Prospective study of risk factors for development of non-insulin dependent diabetes in middle aged British men

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Abstract

***Objective*—To determine the risk factors for non-insulin dependent diabetes in a cohort representative of middle aged British men.**

***Design*—Prospective study.**

***Subjects and setting*—7735 men aged 40-59, drawn from one group practice in each of 24 towns in Britain. Known and probable cases of diabetes at screening (n=158) were excluded.**

***Main outcome measures*—Non-insulin dependent diabetes (doctor diagnosed) over a mean follow up period of 12·8 years.**

***Results*—There were 194 new cases of non-insulin dependent diabetes. Body mass index was the dominant risk factor for diabetes, with an age adjusted relative risk (upper fifth to lower fifth) of 11·6; 95% confidence interval 5·4 to 16·8. Men engaged in moderate levels of physical activity had a substantially reduced risk of diabetes, relative to the physically inactive men, after adjustment for age and body mass index (0·4; 0·2 to 0·7), an association which persisted in full multivariate analysis. A non-linear relation between alcohol intake and diabetes was observed, with the lowest risk among moderate drinkers (16-42 units/week) relative to the baseline group of occasional drinkers (0·6; 0·4 to 1·0). Additional significant predictors of diabetes in multivariate analysis included serum triglyceride concentration, high density lipoprotein cholesterol concentration (inverse association), heart rate, uric acid concentration, and prevalent coronary heart disease.**

***Conclusion*—These findings emphasise the interrelations between risk factors for non-insulin dependent diabetes and coronary heart disease and the potential value of an integrated approach to the prevention of these conditions based on the prevention of obesity and the promotion of physical activity.**

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BMJ 1995;310:560-4

Introduction

Non-insulin dependent diabetes is a common condition affecting at least 3% of the middle aged and elderly population of Britain, with a considerably higher prevalence in specific ethnic groups.[1] Advancing age, obesity, upper body fat distribution, and a family history of diabetes are among the well established risk factors for this condition.[2] Evidence is increasing that in some populations non-insulin dependent diabetes shares common causal factors with cardiovascular disease and in particular with coronary heart disease.[3]

An inverse relation between physical activity level and the risk of subsequent non-insulin dependent diabetes (reported by patients to have been diagnosed by a doctor), has been described in prospective studies from selected populations.[4-6] Data on potential confounding or mediating factors in these studies have been relatively limited. Prospective studies on the role of alcohol in the development of non-insulin dependent diabetes have produced contradictory findings.[7-9] Cigarette smoking has not been extensively investigated as a risk factor for diabetes. Smokers were at higher risk of non-insulin dependent diabetes over 25 years of follow up in the Zutphen study,[10] and evidence exists that cigarette smoking leads to insulin resistance.[11] Resistance to insulin mediated glucose uptake (insulin resistance) antedates non-insulin dependent diabetes[12] and is linked with dyslipidaemia, hypertension, and several other risk factors for coronary heart disease.[13,14]

We report on a prospective study of risk factors for non-insulin dependent diabetes among men recruited for the British regional heart study. We have focused on factors that have been linked with coronary heart disease, such as body mass index, physical activity, alcohol intake, cigarette smoking, and established biological risk factors for coronary heart disease, such as dyslipidaemia and hypertension.

Subjects and methods

In the British regional heart study 7735 men aged 40 to 59, were selected at random from the age-sex register of one general practice in each of 24 towns in England, Wales, and Scotland between January 1978 and June 1980 for a prospective study of cardiovascular disease. The criteria for selecting the towns, general practices, and subjects and methods of data collection have been described.[15,16] Men with cardiovascular or other disease or those receiving regular drug treatment were not excluded. The overall response rate was 78%, ranging from 70% to 85% across the 24 towns. Known diabetic subjects (n=121), men diagnosed within the calendar year in which they were screened (n=14), and those with non-fasting glucose concentrations in the diabetic range (≥11·1 mmol/l, n=23) were excluded. Hence the analysis was based on 7577 men.

DATA COLLECTION: BASELINE ASSESSMENT

Research nurses administered a standard questionnaire and completed an examination of each man, including electrocardiography.[17] The questionnaire included questions on occupation, the usual pattern of physical activity, alcohol intake, smoking habits, medical history, and use of drugs, including antihypertensive drugs.[15-19]

Physical activity—A physical activity score was derived, based on the frequency and intensity of the activities reported.[18] The men were grouped into six physical activity categories: inactivity (n=664), occasional activity (n=2282), light activity (n=1734), moderate activity (n=1181), moderately vigorous activity (n=1104), and vigorous activity (n=510). Data were not available for 102 men.

Alcohol intake—The men were classified into five groups according to their current alcohol intake: none (n=451), occasional (<1 unit/week; n=1809), light (1-15 units/week; n=2490), moderate (16-42 units/week; n=2006) and heavy (>42 units/week; n=815). Data were not available for six men.[19]

Cigarette smoking—The men were categorised as those who had never smoked (n=1787), former

smokers (n=2649), and current smokers, (n=3125), with the latter group further subdivided by the number of cigarettes smoked daily. Data were not available for 16 men.[18]

Prevalent coronary heart disease—With the World Health Organisation's Rose chest pain questionnaire and an electrocardiogram prevalent coronary heart disease at screening was defined on the basis of any of the following crtiteria: recall of a doctor diagnosing angina or heart attack, a response to the WHO's Rose chest pain questionnaire indicating angina or possible myocardial infarction, or electrocardiographic evidence of definite or possible myocardial ischaemia or infarction.[17] In all, 24% (1834) of the men were characterised as having prevalent coronary heart disease at screening. This group did not include men who reported a history of non-specific "other heart disease."

Body mass index calculated as weight (kg)/(height (m)^2) was used as an index of relative weight. Men with a body mass index of ≥ 28 were categorised as obese. Blood pressure was recorded with a London School of Hygiene sphygmomanometer. Two successive recordings were taken, and the mean was used in the analysis with adjustment for interobserver variation. Heart rate was determined from the electrocardiogram.

Non-fasting blood samples were obtained between 8 30 am and 6 30 pm.[20] Glucose, total cholesterol, and uric acid concentrations were analysed in serum with an automated analyser (Technicon SMA 12/60).[20-21] Diurnal variation in glucose concentrations was modest, with a peak-trough difference of 0·4 mmol/l.[20] High density lipoprotein cholesterol and triglyceride concentrations were measured with enzymatic methods.[20] As triglyceride concentrations were not determined for men in the first six towns, data on this variable were available for only 5327 men.

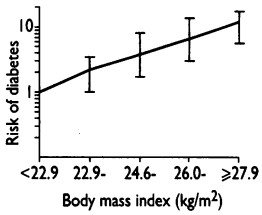

FIG 1—*Relative risk of non-insulin dependent diabetes (log scale) adjusted for age with 95% confidence intervals, by fifth of body mass index relative to the lower fifth*

FOLLOW UP FOR DEVELOPMENT OF NON-INSULIN DEPENDENT DIABETES

The men were followed for morbidity and mortality up to December 1991, a mean period of 12·8 years.[22] Less than 1% (73) of men were lost to follow up, of whom 44 (0·6% of total) emigrated from Britain. New cases of non-insulin dependent diabetes were ascertained by means of (*a*) a postal questionnaire sent to the men at year 5 of follow up for each individual, (*b*) systematic reviews of primary care records in 1990 and 1992, (*c*) a further questionnaire to 6483 surviving members of the cohort resident in Britain in 1992, and (*d*) review of all death certificates for any mention of diabetes. The questionnaire at year 5 achieved a response rate of 98%[22] and on the 1992 questionnaire a response rate of 91%. A diagnosis of diabetes was not accepted on the basis of questionnaire data unless confirmed in the primary care records.

STATISTICAL ANALYSIS

Cox's proportional hazards models were used to assess the independent contributions of the risk factors to the subsequent risk for non-insulin dependent diabetes and to obtain the relative risks adjusted for the other risk factors.[23]

Physical activity (six levels), smoking (three levels), alcohol intake (five levels), and pre-existing ischaemic heart disease (yes/no) were fitted as categorical variables in the proportional hazards model. The adjusted relative risks in figures 1 and 3 were obtained by fitting body mass index, systolic and diastolic blood pressure, heart rate, and concentrations of high density lipoprotein cholesterol, triglyceride, and uric acid as four dummy variables for the five equal divisions of each risk factor. Tests for trend were carried out by fitting the quantitative variables in their continuous form. For table I analysis of covariance was used to derive the means adjusted for age and body mass index, and logistic regression was used to calculate prevalences adjusted for age and body mass index on the basis of conversion of adjusted odds ratios to estimated proportions. For tables II and III the validity of the proportional hazards assumption in Cox's models was checked by fitting a time dependent interaction variable $x=x(t)$, where $x(t)=\log(t)$. Subjects with missing values for covariates in the various adjustments with Cox's model were excluded from that particular analysis.

As glucose and triglyceride concentrations were not normally distributed log transformation and geometric means were used. Because of the pronounced diurnal variation in serum triglyceride concentrations[20] the log transformed data on this variable were adjusted for time of sampling.[24]

Results

After a mean follow up period of 12·8 years there were 194 new cases of non-insulin dependent diabetes in the 7577 men, an incidence of 2·15 per 1000 person years of follow up. Men who developed diabetes had significantly higher mean blood glucose concentrations at screening than those who remained free of diabetes (6·2 *v* 5·4 mmol/l; $P<0.0001$). Little difference in mean age existed between the two groups (50·4 *v* 50·2). Those who developed diabetes had a significantly higher mean body mass index than those who did not (27·9 *v* 25·4; $P<0.0001$). Forty four per cent (85/194) of the men who developed diabetes were obese (body mass index of ≥ 28) compared with 18% (1328/7383) of those who did not. The risk of non-insulin dependent diabetes increased exponentially with increasing body mass index, with an over 11-fold excess risk in the upper fifth (≥ 27.9) relative to the lower fifth (≤ 22.9) (relative risk=11·6; 95% confidence interval 5·4 to 16·8) (fig 1).

Table I shows the baseline characteristics of the men who subsequently developed diabetes compared with the rest of the cohort, adjusted for age and body mass index. No adjustments were made for serum glucose concentration, which is assumed to be the causal pathway between the relevant exposures and non-insulin dependent diabetes. Significantly fewer of the men who developed diabetes compared with those who did not were moderate drinkers and physically active. Those who developed diabetes were more likely to be smokers (P=0·06), and they had a significantly higher prevalence of pre-existing coronary heart disease, but

TABLE I—*Baseline values of selected variables (adjusted for age and body mass index) in 7577 middle aged men initially free of diabetes, by incidence of non-insulin dependent diabetes during a mean follow up of 12·8 years*

Variable	Men who did not develop diabetes during follow up (n=7383)	Men who developed diabetes during follow up (n=194)	P value
From logistic regression*:			
Manual occupation	57	56	
Current smokers	41	48	0·06
Moderate drinkers†	27	20	0·05
Physically active‡	37	28	0·01
Evidence of coronary heart disease	24	32	0·01
Other heart disease	5·9	8·5	
Treatment with antihypertensive drugs	4·7	6·7	
Any regular drug treatment	28	32	
From analysis of covariance§:			
Heart rate (beat/min)	70·6 (0·15)	73·2 (0·90)	0·005
Systolic blood pressure (mm Hg)	145·0 (0·23)	148·2 (1·43)	0·03
Diastolic blood pressure (mm Hg)	82·2 (0·14)	84·10 (0·90)	0·04
Total cholesterol (mmol/l)	6·30 (0·01)	6·34 (0·07)	
High density lipoprotein cholesterol (mmol/l)	1·15 (0·003)	1·11 (0·02)	0·004
Triglyceride (mmol/l)‖	1·73	2·16	<0·0001
Uric acid (μmol/l)	359·1 (0·8)	370·5 (4·8)	0·02

*Values are estimated percentages of men (see methods section).
†16-42 Units/week.
‡Level of activity was moderate or higher.
§Values are means (SE) (see methods section).
‖Geometric mean (5197 *v* 130).

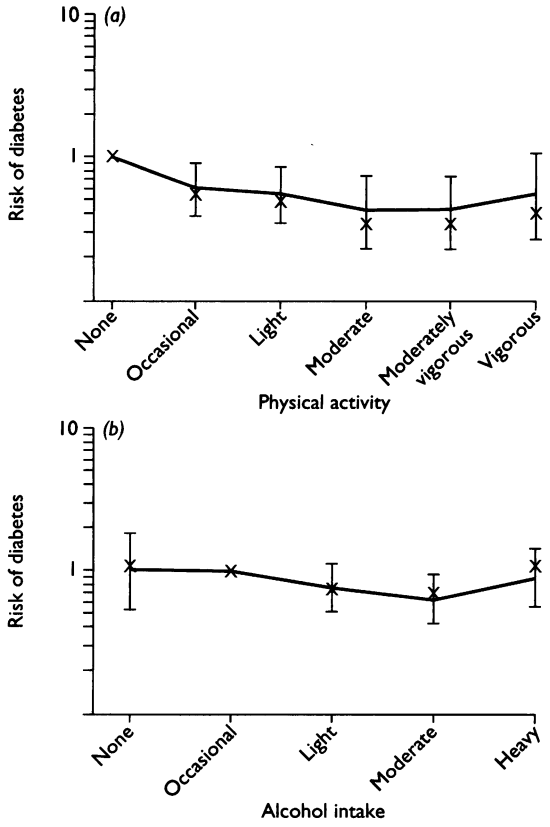

FIG 2—*Relative risk of non-insulin dependent diabetes (log scale) adjusted for age and body mass index with 95% confidence intervals, by (a) physical activity level and (b) alcohol intake. The x shows each relation adjusted for age alone. The lowest physical activity group (inactive) forms baseline group for this variable, and occasional drinkers form baseline group for alcohol intake*

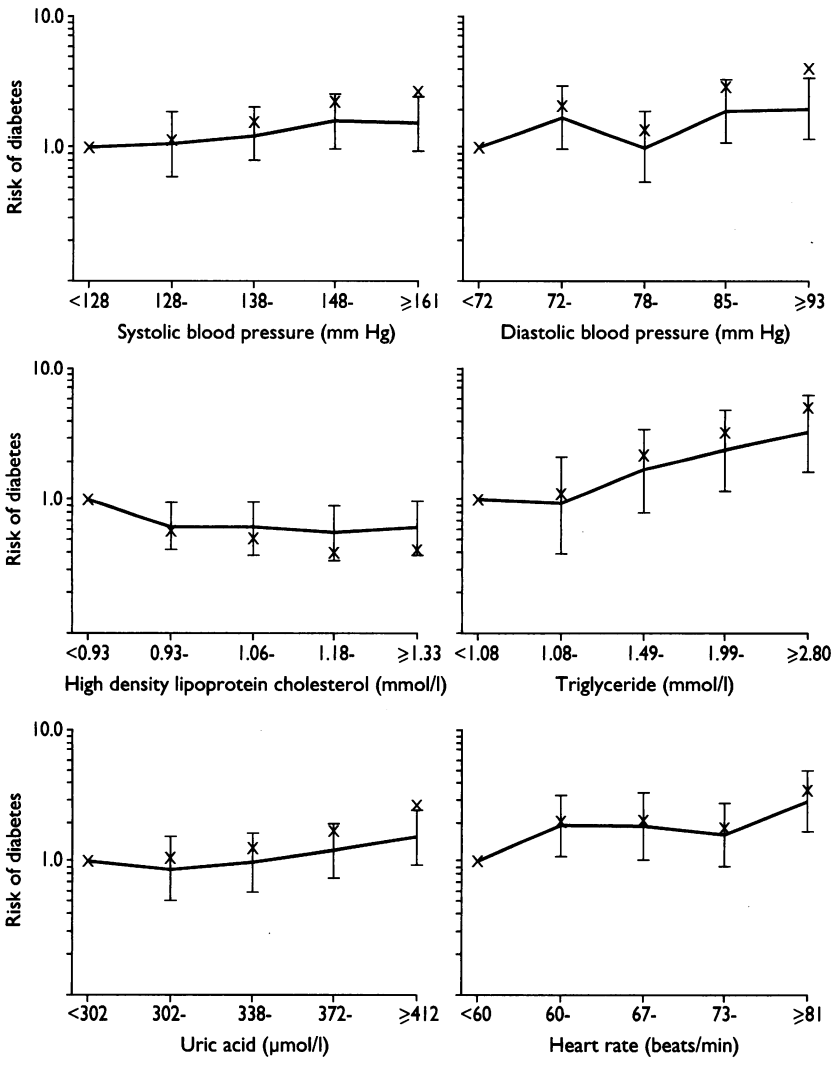

FIG 3—*Relative risk of non-insulin dependent diabetes (log scale) adjusted for age and body mass index with 95% confidence intervals, by fifths of systolic and diastolic blood pressure, heart rate, and concentrations of high density lipoprotein cholesterol, triglyceride, and uric acid relative to lower fifth of each variable. The x shows each relation adjusted for age alone*

not of "other heart disease." No differences existed in social class status and in the use of antihypertensive drugs or other medication. The men with diabetes had significantly higher systolic and diastolic blood pressure, heart rate, and triglyceride and uric acid concentrations and significantly lower high density lipoprotein cholesterol concentrations. No significant difference in mean total cholesterol concentration existed between the men with diabetes and those without.

PHYSICAL ACTIVITY, ALCOHOL INTAKE, AND CIGARETTE SMOKING

Figure 2 shows the relative risk of non-insulin dependent diabetes with 95% confidence intervals at different levels of physical activity and alcohol intake, adjusted for age and separately for age and body mass index. The risk of diabetes progressively decreased with increasing levels of physical activity up to moderate activity (0·4; 0·2 to 0·7) relative to the inactive group. A shallow "U shaped" relation was seen between alcohol intake and the risk of diabetes, with the lowest risk seen in moderate drinkers (0·64; 0·43 to 0·96) relative to the baseline group of occasional drinkers. Current smoking was associated with a 50% increase in the risk of diabetes relative to those who had never smoked, adjusted for age and body mass index, (1·5; 1·0 to 2·2; P=0·04). No association with the number of cigarettes smoked was detected. Former smokers were at similar risk of diabetes as men who had never smoked (1·2; 0·8 to 1·8).

ADDITIONAL RISK FACTORS FOR NON-INSULIN DEPENDENT DIABETES

Men with evidence of coronary heart disease at screening showed a 50% increase in the risk of developing diabetes on adjustment for age and body mass index (1·53, 1·13 to 2·07). Figure 3 shows the relative risks of diabetes, with 95% confidence intervals, by fifths of systolic and diastolic blood pressure, heart rate, and concentrations of high density lipoprotein cholesterol, triglyceride, and uric acid, adjusted for age and separately for age and body mass index. The positive association seen between systolic blood pressure and the age adjusted risk of diabetes was appreciably attenuated on adjustment for body mass index, although the trend remained significant (P=0·02). A similar though weaker association was seen for diastolic blood pressure. For heart rate the risk of diabetes was appreciably increased in the top fifth relative to the bottom fifth (adjusted relative ratio=2·9; 1·7 to 4·9). A significant inverse association was seen between high density lipoprotein cholesterol concentration and risk of diabetes after adjustment for age and body mass index (trend P=0·004). A particularly strong positive association was seen between triglyceride concentration and risk of diabetes after adjustment for age and body mass index (trend P<0·0001), with a more than threefold increased risk in the top fifth relative to the bottom fifth. A positive association with serum uric acid concentrations was also observed (fig 3).

MULTIVARIATE ANALYSIS

Table II shows the findings from multivariate analysis of independent predictors of diabetes. There was an over sevenfold increased risk of diabetes in the upper fifth of body mass index relative to the lowest in multivariate analysis, and the strong, linear inverse association with physical activity was not attenuated. The associations with moderate drinking, pre-existing coronary heart disease, heart rate, and concentrations of high density lipoprotein cholesterol and uric acid remained significant. The associations with current

smoking and systolic blood pressure were no longer significant in this multivariate model.

Variables which emerged as significant predictors of diabetes in the multivariate model presented in table II were further adjusted for triglyceride concentration in a separate model based on data from the subgroup of 5327 men with data on serum triglyceride concentration (table III). No association between high density lipoprotein cholesterol concentration and the risk of diabetes was observed on adjustment for triglyceride concentration, and the association with heart rate was attenuated.

EFFECT OF PRE-EXISTING CORONARY HEART DISEASE

The factors shown to be independently associated with diabetes—namely, body mass index, physical activity, alcohol intake, and uric acid and triglyceride concentrations—were also examined separately in men without pre-existing coronary heart disease (n=3981 men; 83 cases of diabetes) and in men with pre-existing coronary heart disease (n=1346 men; 47 cases) at baseline. This analysis was confined to the subset of men with available data on triglyceride concentration. Similar associations were seen in both groups between body mass index, physical activity, triglyceride and uric acid concentrations, and non-insulin dependent diabetes. The lower risk of diabetes seen in moderate drinkers was more apparent in men with pre-existing coronary heart disease than in men without evidence of coronary heart disease at screening, but a formal test for interaction was not significant.

In a separate analysis in which we excluded men with pre-existing coronary heart disease and men with a diagnosis of either hypertension or stroke at screening (n=3574, 69 cases) these findings were unchanged.

Discussion

In this study we have shown that obesity and physical inactivity are important independent risk factors for non-insulin dependent diabetes in middle aged men, whereas evidence incriminating alcohol intake and cigarette smoking is lacking. We have shown that several cardiovascular risk factors that are linked with insulin resistance (triglyceride, high density lipoprotein cholesterol and uric acid concentrations)[13] predict the development of non-insulin dependent diabetes over a decade before the onset of clinically manifest disease. These associations persisted after adjustment for body mass index and for other factors that might increase the probability of diagnosis, such as hypertension and prevalent coronary heart disease at screening. Additional important coronary heart disease risk factors—notably, serum total cholesterol concentration and blood pressure—did not predict non-insulin dependent diabetes.

The data on physical activity and non-insulin dependent diabetes in this study complement and extend the findings from previous prospective studies that have addressed this issue in selected populations.[4-6] We have also shown an association between heart rate, which may be regarded as a proxy measure of physical fitness, and diabetes. Indeed lower heart rate was an independent predictor of diabetes in multivariate models which included physical activity. Though this may simply reflect the relatively high precision with which heart rate was measured, the possibility that heart rate is also acting as a marker for sympathetic nervous system activation (which is linked with insulin resistance[25]) should be considered.

The data from this study provide evidence of a protective effect of alcohol on the risk of non-insulin dependent diabetes. This finding, however, should be interpreted cautiously as it was significant only in men with evidence of coronary heart disease at baseline. It is clear, however, that the data provide no support for the hypothesis of a causal positive link between alcohol intake and non-insulin dependent diabetes.[8]

This study had adequate power to examine the association between cigarette smoking and non-insulin dependent diabetes, and the findings do not suggest an important independent role for cigarette smoking in the development of this condition.

TABLE II—*Predictors of non-insulin dependent diabetes in multivariate analysis. Analysis includes 7097 men, 178 cases with data on all covariates in table*

Variable*	Adjusted relative risk (95% confidence interval)	P value†
Body mass index‡	7·3 (3·4 to 15·6)	0·0001
Prevalent coronary heart disease (yes/no)	1·4 (1·0 to 1·9)	0·04
Physical activity (moderate *v* inactive)	0·4 (0·2 to 0·8)	0·003
Alcohol intake (moderate *v* occasional)	0·6 (0·4 to 1·0)	0·04
Current smoker (yes *v* never smoked)	1·2 (0·8 to 1·8)	
Systolic blood pressure‡	1·3 (0·8 to 1·7)	
High density lipoprotein cholesterol‡	0·7 (0·5 to 1·2)	0·03
Heart rate‡	2·2 (1·1 to 4·2)	0·01
Uric acid‡	1·5 (0·9 to 2·5)	0·01

*Each variable has been adjusted for age and for each of the other variables in model.
†Test for linear trend.
‡Upper fifth *v* lower fifth.

TABLE III—*Predictors of non-insulin dependent diabetes in subset of men with available data on triglyceride concentration (5327 men; 130 cases)*

Variable	Relative risk (95% confidence interval)		
	Partially adjusted*	Fully adjusted†	P value‡
Body mass index§	6·6	5·8 (2·6 to 13·2)	<0·0001
Prevalent coronary heart disease (yes/no)	1·4	1·4 (1·0 to 2·0)	0·05
Physical activity (moderate *v* inactive)	0·5	0·5 (0·2 to 0·9)	0·02
Alcohol intake (moderate *v* occasional)	0·6	0·6 (0·3 to 1·0)	0·04
High density lipoprotein cholesterol§	0·8	1·4 (0·8 to 2·6)	
Heart rate§	2·3	2·0 (1·0 to 4·0)	
Uric acid§	1·4	1·3 (0·7 to 2·2)	0·06
Triglyceride§	2·8 (1·4 to 5·8)		<0·001

*Adjusted for age, body mass index, smoking, pre-existing ischaemic heart disease, alcohol intake, physical activity, systolic blood pressure, high density lipoprotein cholesterol concentration, heart rate, uric acid concentration.
†Adjusted as for partially adjusted model together with serum triglyceride concentration.
‡Test for linear trend in fully adjusted model.
§Upper fifth *v* lower fifth.

CORONARY HEART DISEASE RISK FACTORS AND NON-INSULIN DEPENDENT DIABETES

Reaven and others have developed the concept of a metabolic syndrome based on insulin resistance that includes glucose intolerance, hypertriglyceridaemia, decreased high density lipoprotein cholesterol concentration, hypertension, and hyperuricaemia.[13] As clinically overt non-insulin dependent diabetes is preceded by a prolonged period of insulin resistance[12] risk factors for cardiovascular disease that cluster with insulin resistance should also predict diabetes. The data from this study support this hypothesis and add to the evidence that the increased risk of vascular disease in diabetes is well established before the onset of clinically manifest disease.[26] We observed, however, weak associations between blood pressure and non-insulin dependent diabetes that were appreciably attenuated on adjustment for body mass index and were non-significant in the full multivariate analysis model. It is noteworthy that the link between blood pressure and insulin resistance or hyperinsulinaemia in cross sectional studies is more tenuous and inconsistent[14,25] than that between dyslipidaemia (or hyperuricaemia) and insulin resistance.[13,14]

CONCLUSIONS

The current *Health of the Nation* targets for obesity focus on reducing the prevalence of obesity (defined as body mass index of ≥ 30) rather than on achieving a downward shift in the overall distribution of body mass

Key messages

- Recent findings have suggested that non-insulin dependent diabetes and cardiovascular disease share common causal factors
- This study shows a strong, graded association between body mass index and risk of diabetes in middle aged men, with no evidence of a threshold effect
- The risk of diabetes is reduced by more than 50% among men who take moderately vigorous exercise
- Cardiovascular disease risk factors that are linked with insulin resistance, such as hypertriglyceridaemia and hyperuricaemia, predict non-insulin dependent diabetes
- These findings support an integrated approach to the prevention of non-insulin dependent diabetes and cardiovascular disease based on the prevention of obesity and the promotion of physical activity

index.[27] As 75% of cases of diabetes in this study, however, ocurred in men with a body mass index of <30, substantial progress towards the prevention of non-insulin dependent diabetes and its sequelae will require a population based rather than a high risk approach to the problem of obesity. The findings from this study support the concept of an integrated approach to the prevention of non-insulin dependent diabetes and atherosclerotic vascular disease based on the prevention of obesity and the promotion of physical activity. However, not all vascular risk factors predict non-insulin dependent diabetes. This suggests that there are critical factors within populations (as well as between populations[28]) that modulate the progression from insulin resistance to non-insulin dependent diabetes or atherosclerotic vascular disease, or both of these conditions.

The British regional heart study is a British Heart Foundation research group. Support is also provided by the Stroke Association and the Department of Health. Biochemical estimations were carried out at the Wolfson Research Laboratories, Queen Elizabeth Hospital, Birmingham. IJP was supported by the Wellcome Trust.

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(Accepted 31 January 1995)

ONE HUNDRED YEARS AGO

BICYCLE OR HORSE EXERCISE FOR WOMEN?

Dr. Dickinson, of Brooklyn, declares that bicycle riding has certain advantages over the present style of horseback riding. The fashionable contorted seat does not develop the body symmetrically, and the awkwardness due to the fact that the transverse diameter of the pelvis and the transverse diameter of the upper trunk do not correspond means strain, to say nothing of the useless effort entailed in trotting. When women get into the habit of riding part of the time with the stirrup on the right side and part with the stirrup on the left, one objection to the spiral rotation and the unsymmetrical development will be overcome; and it is to be presumed, Dr. Dickinson thinks, that eventually they will all ride astride as their ancestresses did before the days of Queen Elizabeth. The expense precludes this form of exercise for most women. Cheapness, safety, accessibility, and the small amount of preparation required are all on the side of the wheel, and holds good to even a greater degree for the woman than for the man. The woman on a bicycle is at an advantage as compared with the woman on horseback, as custom does not enforce the tailor-made, hour glass, shop-window figure, and she can wear a jacket open in front with a short waist beneath it. Dr. Dickinson commends the elegant costumes worn in Paris by bicyclists. In view of woman's disabilities, and the disadvantages under which she has suffered in attempts to obtain interesting and beneficial muscular exercise, Dr. Dickinson considers that it seems hardly too much to say that the promise from the bicycle is far reaching. Through it and the habits it will engender we look for better dress, freer dress, shorter dress in bad weather; for better exercise, for out-of-door activity, for steadier nerves, and stronger muscle. (*BMJ* 1895;i:720.)