Changes in blood pressure and body weight over ten years in men selected for glucose intolerance

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SUMMARY   Relative changes in body weight and blood pressure over ten years of observation are reported in men recruited for a trial of therapy in relation to the natural history of glucose intolerance. Half were recommended a diet restricting carbohydrate to 120 g daily (diet group) and half were recommended to 'limit use of table sugar' (no diet). In both groups average weight and blood pressure fell over the 12 to 18 months after treatment allocation, the decline being proportionately greater for both variables in the diet group. Subsequently, average weight remained constant up to the end of the ten year study, but blood pressure levels rose, though remaining below baseline levels in the diet group. Statistical analysis of changes in blood pressure and weight between initial (pre-treatment) and third follow-up visit measurements indicated that the proportional change in blood pressure was related principally to change in weight, with little relation to initial level of blood pressure. Although a reduction in weight results in a fall in blood pressure, it does not necessarily prevent a subsequent age related increase in blood pressure.

A *Lancet* editorial[1] concluded that "there is sufficient evidence to support the view that every overweight hypertensive should be encouraged strongly to lower weight". This confident statement was based on extrapolation from several relatively short term studies of weight loss and blood pressure change.[2,3] There is only one long term (> 5 years) study in the literature.[4] We report here a ten year observational study of weight and blood pressure change from the follow-up of the Whitehall Study.[5] The primary purpose of the investigation was to study the effects of a recommended diet, with or without an antidiabetic drug, on glucose tolerance and progression to diabetes. Blood pressure levels were recorded systematically throughout, but apart from a policy of referral of subjects with systolic pressures of 200 mmHg or more and/or diastolic pressures (phase 4) of 115 mmHg or more to their general practitioner, there was no attempt to influence blood pressure levels. In the survey examination, these were on average significantly higher in men with glucose intolerance than in age-matched normoglycaemic controls.[6]

Population and methods

Altogether 204 men aged 40 years or over were

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enrolled for a controlled study of the effects of therapy on impaired glucose tolerance. The men were derived from participants in the Whitehall Study and from a smaller pilot study in the Post Office.[7] Criteria for entry comprised a screening capillary blood glucose level two hours after a 50g oral glucose load in the range 110–199 mg/dl (6·1–11·0 mmol/l) with glucose intolerance confirmed in a subsequent oral glucose tolerance test shortly after the survey.[5]

In the survey, blood pressure measurements were made by a team of specially trained nurses and doctors, using the London School of Hygiene 'blind' sphygmomanometer, in the right arm with the subject seated. During the follow-up, blood pressure measurements were made similarly, the great majority by two of the authors (HK and RJJ). Both phases of diastolic blood pressure were recorded; only the results of phase 4 measurements are reported. At the survey and subsequently, weight was measured using a lever balance, after removing shoes and coats or jackets.

Treatment was randomly allocated and was prescribed at the first follow-up visit after the glucose tolerance criteria had been satisfied; this was approximately four months after the survey attendance. Subjects were allocated to one of four treatment groups:

1   recommended 120 g/day carbohydrate diet +

placebo capusule;

2 recommended to 'reduce sucrose (ie, table sugar) intake' + placebo capsule;

3 recommended 120 g/day carbohydrate diet + 50 mg phenformin SA once daily;

4 recommended to 'reduce sucrose intake' + 50 mg phenformin SA once daily.

The restricted carbohydrate diet was carefully taught and a specially prepared explanatory booklet was provided. No recommendations were made about non-carbohydrate foods or drinks. The dietary part of the trial was not 'blind', so that periodic reinforcement of dietary advice could be given. The drug trial was 'blind' but was planned to continue for only the first five years of the study.

Subjects attended approximately six-monthly for the first five years, then annually for the second five years.

Two forms of analysis have been carried out. In the first, blood pressure and weight changes were calculated for the ten years of observations. To avoid bias due to drop-out, we excluded men who were absent from either the final or penultimate visit and/or men who missed four or more follow-up examinations. In addition, we excluded four men who were on hypotensive therapy at the time of the survey and 17 men who were started on such therapy during the follow-up. This left 117 men for study (table 1). The second analysis was of variables related to blood pressure change between the survey and third follow-up visit, when both average blood pressure levels and weight had reached their respective nadir. With the exclusion of those on hypotensive therapy and those absent from visit 3, this left 157 men for study.

The statistical analysis of blood pressure change has aroused considerable controversy. A note on the methods used here is appended.

Results

Using analysis of covariance, over the first five years of the study during which placebo and/or phenformin capsules were administered, allocation to either of these 'treatments' was not significantly related to subsequent blood pressure behaviour. We present, therefore, only the results for restricted carbohydrate versus sucrose reduction, referred to subsequently as diet and no-diet. The characteristics of the two groups are presented in table 1. The only significant differences were in blood pressure levels which were higher in the 'diet' group.

Figure 1 illustrates the average change in weight over the 10 years expressed as a percentage of the weight measured at the survey examination. In both groups there was a slight fall in weight between the survey and the first follow-up clinic visit at which allocation to treatment was made. There was a further decline over the next 12 months, after which the average weight of the groups remained remarkably constant. The average reduction by the third follow-
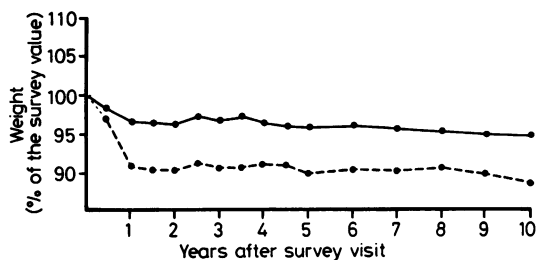

Fig 1   *Mean weight expressed as a percentage of the weight at the survey examination (= 100%). No-diet group—solid line; diet group—interrupted line.*

Table 1   *Characteristics of the treatment groups after exclusions (continuous variables—mean ± SEM).*

	Placebo no diet	Phenformin no diet	Placebo diet	Phenformin diet	No diet	Diet
Number	32	33	25	27	65	52
Age (yrs)	55·5 ±1·1	52·6 ±1·3	55·7 ±1·3	56·7 ±1·7	54·0 ±0·9	56·2 ±1·1
Weight (lbs)	172·6 ±5·0	169·1 ±4·4	178·5 ±6·0	172·9 ±4·8	170·8 ±3·3	175·6 ±3·8
Systolic BP	138·1 ±4·5	136·2 ±3·6	148·3 ±4·8	147·7 ±3·6	137·1 ±2·8	148·0 ±2·9
Diastolic BP	84·9 ±2·8	82·5 ±2·1	88·4 ±2·7	89·7 ±2·5	83·7 ±1·7	89·1 ±1·8
Body mass index	25·5 ±0·6	24·7 ±0·6	27·1 ±0·7	26·4 ±0·6	25·1 ±0·4	26·7 ±0·5

up visit (approximately one year after treatment allocation) was 16·9 1b (9·7%) in the diet group and 6·0 1b (3·5%) in the no-diet group.

Figures 2 and 3 similarly illustrate the changes in systolic and diastolic blood pressure levels. The mean systolic blood pressure level fell in both groups before treatment allocation. In the diet group there was a further substantial decline, reaching a minimum level at the one year examination (visit 2). There was a lesser decline in the no-diet group the minimum level occurring at the 1½ year examination (visit 3). The greater fall in systolic blood pressure early in the follow-up in the diet group was maintained throughout the observation period. In both groups, mean blood pressure levels rose after the initial fall and there was a second, though lesser, fall between five and eight years. The behaviour of diastolic blood pressure levels (fig 3) was similar.

The second analysis considered the changes in weight and blood pressure from survey to visit 3 irrespective of treatment allocation. In 23 men no change or a gain in weight was noted. The remaining 134 men were divided into tertiles of weight loss expressed as percentage change from the initial value. Table 2 presents the average change in systolic and diastolic (phase 4) blood pressure in relation to weight changes. For both, the decline in blood pressure was directly related to the decline in weight. For systolic blood pressure the decline (0·1%) was negligible for those who did not lose or actually gained weight; for diastolic pressure there was a small rise (1·7%) in this group. The relation between change in systolic blood pressure and change in weight is further illustrated in figure 4.
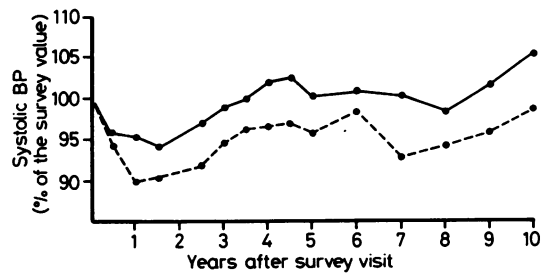

Fig 2 *Mean systolic blood pressure as a percentage of the level measured at the survey (= 100%). No-diet group—solid line; diet group–interrupted line.*
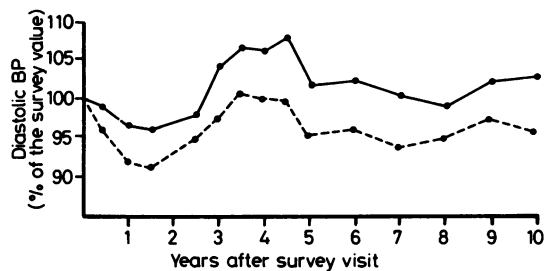

Fig 3 *Mean diastolic blood pressure (phase 4) as a percentage of the level measured at the survey (= 100%). No-diet group—solid line; diet group—interrupted line.*

Table 3 presents the mean systolic and diastolic blood pressures, the mean age, and the mean weight at the survey examination in relation to weight change category. There are no obvious trends for blood pressure and age, but initial weight was directly related to the weight change, with the highest average weight in the group with greatest precentage weight loss.

Thus these analyses suggest that the proportional fall in blood pressure was directly related to the degree of weight loss, which was itself related to the initial weight but not to the initial blood pressure. This was further examined by linear regression analysis (see statistical appendix) which confirmed the impression that the effect of weight loss upon blood pressure was not related to initial blood pressure.

Table 2 *Change in blood pressure in relation to change in weight*

	% Change in weight	N	% Change in BP	
			Systolic	Diastolic
Loss	9–20	45	–10·4	–10·7
	4·5–<9	45	– 7·2	– 8·8
	>0·1–<4·5	44	– 6·3	– 3·2
Gain	0–7·0	23	– 0·1	+ 1·7

Table 3 *Change in weight in relation to initial (survey) mean values of blood pressure, age and weight*

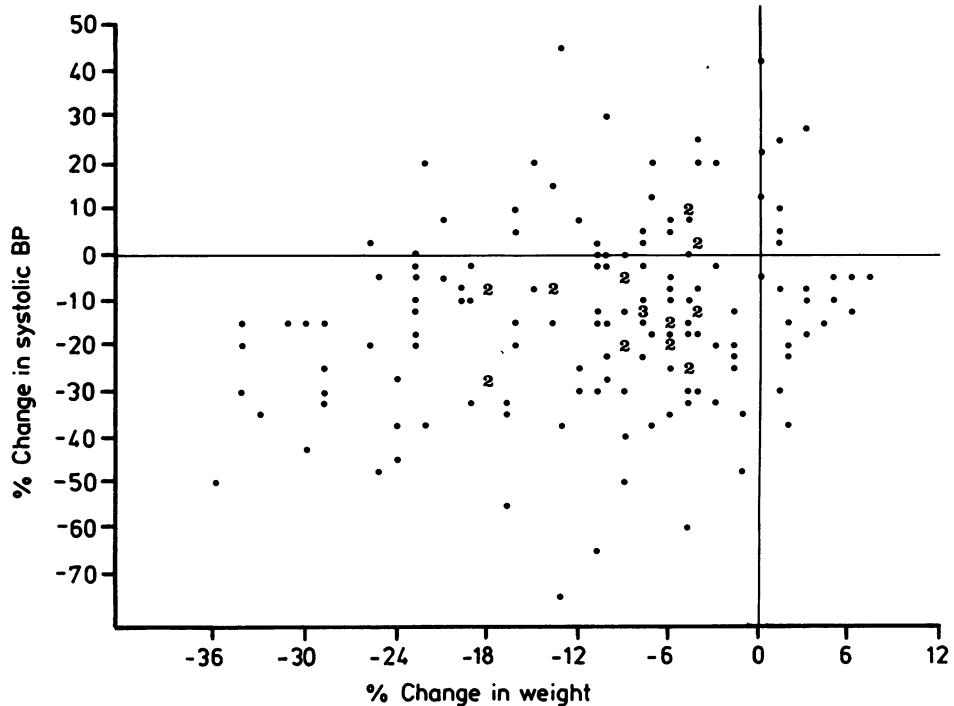|	% Change in weight	N	Systolic BP	Diastolic BP	Age (yrs)	Weight (lb)
Loss	9–20	45	149·8	91·5	54·7	183·2
	4·5–<9	45	139·5	85·6	57·4	172·2
	>0–4·5	44	147·0	88·2	55·0	169·6
Gain	0–7·0	23	136·7	84·6	55·2	162·7

Fig 4 *Correlation of percent change in weight and percent change in systolic blood pressure between the survey and the third follow-up visit in 157 men not taking hypotensive drugs (r = 0·23; p (two tailed test) < 0·01).*

Discussion

The level of blood pressure is one of the principal determinants of cardiovascular morbidity and mortality. Indeed, in the 204 men in this study, of baseline variables, blood pressure was the only significant predictor of both all causes and coronary heart disease mortality during ten years' follow up.[8] As many epidemiological studies have shown, the risk is directly related to the blood pressure level. Nevertheless, as with serum cholesterol,[9] the greater part of morbid events arises from individuals with only modest elevations of blood pressure. The disappointing results of drug therapy in 'mild hypertension' have stimulated interest in alternative methods of blood pressure reduction, including weight control.[1]

Our study was not designed to investigate the effects of weight loss upon blood pressure but to examine its effect upon glucose intolerance and its progression to diabetes. Weight loss was attempted in half the group by a recommended low carbohydrate diet, not a method that we would recommend today. Nevertheless, the study does allow an examination of the effects of weight loss on blood pressure levels, with

the proviso that other methods of dietary manipulation might have produced different results.

The men with 'borderline diabetes' in this study had blood pressure levels during the survey which were, on average, significantly higher than those of age-matched normoglycaemic controls, differences that could not be entirely explained by their slightly greater average adiposity.[6] Although the men were not selected because of a raised blood pressure, some subsequent decline in blood pressure might be attributed to 'regression to the mean', though habituation to the procedure and the investigators would be a more likely explanation. However, there was an additional fall in blood pressure associated with a fall in weight, seen both in the comparison of diet versus non-diet allocation and in the analysis of the larger group from the survey to the third follow-up measurement.

The only comparable long term study is that of Stamler *et al*[4] who reported five years of follow-up on a cohort of men selected for one or more putative coronary risk factors (obesity, hypercholesterolaemia, hypertension, cigarette smoking, physical inactivity). The average weight of these men was substantially greater than in our study. Change in weight was

significantly related to the change in both systolic and diastolic (phase 5) blood pressures.

The present study suggests that the effects of weight loss persist for at least ten years, though they are superimposed upon and only modify an age-related increase. In this respect, our results differ from those of Stamler *et al*, who reported a blood pressure fall during the first year of observation with average levels remaining roughly constant for the ensuing four years, despite some average weight regain. This difference may possibly be due to different dietary approaches, for the Stamler group individualised the diets in relation to the baseline risk factors in contrast to our standard restriction of carbohydrate. An effect related to the different methods of selection into the respective studies is also possible.

We have no explanation of the apparently biphasic behaviour of average blood pressure levels in both treatment groups. Because recruitment to the study occurred throughout the survey, which took over two years to complete, the average level for a particular follow-up visit was derived from measurements aggregated over a period of at least two years; thus it seems unlikely that environmental conditions, such as seasonal variation in temperature,[10] could have been responsible.

The statistical analysis of the change in blood pressure and weight betwen the survey and the third visit (approximately 18 months) suggests that the change in blood pressure is not related to the initial level but related principally to the change in weight. These results are compatible with those reported from the Hypertension Detection and Follow-up Program[11], with a two year follow-up where change in systolic and diastolic blood pressures varied positively with changes in weight, with apparently little effect attributable to baseline blood pressure or weight. In the Framingham Study,[12] changes in weight between the biannual examinations also varied positively with systolic blood pressure irrespective of weight at the first of the paired examinations.

There are several possible explanations for the association between changes in blood pressure and weight. It is well known that artefactually high blood pressure levels may be recorded by sphygmomanometry in people with increased upper arm girth.[13] However, very few of our subjects were excessively obese, and this seems not to be an important factor. Salt restriction results in blood pressure reduction, but the prescribed diet was not intended to reduce salt intake and, on the basis of analysis of dietary recall data (Hunt *et al*, unpublished observations), seems not to have done so. Furthermore, a relatively drastic restriction of salt intake appears to be required to reduce significantly blood pressure levels.[14] It has been shown that weight reduction leads to a concomitant fall in plasma noradrenaline levels,[15] though it is uncertain whether this applies to lesser degrees of adiposity.

Whatever the explanation, our study confirms others in demonstrating an effect of weight reduction on blood pressure and suggests that this may be maintained for at least ten years. However, benefit in terms of reduced morbidity remains hypothetical, and the ideal composition of the hypocaloric diet requires further long term study.

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Statistical appendix

The problems associated with regressing change on its initial value have raised much discussion recently in the Lancet[1-6] and in the past [7-10]

In this paper we attempt to resolve this by adopting the multi-point method proposed by Blomqvist and Svärdsudd[11,12] to find the true relation between blood pressure change and its initial value. A modification of this method has been used to regress blood pressure change on weight change, correcting for measurement error in the latter.

The multi-point method assumes that $k > 2$ measurements are made for each individual at epochs of time $t_1, t_2, \ldots, t_k$. Therefore, we set $t_n = n\text{-}1; n = 1, \ldots, 4$ since the visits were equally spaced* where $t_1 = 0$ refers to the survey (initial) visit. The method requires estimates of blood pressure change b' and initial blood pressure m' for each individual and assumes that an individual's blood pressure changes linearly with time. These are obtained from a linear regression of blood pressure on time

$$x = m' + b't \tag{1}$$

where x is the estimated blood pressure at time t. The residual variance s^2 about each individual's regression line is also calculated. The slope b' becomes the dependent variable and intercept m' the independent variable in the subsequent regression.

The regression of b' on m' gives a regression coefficient, denoted by θ', which is a biased estimate of the true slope/ true initial value regression coefficient. Svärdsudd and Blomqvist[12] show that an adjusted coefficient θ, which is an unbiased estimate of the true regression coefficient, may be obtained from the formula

$$\theta = \frac{\theta' + \lambda a_1}{1\text{-}\lambda a_2} \tag{2}$$

where λ = average $(s^2)/\text{Var}(m')$, $a_1 = \bar{t} / \sum_{i=1}^{k} (t_i\text{-}\bar{t})^2$ and

* The method also works for unequally spaced visits.

$$a_2 = \sum_{i=1}^{k} t_i^2 / \varkappa \sum_{i=1}^{k} (t_i\text{-}\bar{t})^2.$$

The standard error of θ is obtained from the formula

$$\frac{\text{Var}(\theta)}{(a_1 + a_2\theta)2} \sim \frac{\text{Var}(\theta')}{(a_1 + a_2\theta')^2} + \frac{2\lambda^2}{(1\text{-}\lambda a_2)^2} \left[\frac{1}{f} + \frac{1}{f_1} \right] \tag{3}$$

where $f = n(k\text{-}2)$ and $f_1 = n\text{-}1$ are the degrees of freedom of the numerator and denominator of λ respectively. Var (θ') is obtained from the regression analysis of b' on m'.

To investigate the effect of weight on blood pressure we replace initial blood pressure with weight change in the regression analysis. Weight change w' and the residual variance s_w^2 are estimated for each individual by linearly regressing weight on time. The adjusted regression coefficient for blood pressure change on weight change is obtained from a simplification of equation (2)

$$\theta = \frac{\theta'}{1\text{-}a\lambda}$$

where λ = average $(s_w^2)/\text{Var}(w')$, $a = 1/\sum_{i=1}^{k}(t_i\text{-}\bar{t})$ and

Var(w') is the variance of the individual slopes from the linear regression of weight on time. This simplification arises because the convariance of b' and w' is invariant to measurement error.

The standard error of θ is obtained from the formula

$$\frac{v(\theta)}{\theta^2} \sim \frac{v(\theta')}{\theta'^2} + 2 \left[\frac{a\lambda}{1\text{-}a\lambda} \right]^2 \left[\frac{1}{f} + \frac{1}{f_1} \right]$$

Appendix table   *Adjustment of directly computed regression coefficients for blood pressure change on initial value and weight change (standard errors in brackets).*

(a) *Systolic blood pressure change*

	Directly computed regression Coefficients			Adjusted regression coefficients		
		(θ')			(θ')	
Initial value (b'	-0·0964 (0·0203)	–	-0·0863 (0·0200)	0·0070 (0·0327)	–	0·0320 (-)
Weight change (w')	–	0·4510 (0·1233)	0·3694 (0·1183)	–	0·6610 (0·1807)	0·7055 (-)

(b) *Diastolic blood pressure change*

	Directly computed regression coefficients			Adjusted regression coefficients		
		(θ')			(θ')	
Initial value (b')	-0·1908 (0·0213)	–	-0·1811 (0·0211)	-0·1118 (0·0320)	–	-0·0876 (-)
Weight change (w')	–	0·3127 (0·0893)	0·2058 (0·0746)	–	0·4583 (0·1309)	0·3825 (-)

where $V(\theta')$ comes from the regression analysis of b' on w' and f and f_1 are the degrees of freedom as before.

Blomqvist[11] extends the multi-point method to a multiple regression model. We have followed this method by regressing b' on m' and w'. Blomqvist shows that estimates of the regression coefficients are obtained using the standard multiple regression procedure after a simple adjustment to the covariance matrix. The derivation of formulae for the standard errors of the regression coefficients becomes intractable as the number of independent variables in the regression equation increase and is complicated further by the inclusion of variables which have measurement errors. In our case weight change has a relatively small measurement error and we could be justified in regarding such error as negligible. For completeness the multiple regression coefficients have been calculated making adjustments for measurement error in b', m', and w'. We therefore have not attempted to derive standard errors for reasons mentioned above.

The Appendix table shows direct and adjusted regression coefficients for b' on m', b' on w', and b' on m' and w'. For systolic blood pressure the apparent negative regression for b' on m', as suggested by the direct regression, becomes small and positive after adjustment using equation (1). The adjusted regression coefficients suggest that weight change, and not initial value, is the better predictor of systolic blood pressure change. For diastolic blood pressure, despite the regression coefficient for b' on m' becoming less negative with adjustment, some of the change is still partly explained by initial value. Weight change appears to be an important predictor of diastolic blood pressure change both before and after adjustment and in the presence of initial value.

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