linear association of blood pressure with sodium intake), and trials in different age groups (average age 22-62 years). Observed reductions were below predicted values in trials lasting four weeks or less and longer time was probably needed to attain the full effect. The results of

Comparison of observed and predicted reduction in systolic blood pressure (mmHg) for 78 trials of salt reduction according to duration of trial

<	Trial (first author)	Duration (weeks)	Predicted reduction	Observed reduction	Observed – predicted reduction (standard error)
Parfrey* 0-7 21-4 21-2 - 0-2(2-6) Masagi 0-7 15-4 9+0 - 6-4(2-9) Cappucció* 0-7 15-5 14-9 - 1-6(2-6) Parfrey* 0-7 13-5 11-0 - 2-5(4-2) Stokes* 0-7 13-5 11-0 - 2-5(4-2) Stokes* 0-7 5-2 - 30 - 7-4(2-3) Stokes* 0-0 19-6 14-0 - 5-6(2-3) Kielden* 1-0 19-6 14-0 - 5-6(2-3) Kielden* 1-0 9-1 5-0 - 44(3-5) Ashida* 1-0 8-3 8-5 - 0-8(2-0) Warren* 1-0 9-1 5-0 - 44(3-5) Ashida* 1-0 8-3 3-3 1 - 5-2(4-5) Warren* 1-0 8-3 8-5 - 0-8(2-0) Warren* 1-0 8-3 8-5 - 0-8(2-0) Warren* 1-0 8-3 8-3 - 0-8(2-0) Warren* 1-0 8-3 8-5 - 0-8(2-0) Warren* 1-0 8-5 0-2 - 0-3(1-5) Warren* 2 - 0-6 - 3-3 - 2-3(1-7) Myers* 2 - 0-6 - 3-3 - 2-3(1-7) Myers* 2 - 0-6 - 1-6(0-7) Myers* 2 - 0-6 - 1-6(0-7) Strabal* 4 - 10-7 5-6 - 5-1(2-7) Myers* 2 - 0-6 - 1-6(0-7) Strabal* 4 - 10-7 5-6 - 5-1(2-7) MacGregor* 4 - 7-4 10-0 - 2-5(2-3) Strabal* 4 - 10-7 5-6 - 1-2(2-3) Strabal* 4 - 2-3 10 - 1-3(0-6) Warren* 4 - 2-3 10 - 1-3(0-6) Warren* 4 - 2-3 10 - 1-3(0-6) Myers* 2 - 0-6 - 1-6(0-7) MacGregor* 4 - 1-2 - 0-2(2-2) MacGregor* 4 - 1-2 - 0-2(2-2) MacGregor* 4 - 1-2 - 0-2(2-2) MacGregor* 4 - 1-2 - 0-2(2-2) Name* 4 - 2-3 10 - 1-3(0-6) Strabal* 5 - 0-0-0(1-1) MacGregor* 2 - 0-6 - 1-0-0(2-3) Strabal* - 0-0-1-1-1) MacGregor* 2 - 0-6 - 1-0-0-7 Strabal* - 0-0-1-1-1) Strabal* - 0-0-1-1-1 Straba* - 0-0-0-1-1-1) Straba* - 0-0-0-1-1-1 Str					
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	Ashidan	1.0	22.1	15.5	- 6.6 (2.4)
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Kojima* 10 18-1 16-0 $-221(57)$ Warren* 10 9-3 8:5 $-08(20)$ Pridle* 10 8-3 3-1 $-52(45)$ Romoff** 10 5-5 0.2 $-63(15)$ Weissberg** 10 $5-5$ 0.2 $-63(15)$ Veissberg** 10 $5-5$ $1-0$ $-25(15)$ Perca* 10 $3-5$ $1-0$ $-25(15)$ versite 2 $2-3$ $16-0$ $37(4-6)$ Longworth* 1-4 12.9 3.0 $-927(3-3)$ Myers* 2 $1-9$ $1-0$ $-52(0.8)$ Morgan* 2 $6-4$ $1-0$ $-54(2.3)$ Norgan* 2 $6-4$ $1-0$ $-54(2.3)$ Norgan* 2 $6-6$ $-02(2.3)$ Poston* 2 $4-6$ 2.5 $-21(1-5)$ Cooper** 3 2.2 $0-6$ $-16(2.25)$ <t< td=""><td></td><td></td><td></td><td></td><td></td></t<>					
Warren'1-09-38-50.8(2.0)Ashida''*1-08-33-152(4.5)Komoff'*1-06-50-263(1-5)Weisberg**1-05-63-323(1-7)Linares'*1-03-51-025(1-5)Percari*1-115-312-429(2-8)van Brummelen''1-412-93-09(1-6)Longvorth'1-412-93-09(1-6)Van Brummelen''1-312-316-0-73(4-6)Longvorth'1-412-93-09(1-6)Mvers*'211-911-30.6(1-6)Kolen''27-63-54.1(2-3)Morgan''26-41-05.4(2-3)Skarabal'*26-41-05.4(2-3)Skarabal'*26-22-43.8(0-9)Poston**225-70.56.2(2-3)Skarabal'*32-20-61.6(0-7)Simth'412-210-02.2(3-1)Skrabal'*48-28-90-7(2-1)MacGregor''47-410-02-6.3(2-1)Skrabal'*45-02-7-2.5(2-2)Wart*45-02-7-2.3(2-1)Mart*45-02-7-2.3(2-1)Mart*45-02-7-2.3(2-1)Mart*45-02-7-2.3(2-1)Mart*					
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Linares ¹⁵ 10 3.5 1.0 $-2.5(15)$ Perera ²⁷ 1.1 15.3 12.4 $-2.9(2.8)$ van Brummelen ²⁷ 1.4 12.9 3.0 $-9.9(15)$ -9.9(15) Poston ⁴ 2 23.2 31.0 $7.8(6.5)$ Myers ³⁷ 2 11.9 11.3 $-0.6(1.6)$ Koolen ²⁷ 2 7.6 3.5 $-4.1(2.3)$ Myers ³⁸ 2 6.4 1.2 $-5.2(0.8)$ Poston ⁴⁸ 2 6.4 1.2 $-5.2(0.8)$ Norgan ²⁸ 2 6.4 1.2 $-5.2(0.8)$ Nargan ²⁹ 2 6.4 1.2 $-5.2(0.8)$ Poston ⁴⁹ 2 6.2 2.4 $-3.8(0.9)$ Hargreaves ⁴⁹ 2 5.8 6.0 0.2(3.1) El Ashry ⁴¹ 2 5.7 -0.5 $-6.2(2.5)$ Smith ⁴⁰ 4 10.0 $-2.2(3.1)$ El Ashry ⁴¹ 4 10.7 5.6 $-5.1(2.7)$ Smith ⁴¹ 4 12.2 10.0 $-2.2(3.1)$ Skirabal ⁴¹ 4 10.7 5.6 $-5.1(2.7)$ Parijs ⁴⁰ 4 7.4 10.0 $2.6(3.2)$ Skirabal ⁴¹ 4 5.0 0.7 $-2.5(3.2)$ Watt ⁴⁴ 4 5.0 0.7 $-2.3(2.2)$ Watt ⁴⁴ 4 5.0 0.7 $-1.3(0.6)$ Firvteman ⁴⁴ 5.0 2.7 $-2.3(2.2)$ Watt ⁴⁴ 4 5.0 0.7 $-1.3(0.6)$ Firvteman ⁴⁴ 5.0 2.7 $-2.3(2.2)$ Watt ⁴⁴ 4 5.0 $-1.3(0.6)$ Si taceks Richards ⁴⁵ 5 8.4 5.2 $-3.2(2.1)$ Kobayashi ⁴⁴ 5 5 5.6 8.3 2.2(2.1) Kobayashi ⁴⁴ 5 5 5.6 8.3 2.2(2.1) Kobayashi ⁴⁴ 5 5 5.5 8.4 $-2.2 -3.2(2.1)$ Matomic 6 5.1 5.0 $-0.1(1.5)$ Groupse ⁴⁵ 8 7.4 6.0 $-1.1(1.4)$ Dah ⁴⁷ 7 2.44.8 18.8 $-6.0(3.3)$ Dah ⁴⁷ 8 2.2 $3.62 - 1.10(7.8)$ Jest ⁴⁷ 8 7.4 6.0 $-1.1(4.1)$ Dah ⁴⁷ 7 2.44.8 18.8 $-6.0(3.3)$ Dah ⁴⁷ 8 7.7 10.0 2.3(3.6) Miller ⁴⁴ 12.2 $-7.7 1.7 -1.00(3.3)$ Multer ⁴⁴ 12.2 $-7.7 1.7 -1.00(3.3)$ Multer ⁴⁴ 12.2 $-7.7 1.7 -1.00(3.3)$ Joha ⁴⁷ 8 7.7 $-0.9(3.2)$ Matom ⁴⁷ 9 9.43 1.4 2.2 $-0.0(3.3)$ Joha ⁴⁷ 9 9.53 1.3.3 $-0.0(5.3)$ Multer ⁴⁴ 12.2 $-7.0 -1.3(2.2)$ Matom ⁴⁷ 10 5.5 5.8 $-0.0(3.3)$ Jinan ⁴ 7.1 10.0 $-5.3(2.2)$ Matom ⁴⁷ 10 5.5 5.9 $-0.0(1.1)$ Miller ⁴⁴ 12.2 $-0.0(1.2)$ Matom ⁴⁷					
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van Brummelen ¹¹ 1:3 12:3 16:0 3.7 (4:6) Longworth ²¹ 1:4 12:9 3:0 - 9.9 (1:5) Poston ² 2 23:2 31:0 7.8 (6:5) Myers ²⁵ 2 11:9 11:3 - 0.6 (1:6) Koolan ² 2 7:6 3:5 - 4.1 (2:3) Morgan ² 2 6:4 1:0 - 5.4 (2:3) Skarabal ²⁴ 2 6:4 1:0 - 5.4 (2:3) Skarabal ²⁴ 2 6:2 2:4 - 3.8 (0.9) Hargreaves ³⁵ 2 5:7 - 0.5 - 6.2 (2:5) Skarabal ²⁴ 2 5:7 - 0.5 - 6.2 (2:5) Smith ⁴ 4 122 10:0 - 2.2 (3:1) El Ashry ⁴ 2 4:6 2:5 - 2.2 1 (1:5) Cooper ⁴⁴ 3 2.2 0:6 - 1.6 (0:7) Skrabal ²⁴ 4 10.0 - 2.2 (3:1) El Ashry ⁴ 4 10.7 5:6 - 5.1 (2:7) MacGregor ⁴⁵ 4 5:0 2:7 - 2.5 (1:5) Kirkendall ³⁴ 4 5:0 0:7 - 2.5 (1:2) Mat ⁴⁴ 4 5:0 0:7 - 2.5 (3:2) Wat ⁴⁴ 4 5:0 0:7 - 2.5 (3:2) Wat ⁴⁴ 4 5:0 0:7 - 2.5 (1:2) Mat ⁴⁴ 5:0 0:7 - 2.5 (1:2) Wat ⁴⁴ 5:0 0:7 - 2.5 (1:2) Wat ⁴⁴ 5:0 0:7 - 2.5 (1:2) Wat ⁴⁵ 5 5:0 8:4 5:2 - 2.3 (3:1) Wat ⁴⁵ 4 5:0 2:7 - 2.5 (1:2) Wat ⁴⁵ 5 5:0 8:3 2.2 (2:2) Wat ⁴⁴ 4 5:0 0:7 - 2.5 (2:2) Wat ⁴⁴ 5 5 5:0 0:7 - 4.5 (1:5) Kobayashi ⁴⁴ 5 5 5:0 8:3 2.2 (2:2) Wat ⁴⁴ 8 2:2 8:9 0.7 (2:1) MacGregor ⁴⁵ 8 8:1 1:0 - 1.8 (54) Corobec ⁴ 6 5:1 5:0 0:- 0.1 (1:5) Grobbec ⁴ 6 5:1 5:0 0:- 0.1 (1:5) Cooper ⁴⁵ 8 8:1 1:0 0:- 1.2 (3:2) Kobayashi ⁴⁴ 5:5 5:5 8:3 3:2 2.8 (2:6) Puska ⁴⁴ 8:1 1:0 0:- 1.8 (54) Corobec ⁴⁵ 6 4:9 0:8 - 4.1 (1:4) Dah ⁴⁴ 7 2.2 3:0 0:- 0.1 (1:5) Matrin ⁴⁵ 8 7:4 6:0 0:- 0.1 (1:5) Corobec ⁴⁵ 1:5 5:5 8:8 0:0 0.9 (2:1) Matrin ⁴⁶ 8 7:1 5:5 0:- 0.6 (1:1) Matrin ⁴⁷ 8 2:2 3:1 0:0 0:- 0.2 (3:0) Miller ⁴⁴ 1:2 2:7 1:0 0:- 0.2 (3:0) Miller ⁴⁴ 1:2 2:7 1:0 0:- 0.2 (3:0) Miller ⁴⁵ 1:5 5:- 0.0 (1:1) Matrin ⁴⁷ 1:8 0:- 0.9 (1:0) Miller ⁴⁶ 1:0 5:5 5:8 0:- 0.5 (1:1) Matrin ⁴⁷ 2:2 1:2 7:7 1:7 - 1.9 (0:9) Miller ⁴⁶ 1:0 0:- 0.9 (3:7) Miller ⁴⁶ 1:0 0:- 0.9 (3:7) Matrin ⁴⁷ 1:1 0:- 0.9 (3:0) Ninchos ⁴⁷ 2:2 1:2 7:1 18:0 0:- 0.9 (3:7)					
2-4 weeksPoston"2 2^{23} $31\cdot 0$ $7\cdot 8(6\cdot 5)$ Myers"2 $11\cdot 9$ $11\cdot 3$ $-0\cdot 6(1\cdot 6)$ Koolen"2 $7\cdot 6$ $3\cdot 5$ $-4\cdot 1(2\cdot 3)$ Morgan"2 $6\cdot 4$ $1\cdot 0$ $-3\cdot 7(3\cdot 1)$ Myers"2 $6\cdot 4$ $1\cdot 0$ $-5\cdot 4(2\cdot 3)$ Skarabal"*2 $6\cdot 4$ $1\cdot 0$ $-5\cdot 4(2\cdot 3)$ Skarabal"*2 $6\cdot 4$ $1\cdot 0$ $-5\cdot 4(2\cdot 3)$ Skarabal"*2 $6\cdot 2$ $2\cdot 4$ $-3\cdot 8(0\cdot 9)$ Hargreaves"2 $5\cdot 7$ $-0\cdot 5$ $-6\cdot 2(2\cdot 5)$ Cooper'*3 $2\cdot 2$ $0\cdot 6$ $-1\cdot 6(\cdot 7)$ Smith"4 $12\cdot 2$ $10\cdot 0$ $-2\cdot 2(3\cdot 1)$ Skarabal"4 $10\cdot 7$ $5\cdot 6$ $-5\cdot 1(2\cdot 7)$ Parijs"4 $8\cdot 2$ $8\cdot 9$ $0\cdot 7(2\cdot 1)$ MacGregor"4 $7\cdot 4$ $10\cdot 0$ $2\cdot 6(3\cdot 2)$ Kirkendall"*4 $5\cdot 0$ $2\cdot 7$ $-2\cdot 2(3\cdot 1)$ Karabal"4 $5\cdot 0$ $2\cdot 7$ $-2\cdot 2(3\cdot 1)$ Kirkends"5 $8\cdot 4$ $5\cdot 2$ $-3\cdot 2(3\cdot 1)$ Kirkends"5 $8\cdot 4$ $5\cdot 2$ $-3\cdot 2(3\cdot 1)$ Kirkends"5 $8\cdot 4$ $5\cdot 2$ $-3\cdot 2(3\cdot 1)$ Kobavashi"5 $5\cdot 6$ $8\cdot 8$ $3\cdot 2(2\cdot 1)$ Kobavashi"5 $5\cdot 5$ $8\cdot 3$ $2\cdot 8(2\cdot 0)$ Nationin"6 $5\cdot 1$ $5\cdot 0$ $-0\cdot 1(1\cdot 1)$ Grobbee"6 $4\cdot 9$ <td>van Brummelen²³</td> <td>1.3</td> <td>12.3</td> <td>16.0</td> <td></td>	van Brummelen ²³	1.3	12.3	16.0	
Poston"223-231-07-8(6-5)Myers"21-911-3 $-0.6(1.6)$ Koolen"27-63-5 $-4.1(2.3)$ Myers"*26-41-2 $-5.2(0.8)$ Poston"*26-41-0 $-5.4(2.3)$ Skarabal**26-22-4 $-3.8(0.9)$ Hargraves"25.86.0 $0.2(3.1)$ El Ashry"25.7 -0.5 $-6.2(2.5)$ Teow**24-62.5 $-2.1(1.5)$ Cooper'*32.2 0.6 $-1.6(0.7)$ Smith"410-75-6 $-5.1(2.7)$ Paris"48-28-9 $0.7(2.1)$ MacGregor"47-4 10.0 $2.6(3.2)$ Kirkendall**45.0 0.5 $-4.5(1.5)$ Erverman"45.0 0.7 $-2.3(2.2)$ Watt"42.3 1.0 $-1.3(0.6)$ Vatt"*45.58.4 5.2 $-3.2(3.1)$ Jest"*5 5.6 8.8 $3.2(2.1)$ Kokards"5 5.5 8.3 $2.8(2.6)$ Puska"67.9 1.2 $-6.7(2.1)$ Ambrosion"*6 5.1 5.0 $-1.1(0.7.8)$ Jest"*8 2.2 3.62 $11.0(7.8)$ Jest"*8 7.7 $1.0.6$ $-1.4(1.6)$ Dahl"7 $2.4.8$ 18.8 $-6.0(3.3)$ Dahl"8 7.7 10.0 $2.5(3.2)$ <	Longworth24	1.4	12.9	3.0	- 9.9 (1.5)
Poston"223-231-07-8(6-5)Myers"21-911-3 $-0.6(1.6)$ Koolen"27-63-5 $-4.1(2.3)$ Myers"*26-41-2 $-5.2(0.8)$ Poston"*26-41-0 $-5.4(2.3)$ Skarabal**26-22-4 $-3.8(0.9)$ Hargraves"25.86.0 $0.2(3.1)$ El Ashry"25.7 -0.5 $-6.2(2.5)$ Teow**24-62.5 $-2.1(1.5)$ Cooper'*32.2 0.6 $-1.6(0.7)$ Smith"410-75-6 $-5.1(2.7)$ Paris"48-28-9 $0.7(2.1)$ MacGregor"47-4 10.0 $2.6(3.2)$ Kirkendall**45.0 0.5 $-4.5(1.5)$ Erverman"45.0 0.7 $-2.3(2.2)$ Watt"42.3 1.0 $-1.3(0.6)$ Vatt"*45.58.4 5.2 $-3.2(3.1)$ Jest"*5 5.6 8.8 $3.2(2.1)$ Kokards"5 5.5 8.3 $2.8(2.6)$ Puska"67.9 1.2 $-6.7(2.1)$ Ambrosion"*6 5.1 5.0 $-1.1(0.7.8)$ Jest"*8 2.2 3.62 $11.0(7.8)$ Jest"*8 7.7 $1.0.6$ $-1.4(1.6)$ Dahl"7 $2.4.8$ 18.8 $-6.0(3.3)$ Dahl"8 7.7 10.0 $2.5(3.2)$ <	-		2-4 weeks		
Kolen" 2 7-6 3-5 -4 (123) Morgan" 2 6-7 3-0 -3 7(31) Myers"* 2 6-4 1-2 -5 2(0-8) Poston"** 2 6-4 1-0 -5 4(2-3) Skarabal"** 2 6-2 2-4 -3 8(0-9) Hargreaves" 2 5-8 6-0 0 2(3+1) El Ashry" 2 5-7 -0 5 -6 2(25) Cooper"* 3 2:2 0 6 -1 6(0-7) Smith" 4 12:2 10-0 -2 2(3-1) Skrabal" 4 10-7 5-6 -5 1(27) Parijs" 4 8.2 8-9 0 7(2-1) MacGregori" 4 7-4 10-0 26 (3-2) Kirkendall** 4 5.0 0^{-7} 7 -2^{-3} 2(2) Watt" 4 5.0 0^{-7} 7 -2^{-3} 2(2) Watt" 4 5.0 0^{-7} 7 -2^{-3} 2(2) Watt" 4 5.0 0^{-7} 1 -2^{-7} 2(2)	Poston ²⁵	2		31.0	7.8(6.5)
$\begin{array}{llllllllllllllllllllllllllllllllllll$	Myers ²⁶		11.9	11.3	- 0.6 (1.6)
$\begin{array}{llllllllllllllllllllllllllllllllllll$	Koolen	2			- 4.1 (2.3)
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Skarabal ^{**} 2 $6\cdot 2$ $2\cdot 4$ $-3\cdot 8(0\cdot 9)$ Hargreaves" 2 $5\cdot 8$ $6\cdot 0$ $0\cdot 2(3\cdot 1)$ El Ashry" 2 $5\cdot 7$ $-0\cdot 5$ $-6\cdot 2(2\cdot 5)$ Teow** 2 $4\cdot 6$ $2\cdot 5$ $-2\cdot 1(1\cdot 5)$ Cooper** 3 $2\cdot 2$ $0\cdot 6$ $-1\cdot 6(0\cdot 7)$ Smith" 4 $12\cdot 2$ $10\cdot 0$ $-2\cdot 2(3\cdot 1)$ Skrabal" 4 $12\cdot 2$ $10\cdot 0$ $-2\cdot 2(3\cdot 1)$ MacGregor" 4 $8\cdot 2$ $8\cdot 9$ $0\cdot 7(2\cdot 1)$ MacGregor" 4 $5\cdot 0$ $0\cdot 5$ $-4\cdot 5(1\cdot 5)$ Kirkendall** 4 $5\cdot 0$ $0\cdot 7$ $-2\cdot 3(2\cdot 2)$ Watt" 4 $5\cdot 0$ $0\cdot 7$ $-2\cdot 3(2\cdot 2)$ Watt" 4 $5\cdot 0$ $0\cdot 7$ $-2\cdot 3(2\cdot 2)$ Watt" 4 $5\cdot 0$ $0\cdot 7$ $-2\cdot 3(2\cdot 2)$ Watt" 5 $5\cdot 6$ $8\cdot 3$ $-2\cdot (2\cdot 1)$ Kobayashi" 5 $5\cdot 5$ $8\cdot 3$ $-2\cdot (2\cdot 1)$ Kobayashi"					
Hargreaves" 2 5-8 6-0 0-2(3-1) El Ashry" 2 5-7 -0.5 $-62(2-5)$ Teow'* 2 4-6 2-5 $-21(1-5)$ Cooper'* 3 2-2 0-6 $-16(07)$ Smith" 4 12-2 10-0 $-22(3-1)$ Skrabal" 4 10-7 5-6 $-51(2-7)$ Parijs" 4 8-2 8-9 $0.7(2-1)$ MacGregor" 4 7-4 10-0 $-26(3-2)$ Kirkendall"* 4 5-8 0-0 $-54(1-5)$ Kartandal" 4 5-0 $0-7$ $-23(2-2)$ Watt"* 4 2-3 1-0 $-13(0.6)$ Vatt"* 5 6-2 5-0 $-12(3-2)$ Kobayashi" 5 5-5 8-3 $-28(2-6)$ Puska" 6 5-1 5-0 $-12(3-2)$ Kobayashi" 5 5-5 8-3 $-28(2-6)$ Puska" 6 5-1 5-0 $-12(3-2)$ Kobayashi"		2			
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Teow ^{5*} 24-62-5- 2-1 (1-5)Cooper ^{1**} 32-20-6 1-6 (0-7)Smith ^{1*} 412-210-0 2-2 (3-1)Skrabal ^{1*} 410-75-6- 5-1 (2-7)MacGregor ^{1*} 48-28-90-7 (2-1)MacGregor ^{1*} 47-410-0- 2-6 (3-2)Kirkendall**45-80-0- 5-8 (1-1)Watt ^{1*} 45-00-5- 4-5 (1-5)Erwteman ^{1*} 45-00-7- 2-3 (2-2)Watt ^{1**} 42-31-0- 1-13 (0-6)Vatt ^{1**} 45-02-7- 2-3 (2-2)Kotayashi ^{1**} 56-25-0- 1-2 (3-2)Kobayashi ^{1**} 55-68-8- 3-2 (2-1)Kobayashi ^{1**} 55-58-32-28 (2-6)Puska ^{***} 67-91-2- 6-7 (2-1)Ambroson ^{****} 67-91-2- 6-7 (2-1)Ambroson ^{***************67-90-8- 4+1 (1-4)Dahl^{1************************************}}		2			
Cooper '*32-20-61-6 (0-7)Smith"412-210-022 (3-1)Skrabal"410-75-651 (2-7)Parijs"48-28-90-7 (2-1)MacGregor"47-410-0-2-6 (3-2)Kirkendall***45-00-54-5 (1-5)Erwteman"45-00-72-3 (2-2)Watt"45-00-72-3 (2-2)Watt"*42-31-013 (0-6)Frikendall***45-02-72-3 (2-2)Watt"*45-02-72-3 (2-2)Watt"*45-02-72-3 (2-2)Watt"*55-68-8-3-2 (2-1)Kobayashit"55-68-8-3-2 (2-1)Kobayashit"55-68-8-3-2 (2-1)Kobayashit"55-68-8-3-2 (2-1)Grobbee"64-90-84 (1-14)Grobbee"64-90-84 (1-14)Grobbee"64-90-84 (1-14)Dahl"724-811-01 (8 (5-4))Carney"812-811-01 (8 (5-4))Koga"87-110-0-2 (3 (5-0))Morgan"85-310-6-5 (3 (2-2))Morgan"85-310-6-5 (3 (2-2))Morgan"105-55-80-3 (2-0)Grober'10 <t< td=""><td></td><td>2</td><td></td><td></td><td></td></t<>		2			
Smith*412-210-0 2-2(3-1)Skrabal*410-75-6- 5-1(2-7)Parijs*48-28-90-7(2-1)MacGregor*47-410-02-6(3-2)MacGregor*45-80-0- 5-8(1-1)Watt*45-00-5- 4-5(1-5)Erwteman*45-02-7- 2-3(2-2)Watt**42-31-0- 1-3(0-6)Freweman*45-02-7- 2-3(2-2)Watt**42-31-0- 1-2(3-2)Jest**56-25-0- 1-2(3-2)Kobayashi*55-58-32-8(2-6)Puska*67-91-2- 6-7(2-1)Ambrosioni**65-15-0- 0-1(1-5)Grobbee*64-90-8- 4+1(14)Dahl*724-818-8- 60(3-3)Dahl*724-818-9- 2-5(3-2)Morgan*87-710-0- 2-3(5-0)Koga*87-18-00-9(5-1)Austrabian MRC*87-18-00-9(5-1)MacGrego*99-313-34-0(3-0)Malle***122-64-31-7(1-2)Dole'1020-92-91-0(6-3)Grupe**86-15-5-0-6(1-1)Marcini*85-310-65-3(4-2)Lipten**122-64-31-7(1-2)<					
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$\begin{array}{c c c c c c c c c c c c c c c c c c c $					
MacGregor" 4 7.4 10-0 $2-6(3-2)$ Kirkendall** 4 5-8 0-0 $-5-8(1-1)$ Watt" 4 5-0 0-5 $-4-5(1-5)$ Erviteman" 4 5-0 2-7 $-2-3(2-2)$ Watt"* 4 2-3 1-0 $-1:3(0-6)$ Erviteman" 4 2-3 1-0 $-1:3(0-6)$ Richards" 5 8-4 5-2 $-3\cdot2(3-1)$ Jest"* 5 6-6 8-8 $3\cdot2(2-1)$ Kobayashi" 5 5-5 8-3 $2\cdot8(2-6)$ Puska" 6 7-9 1-2 $-6.7(2-1)$ Ambrosioni* 6 5-1 5-0 $-0.1(1-5)$ Grobbec" 6 4-9 0-8 $-4+1(1-4)$ Dahl* 7 24-8 18-8 $-6.0(3-3)$ Dahl* 8 25-2 36-2 11-0(7-8) Jest" 8 12-8 11-0 $-1-8(5-4)$ Carney" 8 7-4 6-0 $-1+4(1-5)$ Volger*					
Watt"45-00-5-4+5 (1-5)Erwteman"45-02-7-2-3 (2-2)Watt"*42-31-0-1-3 (0-6)Richards"58-8 weeksJest"*56-25-0-1-2 (3-2)Kobayashi"55-68-83-2 (2-1)Kobayashi"55-68-83-2 (2-1)Kobayashi"55-68-83-2 (2-1)Ambrosioni"67-91-2-67 (2-1)Ambrosioni"65-15-0-0.1 (1-5)Grobbee"64-90.8-4.1 (1-4)Dahl"724-818-8-60 (3-3)Dahl"724-811-0-1-8 (5-4)Garacy"812-414-92-5 (3-2)Morgan"87-710-02-3 (5-0)Koga"87-18-0-0-9 (5-1)Australian MRC"85-310-65-3 (4-2)Pagerberg"99-313-34-0 (3-0)Dole"1020-921-91-0 (6-3)Gillum"105-55-80-3 (2-0)Chamers"122-64-31-7 (1-2)Dodor"137-513-05-5 (3-9)Lijnen"**122-64-31-7 (1-2)Dodor"137-513-05-3 (2-1)Morgan"2212-718-05-3 (2-1)Marcins"13<					
Erwteman**45.02.7 $-2.3(2.2)$ Watt**42.31.0 $-1.3(0.6)$ Statests555Richardst*56.25.0Jest**56.25.0Kobayashi*55.68.83.2(2.1)Kobayashi*55.68.83.2(2.1)Ambrosioni*67.91.2 $-6.7(2.1)$ Ambrosioni*65.15.0 $-0.1(1.5)$ Grobbee*64.90.8 $-4.1(1.4)$ Dahl*724.81.88 $-6.0(3.3)$ Dahl*710.0 $-1.8(5.4)$ Carney*812.81.10 $-1.8(5.4)$ Carney*87.46.0 $-1.4(1.5)$ Volge**87.46.0 $-1.4(1.5)$ Volge**87.18.00.9(5.1)Australian MRC*86.15.5 $-0.6(1.1)$ Mancini**85.310.65.3(4.2)P25 weeksFagerberg**99.31.3.3 $4.0(3.0)$ Dole'1020.921.91.0(6.3)Gillum*105.55.80.3(2.0)Chalmers*122.64.31.7(1.2)Dode''102.9(2.55.99.05.3(2.9)Koga*'137.513.05.5(3.9)Lijnen**122.64.48.3(5.5)Weight**122.64.31.7(1.2)	Kirkendall**		5.8	0.0	-5.8(1.1)
Watt ^{n+**} 4 2·3 1·0 $-1\cdot3(0\cdot6)$ Richards ⁴⁻ 5 8·4 5·2 $-3\cdot2(3\cdot1)$ Jest ^{4+*} 5 6·2 5·0 $-1\cdot2(3\cdot2)$ Kobayashi ⁴⁺ 5 5·6 8·8 $3\cdot2(2\cdot1)$ Kobayashi ⁴⁺ 5 5·5 8·3 $2\cdot8(2\cdot6)$ Puska ⁵⁺ 6 7·9 1·2 $-6\cdot7(2\cdot1)$ Ambrosioni ^{4+*} 6 5·1 5·0 $-0\cdot1(1\cdot5)$ Grobbec ⁴⁺ 6 4·9 0·8 $-4\cdot1(1+4)$ Dahl ^{4+*} 7 24·8 18·8 $-6\cdot0(3\cdot3)$ Dahl ^{4+*} 8 25·2 36·2 11·0(7·8) Jest ^{4+*} 8 12·4 14·9 2:5(3·2) Morgan ¹⁺ 8 7·7 10·0 2:3(5·0) Koga ²⁺ 8 7·4 6·0 $-1\cdot4(1\cdot5)$ Volpe ^{++*} 8 5·3 10·6 5·3(4·2) Marcin ^{1+*} 8 5·3 10·6 5·3(4·2) Volpe ^{++*} 9 9·3 13·3 4·0(3·0)					
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	Morgan ¹²	104	3.1	2.0	-1.1(3.1)

*Trials in people with normal blood pressure (<130 mm Hg).

the trials therefore establish that the association between blood pressure and sodium intake shown by our analysis of the between population observational data corresponds quantitatively to the effect of salt reduction in individuals. Salt reduction lowers blood pressure to an extent that increases with age and with initial blood pressure; data on individual people within trials also support this.⁷⁵

The effect of salt reduction on blood pressure is larger than has previously been thought. It has been underestimated because the duration of some widely cited trials was too short to attain the full effect and because of systematic error in the within population observational studies. It has also been inferred from the trials that salt reduction lowers blood pressure in people with high blood pressure but not in those with normal blood pressure.⁷⁶ This is not the case: it lowers all levels of blood pressure, though, as we have shown, the extent of the reduction depends on the initial blood pressure (figure 1). The apparent difference in effect between people with high and those with normal blood pressure has been exaggerated by two factors: firstly, the subjects with high blood pressure were generally older than those with normal blood pressure and the response of blood pressure to salt reduction increases with age, and, secondly, the duration of salt reduction in people with normal blood pressure was usually short (four weeks or less in 16 out of 21 trials).

Simple dietary manipulation — that is, avoiding salty foods and not adding salt in cooking or at the table reduces sodium intake by about 50 mmol/24 h (about 3 g of salt, or 30% of the average daily intake).^{54,55,59,62,67,70,71} In people aged over 50 this would be expected to lower systolic blood pressure after a few weeks by an average of 5 mm Hg and by 7 mm Hg in those with high blood pressure (170 mm Hg). A reduction in sodium intake of 100 mmol/24 h requires, in addition, avoiding many common processed foods^{45,47,56,61,69} and would be feasible only if manufacturers did not add salt to food in processing. It would, however, lower systolic blood pressure by an average of 10 mm Hg and by 14 mm Hg in those with high blood pressure. For diastolic blood pressure the reduction would be about half these values.

EFFECT ON MORTALITY

Figure 4 compares the effect of treatment of high blood pressure (a) with that of universal moderate (50 mmol/24 h) dietary salt reduction (b) on mortality from stroke in a Western population aged 50-59 years. Blood pressure is plotted on a centile scale against corresponding risk of stroke so that the area under the curve corresponds to the total number of deaths due to stroke. A given reduction in blood pressure thus defines an area that is directly proportional to the number of deaths prevented.

The figure was constructed from the results of a prospective study of blood pressure and mortality from stroke (Wald et al, unpublished data). The results from other prospective studies were similar.^{77 78} Repeat blood pressure measurements were taken in a subset of the cohort, providing an estimate of the between person standard deviation of blood pressure and allowing a correction to be made for the underestimation bias inherent in within population studies. The values of average blood pressure corresponding to each centile are shown on the right vertical axis. For example, the 70th centile corresponds to an average diastolic blood pressure of 89 mm Hg, and a risk of stroke relative to the median risk of 1.5. These reduce, after a 50 mmol/ 24 h reduction in sodium intake (figure 4(b)), to 86 mm Hg (calculated from the regression equations in the appendix of our first paper¹) and 1.2 respectively. The curve is plotted for diastolic blood pressure because this tends to be used in clinical practice

Diastolic blood pressure (mm Hg) (approximate systolic equivalent)

(though it is no more predictive than systolic blood pressure, and possibly less so⁷⁹). The policy for treating high blood pressure (fig 4 (a)), as recommended⁸⁰ and often adopted,⁸¹ is to initiate treatment in people with a diastolic pressure of $\geq 100 \text{ mm Hg}$ (about 5% of the population aged 50-59), and reduce their diastolic pressure to 85 mm Hg.

The treatment of high blood pressure would be expected to reduce mortality from stroke in the entire population by an estimated 15% (the ratio of the shaded area to the total area under the curve in figure 4 (a)). Universal dietary salt reduction by 50 mmol/24 h, reducing the blood pressure of the entire population by 5 mm Hg on average, would have a greater effect, preventing 22% of deaths due to stroke (fig 4 (b)). It would also halve the number of people for whom treatment for high blood pressure was indicated (diastolic pressure $\geq 100 \text{ mm Hg}$), and treatment of those with high blood pressure after salt reduction would prevent a further 6% of deaths due to stroke. If salt were not added to processed food a reduction in salt intake of 100 mmol/24 h would be feasible, and this measure alone would reduce mortality from stroke by 39%. In this case the treatment of high blood pressure would be indicated in less than 1% of the population and would prevent a further 2% of deaths from stroke.

Ischaemic heart disease is also associated with blood pressure, and the risk reduces when blood pressure is lowered (although the full reduction in risk does not occur rapidly, as it does with stroke⁷⁸). Figure 5 compares the effect of treatment of high blood pressure and universal dietary salt reduction on mortality from ischaemic heart disease. The risk corresponding to different levels of average blood pressure was estimated from the same prospective study as for stroke, and again estimates from other studies were similar.⁷⁷ In the long term the above policy for treating high blood pressure would reduce mortality from ischaemic heart disease by an estimated 9%, universal salt reduction by 50 mmol/24 h would reduce it by 16%, and both

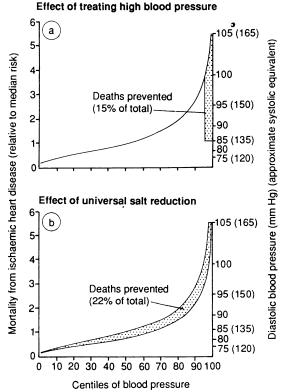


FIG 4—Frequency distribution of blood pressure in population aged 50-59, showing effects of treatment of high blood pressure (a) and universal dietary salt reduction by 50 mmol/24 h (b) on mortality from stroke

policies together would reduce it by 20%. Salt reduction by 100 mmol/24 h would reduce mortality from ischaemic heart disease by an estimated 30% in the long term. Thus, although the two policies are complementary, universal dietary salt reduction has the greater health potential.

Effect of treating high blood pressure

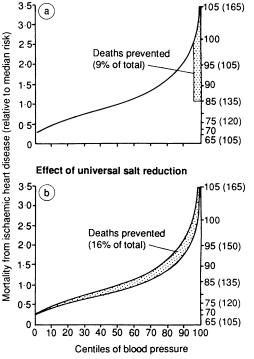


FIG 5—Frequency distribution of blood pressure in population aged 50-59 showing effects of treatment of high blood pressure (a) and universal dietary salt reduction by 50 mmol/24 h (b) on mortality from ischaemic heart disease

A 50 mmol/24 h reduction in sodium intake (achievable by avoiding salty foods and not adding salt to food in cooking or at the table) would reduce the incidence of stroke by a fifth and that of ischaemic heart disease by a sixth. In Britain this would prevent about 6000 deaths a year in people under 65, and 40 000 deaths in all.

Advising the public to reduce consumption of salt is important, but the widepread use of salt in food processing⁸² limits what individual people can readily achieve. Labelling of the salt content of foods and, above all, reduction in the amount of salt added by manufacturers to processed food is a vital public health objective. Such action by food manufacturers, as well as people not adding salt to food themselves, could reduce sodium intake by 100 mmol/24 h. This would reduce the incidence of stroke by 39% and that of ischaemic heart disease by 30%. In Britain this corresponds to preventing about 11 000 deaths a year in people under the age of 65, and 75000 deaths in all. There would also be a major reduction in disability caused by stroke. Few measures in preventive medicine are as simple and economical and yet can achieve so much.

We thank Drs T Ashida and T Kawasaki and Professors T Morgan, F O Simpson, and M H Weinberger for unpublished data; Professors C J Dickinson, M J R Healy, H Kesteloot, G A Rose, and F O Simpson and Dr P Elliott for their comments on the manuscripts of all three papers; and Dr A M Stephen for aggregating some of the trial data and S G Thompson for statistical help in the early part of the work. We also thank the British United Provident Association for its support of the epidemiological research used to obtain the data for figures 4 and 5.

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(Accepted 29 January 1991)

Mortality, neoplasia, and Creutzfeldt-Jakob disease in patients treated with human pituitary growth hormone in the United Kingdom

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Abstract

Objective—To determine the cause of death and incidence of neoplasia in patients treated with human pituitary growth hormone.

Design—A long term cohort study established to receive details of death certification and tumour registrations through the Office of Population Censuses and Surveys and NHS central register.

Patients—All patients (1246 male, 662 female) treated for short stature with pituitary growth hormone under the Medical Research Council working party and health services human growth hormone committee.

Main outcome measures—Death or development of neoplasia.

Results-110 patients died (68 male, 42 female; aged 0.9-57 years) from 1972 to 1990. Fifty three deaths were from neoplasia responsible for growth hormone deficiency (27 craniopharyngioma, 24 other intracranial tumour, two leukaemia); two from histiocytosis X; and 13 from pituitary insufficiency. Six patients died of Creutzfeldt-Jakob disease, six of other neurological disorders, and eight of acute infection. Other deaths were apparently unrelated to growth hormone deficiency or its treatment. Seventeen tumours (in 16 patients) were identified during or after growth hormone treatment. Four were in patients with previous intracranial neoplasia and two were after cranial irradiation. Thirteen were intracranial, the others being Hodgkin's lymphoma, osteosarcoma, carcinoma of colon, and basal cell carcinoma

Conclusions – Recurrence or progression of intracranial tumours and potentially avoidable metabolic consequences of hypopituitarism were the main causes of death. Growth hormone treatment probably did not contribute to new tumour development. Creutzfeldt-Jakob disease after pituitary growth hormone treatment continues to occur in the United Kingdom. This cohort must remain under long term review.

Introduction

Treatment of short stature with human pituitary growth hormone was first described in 1958.¹ A similar preparation was introduced in the United Kingdom under a Medical Research Council working party in 1959, and from 1977 pituitary growth hormone was available through the Health Services Human Growth Hormone Committee.² By 1985 over 850 patients in the United Kingdom and Eire were receiving growth hormone, and its use for causes of short stature other than classical growth hormone deficiency was under reassessment.³ The only adverse effect of this treatment then known was the occurrence of growth hormone antibodies, which rarely inhibited the response.²⁴

In 1985 pituitary growth hormone treatment became associated with fatal Creutzfeldt-Jakob disease, including one case in the United Kingdom,^{5,8} and such preparations were withdrawn almost world wide. Our study was then instigated to review mortality and monitor prospectively the long term health of patients in the United Kingdom treated with growth hormone. We report the mortality and cancer registration data from 1959 to December 1990.

Patients and methods

Patients treated with growth hormone from 1959 to 1985 in the United Kingdom and Eire were identified from Health Services Human Growth Hormone Committee records. These were collated with the NHS central register and registrar's offices in Scotland and Northern Ireland to ascertain deaths and cancer registrations and "flag" survivors so that future deaths and cancer registrations could be notified. In addition, deaths from Creutzfeldt-Jakob disease and similar neurological disorders from 1971 to 1984 were reviewed; none of these patients had been treated with growth hormone. About 40 patients from the United Kingdom received commercial growth hormone preparations and were excluded from the study, as were patients who received only recombinant growth hormone.12

Cause of death was determined from death certificates, case notes, and discussion with doctors caring for the patients. Information from necropsy was available in 44 cases. Comparison between groups was by χ^2 or unpaired Student's *t* test, with significance at the 5% level.

Results

Overall, 1908 patients were registered as having received pituitary growth hormone (fig 1). Treatment started at ages from 1 month (congenital hypopituitarism) to 55 years (idiopathic hypopituitarism). Figure 2 shows their distribution by year of birth, and table I shows diagnoses when treatment started. Patients deficient in two or more anterior pituitary BMJ: first published as 10.1136/bmj.302.6780.819 on 6 April 1991. Downloaded from http://www.bmj.com/ on 19 April 2024 by guest. Protected by copyright

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BMJ 1991;**302**:824-8