

Relationship Between Ethnicity and Glycemic Control, Lipid Profiles, and Blood Pressure During the First 9 Years of Type 2 Diabetes

U.K. Prospective Diabetes Study (UKPDS 55)

TIMOTHY M. E. DAVIS, FRACP¹
CAROLE A. CULL, PHD²
RURY R. HOLMAN, FRCP²

FOR THE U.K. PROSPECTIVE DIABETES
STUDY (UKPDS) GROUP

OBJECTIVE — To assess the relationship among self-reported ethnicity, metabolic control, and blood pressure during treatment of type 2 diabetes.

RESEARCH DESIGN AND METHODS — We studied 2,999 newly diagnosed type 2 diabetic patients recruited to the U.K. Prospective Diabetes Study who were randomized to conventional or intensive glucose control policies if their fasting plasma glucose levels remained >6 mmol/l after a dietary run-in. A total of 2,484 patients (83%) were white Caucasian (WC), 265 patients (9%) were Afro-Caribbean (AC), and 250 patients (8%) were Asian of Indian origin (IA). Variables were assessed at 3, 6, and 9 years.

RESULTS — During the 9-year study period, body weight increased more in WC patients (mean 5.0 kg) than in AC (3.0 kg) and IA (2.5 kg) patients ($P < 0.001$). After adjusting for age, sex, baseline value, treatment allocation, and change in weight, there were no consistent ethnic differences in mean change in fasting plasma glucose or HbA_{1c}. After adjustment for antihypertensive therapy, increase in systolic blood pressure at 9 years was greatest in AC patients (7 mmHg; $P < 0.01$ vs. WC patients). Mean diastolic blood pressure, total cholesterol, and LDL cholesterol decreased progressively during the 9 years in each group. In AC patients, the mean increase in HDL cholesterol (0.16 mmol/l) at 3 years, maintained to 9 years, and the mean decrease in plasma triglyceride level (0.4 mmol/l) at 9 years were greater than in WC and IA patients ($P < 0.001$).

CONCLUSIONS — This study shows important ethnic differences in body weight, lipid profiles, and blood pressure, but not glycemic control, during 9 years after diagnosis of type 2 diabetes. AC patients maintained the most favorable lipid profiles, but hypertension developed in more AC patients than WC or IA patients. Ethnicity-specific glycemic control of type 2 diabetes seems unnecessary, but other risk factors need to be addressed independently.

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The epidemiology of type 2 diabetes and its complications vary significantly between ethnic and racial groups (1–7), but few studies have assessed ethnic differences in cardiovascular risk factor profiles (8). The U.K. Prospective Diabetes Study (UKPDS) studied patients with newly diagnosed type 2 diabetes; most patients (82%) were white Caucasian (WC) and the remainder were Afro-Caribbean (AC) (8%) or Asians of Indian origin (IA) (10%) (9). Although the prevalence of microvascular and macrovascular complications was similar at diagnosis, there were significant ethnic differences in some risk factors (9). AC patients had higher fasting plasma glucose (FPG) concentrations but more favorable lipid levels (lower plasma triglyceride and higher HDL cholesterol levels) than WC and IA patients, whereas blood pressure levels and prevalence of hypertension were lower in IA patients than in the other groups (9). This lack of association between vascular complications and risk factors in the different ethnic groups at diagnosis is difficult to assess in cross-sectional data (9). Comparative U.K. studies of AC and IA patients suggest that ethnic differences in vascular complications of type 2 diabetes emerge with time. In one study, both groups had the same prevalence of ischemic heart disease, but IA patients had less peripheral vascular disease, retinopathy, and renal disease (10). In another study, ischemic heart disease rates were lower in AC patients than in WC patients, despite a greater prevalence of hypertension (2).

The UKPDS randomized patients to conventional or intensive glucose control (11), allowing prospective investigation of the relationships among ethnicity, metabolic control, and blood pressure in patients receiving comparable clinical care

From the ¹Fremantle Hospital, University of Western Australia, and the ²Radcliffe Infirmary, Oxford, U.K. Address correspondence and reprint requests to Rury R. Holman, Diabetes Trials Unit, Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE, U.K. E-mail: rury.holman@dtu.ox.ac.uk.

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For a list of participating centers, please see APPENDIX at the end of the article.

Abbreviations: AC, Afro-Caribbean; DBP, diastolic blood pressure; FPG, fasting plasma glucose; IA, Asian subject of Indian origin; SBP, systolic blood pressure; UKPDS, U.K. Prospective Diabetes Study; WC, white Caucasian.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—Characteristics at randomization, by self-reported ethnic group, of type 2 diabetic patients in the UKPDS cohort followed for at least 3 years

	WC	AC	IA
n	2,484	265	250
Patients in main randomization (%)	83.4	84.2	88.4
Allocated therapy: diet; insulin; sulphonylurea; metformin (%)	22; 28; 39; 11	19; 29; 42; 10	25; 30; 39; 5
Age (years)*	53 ± 9	51 ± 7§	48 ± 8§¶
Male (%)*	56	54	76§
Body weight (kg)	77 ± 16	75 ± 13	69 ± 12§¶
BMI (kg/m ²)	27.5 ± 5.3	27.0 ± 4.5	25.3 ± 3.8§¶
FPG (mmol/l)	8.8 (7.5–11.7)	9.1 (7.7–12.0)	8.6 (7.5–10.7)
HbA _{1c} (%)*	7.3 (6.3–8.8)	7.9 (6.6–9.5)‡	7.2 (6.4–8.6)
Plasma insulin (pmol/l)*	90 (50–163)	78 (44–139)§	105 (64–173)§¶
β-cell function (%)*	47 (28–69)	41 (24–61)	52 (34–73)¶
Insulin sensitivity (%)*	55 (39–80)	59 (46–90)§	50 (36–66)§¶
Hypertensive: not; untreated‡; treated (%)*	59; 23; 18	58; 22; 20	78; 14; 9§
Systolic blood pressure (mmHg)*	137 ± 20	137 ± 19	125 ± 16§¶
Diastolic blood pressure (mmHg)*	83 ± 10	85 ± 10‡	80 ± 9§¶
Plasma total cholesterol (mmol/l)*	5.5 ± 1.2	5.3 ± 1.1§	5.2 ± 1.0§
Plasma LDL cholesterol (mmol/l)*	3.6 ± 1.1	3.5 ± 1.1	3.3 ± 0.9§
Plasma HDL cholesterol (mmol/l)*	1.07 ± 0.24	1.19 ± 0.25§	1.01 ± 0.21§¶
Plasma triglyceride (mmol/l)*	1.6 (1.0–2.7)	1.1 (0.7–1.7)§	1.7 (1.0–2.8)¶

Data are means ± SD, geometric means (± 1 SD interval), medians (interquartile range), or %. * $P < 0.00001$ by Kruskal-Wallis or χ^2 test; ‡SBP > 160 mmHg or DBP > 90 mmHg; † $P < 0.01$ vs. WC; § $P < 0.001$ vs. WC; ¶ $P < 0.01$ vs. AC; ¶ $P < 0.001$ vs. AC.

over the first 9 years after diagnosis of type 2 diabetes.

RESEARCH DESIGN AND METHODS

A total of 5,102 patients aged 25–65 years with newly diagnosed type 2 diabetes (FPG >6 mmol/l on two occasions) were recruited to the UKPDS between 1977 and 1991 (12). Exclusion criteria included 1) severe vascular disease, 2) accelerated hypertension, 3) proliferative or preproliferative retinopathy, 4) renal failure, 5) other life-threatening disease, 6) treatment with systemic steroids, 7) an occupation precluding insulin treatment, 8) language difficulties, and 9) ketonuria. The ethnic origin of the patients excluded is not known.

These analyses are restricted to patients from the first 15 UKPDS centers because the remaining 8 UKPDS centers used a modified intensive glucose control policy and followed few subjects for 9 years or more. Most (83%) of the 2,999 patients analyzed here had FPG <15 mmol/l after dietary run-in and were included in the main randomization to conventional or intensive glucose control policies. The remainder of patients

(17%), with FPG ≥15 mmol/l or persistent hyperglycemic symptoms (primary diet failure), were randomized within the intensive policy (12). A total of 2,484 WC patients (83%), 265 AC patients (9%), and 250 IA patients (8%) were included in the study; 1,424 obese patients (>120% of ideal body weight) (13) were of similar self-reported ethnicity (86, 9, and 5%, respectively).

The study protocol was approved by the institutional ethics committee in each UKPDS center. All recruited patients gave informed consent to participation. After an initial 3-month run-in period of treatment with diet alone, the patients were randomized according to the UKPDS protocol (12). Those allocated to remain on treatment with diet alone comprised the conventional glucose control group and those randomized to sulphonylurea, insulin, or metformin (in obese patients only) comprised the intensive glucose control group. Patients were seen every 3 months in UKPDS clinics.

Clinical and biochemical data were collected at regular 3-month visits as described previously (9,14). HbA_{1c} was measured annually by high-performance liquid chromatography (Diamat Auto-

mated Glycosylated Haemoglobin Analyser; Bio-Rad, Hemel Hempstead, U.K.) aligned to the Diabetes Control and Complications Trial with a normal range of 4.5–6.2%. β-cell function and insulin sensitivity were derived (15) using the homeostasis model assessment.

Data analysis

Statistical analyses were performed using SAS software (SAS Institute, Cary, NC) (16). All analyses were by intention to treat. Data are reported as mean (±1 SD), geometric mean (±1 SD interval), median (interquartile range), or percentages. Changes in variables at 3, 6, and 9 years are expressed relative to the value at randomization as mean (confidence interval). Comparison of multiple means was by analysis of variance with Scheffe's test for contrasts, given the number of comparisons. Multiple linear regression analysis was performed to assess associations between self-reported ethnicity and changes in FPG, HbA_{1c}, lipid profiles, and blood pressure. Analysis of covariance was used to adjust for ethnic differences in potential confounding variables. Plasma insulin is not included in the follow-up analysis because some patients were randomized to insulin treatment. A two-tailed level of significance of $P < 0.01$ was used throughout.

RESULTS

Patient characteristics

Table 1 shows patient details at randomization by self-reported ethnic group. The IA patients were significantly younger, included more men, and had a lower mean BMI than WC and AC patients ($P < 0.001$). AC patients had the highest HbA_{1c} levels and the lowest plasma insulin levels ($P < 0.01$) as well as the highest HDL cholesterol concentrations ($P < 0.0001$ vs. WC and IA patients). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were lowest in IA patients, who were also significantly less likely to be hypertensive (blood pressure >160 mmHg systolic or >90 mmHg diastolic in untreated patients) or to be taking anti-hypertensive therapy ($P < 0.0001$).

Run-in period

During the dietary run-in period, significant reductions in body weight, FPG, and HbA_{1c} occurred in all groups. After adjusting for age, sex, and BMI at diagnosis, a greater decrease in body weight oc-

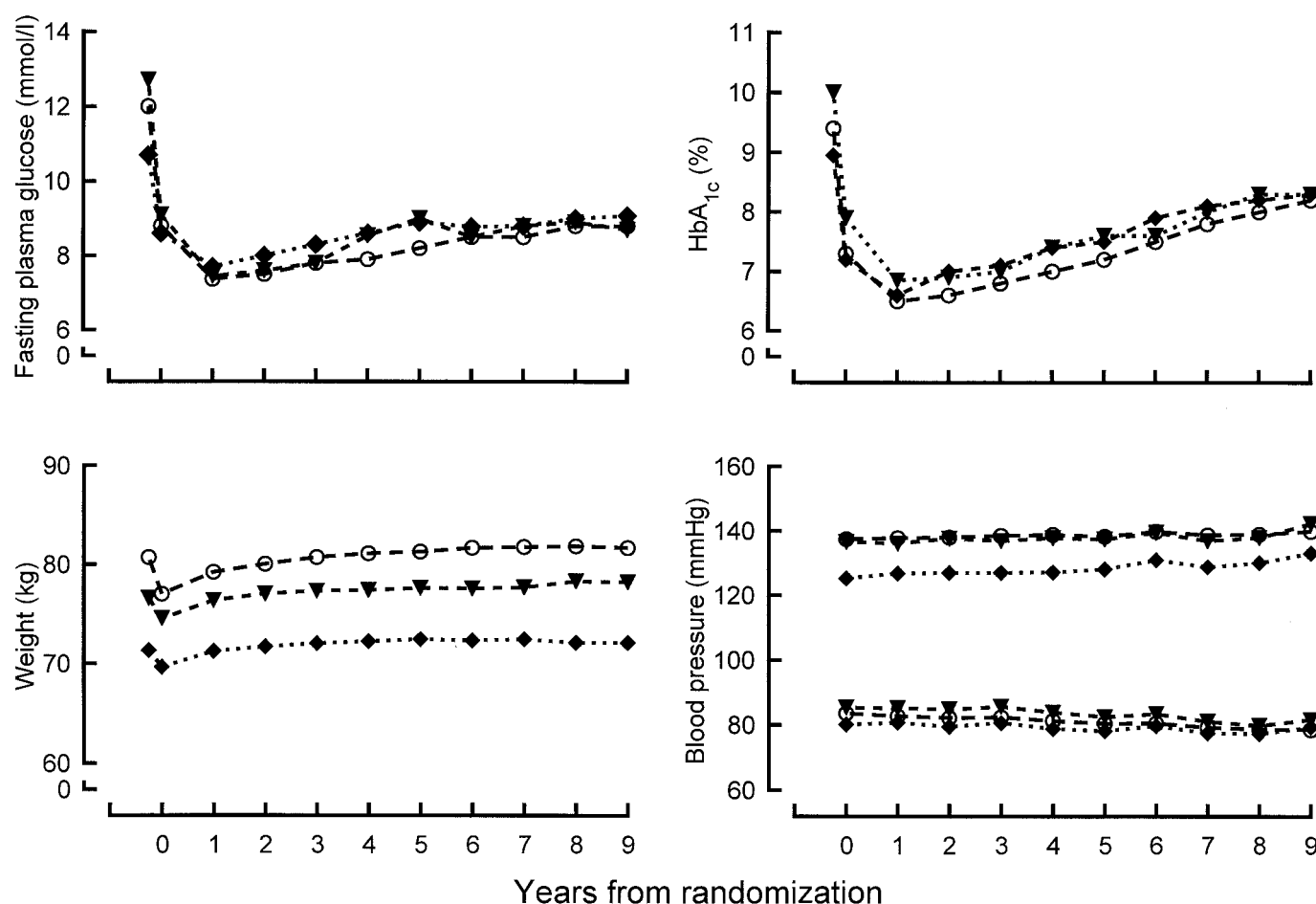


Figure 1—Unadjusted cross-sectional median FPG, HbA_{1c}, mean body weight, and mean SBP and DBP in WC (○), AC (▼), and IA (◆) patients at diagnosis, at randomization (after a 3-month dietary run-in, time 0), and at yearly intervals over 9 years.

curring in WC patients (mean 3.7 kg [99% CI 3.5, 3.9] or 4.6% of baseline) than in AC patients (mean 2.1 kg [1.5, 2.6] or 2.7% of baseline) and IA patients (mean 1.8 kg [1.3, 2.4] or 2.5% of baseline; $P < 0.00001$). IA patients showed least reduction in FPG compared with AC and WC patients (mean 1.8 mmol/l [1.3 and 2.3] vs. 2.7 mmol/l [2.2 and 3.2] and 2.2 mmol/l [2.1 and 2.4], respectively; $P = 0.002$), but there were no significant differences between the groups for changes in HbA_{1c} or lipid levels.

Prospective data

Proportions of patients (Table 1) allocated to different blood glucose-lowering therapies were similar by ethnic group at randomization ($P = 0.28$) and after 9 years ($P = 0.33$); ~25% of patients were allocated to treatment by diet, ~33% of patients were treated with insulin, and the remainder were treated with sulfonylurea

or, in the case of overweight patients, metformin. Unadjusted values for glycaemia, weight, blood pressure, and lipid levels during the first 9 years of diabetes are shown in Figs. 1 and 2, and the changes are summarized in Table 2.

Body weight increased significantly more in WC patients than in IA or AC patients ($P < 0.001$). Changes in both FPG and HbA_{1c} were similar across the groups over 9 years. SBP increased consistently in all groups. By contrast, DBP decreased, with significantly greater absolute reduction in DBP in both WC and AC patients compared with IA patients ($P < 0.01$). The increase in HDL cholesterol was greater in AC patients at 9 years than in the other groups ($P < 0.001$).

Changes over time were reanalyzed after adjusting for significant differences in age, sex, BMI, and baseline values, as well as changes in body weight during follow-up and treatment allocation.

Changes in SBP and DBP were adjusted for concurrent antihypertensive therapy. Approximately 25% of patients were included in the UKPDS blood pressure control study (17). Randomization of blood pressure-lowering therapies was similar across ethnic groups ($P = 0.78$); however, fewer IA patients participated (10 vs. 24 and 22% of WC and AC patients, respectively; $P < 0.0001$). Fewer IA patients were taking antihypertensive medications during follow-up (29 vs. 42 and 47% of WC and AC patients, respectively, at 9 years; $P < 0.0001$).

Adjusted changes at 3, 6, and 9 years are summarized in Figs. 3 and 4. Changes in FPG showed no significant differences between ethnic groups. There was a reduction from baseline at 3 years and then a consistent, progressive rise to 9 years. A similar pattern was observed for HbA_{1c}, but the reduction at 3 years was significantly greater in WC patients compared

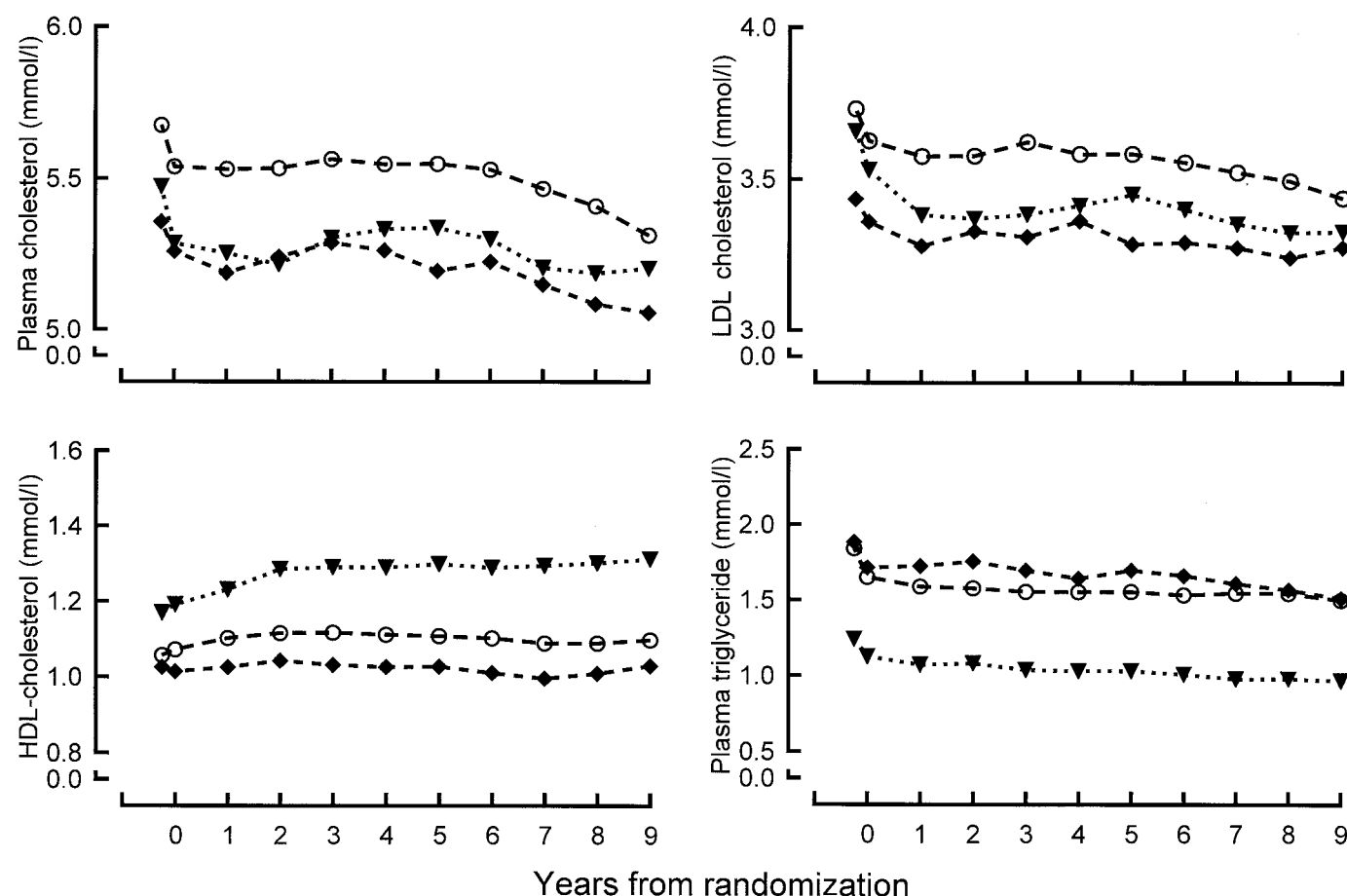


Figure 2—Unadjusted cross-sectional mean plasma lipid profiles in WC (○), AC (▼), and IA (◆) patients at diagnosis, at randomization (after a 3-month dietary run-in, time 0), and at yearly intervals over 9 years.

with AC and IA patients ($P < 0.009$). These findings were confirmed in the cohort of patients with complete data for FPG and HbA_{1c} over 9 years (data not shown). To investigate group-specific glycemic responses to different therapies,

an analysis of variance of both FPG and HbA_{1c} testing for interactions between self-reported ethnicity and treatment was performed. No interactions were observed at 3, 6, or 9 years ($P > 0.18$).

Adjusted changes in blood pressure

are summarized in Fig. 3. There were no significant differences for change in SBP between ethnic groups at 3 or 6 years, but AC patients had a significantly greater increase in SBP at 9 years compared with WC patients ($P = 0.002$). In all groups,

Table 2—Unadjusted mean (99% CIs) for changes in variables over 9 years by self-reported ethnic group

	WC	AC	IA
n	2,015	222	224
Δ Body weight (kg)	5.0 (4.7 to 5.4)	3.0 (2.0 to 4.0)†	2.5 (1.5 to 3.5)†
Δ Body weight as % of weight at randomization	7.8 (6.8 to 8.8)	5.3 (2.4 to 8.2)	4.7 (1.8 to 7.6)
Δ BMI (kg/m ²)	1.97 (1.79 to 2.15)	1.33 (0.79 to 1.87)†	1.12 (0.58 to 1.65)†
Δ FPG (mmol/l)	−0.66 (−0.95 to −0.37)	−0.89 (−1.77 to −0.01)	0.06 (−0.81 to 0.94)
Δ HbA _{1c} (%)	0.62 (0.45 to 0.78)	0.47 (−0.03 to 0.98)	1.11 (0.61 to 1.62)
Δ SBP (mmHg)	3.2 (1.9 to 4.6)	5.6 (1.7 to 9.6)	7.6 (3.6 to 11.5)
Δ DBP (mmHg)	−4.7 (−5.4 to −3.9)	−3.2 (−5.5 to −0.9)	−1.3 (−3.5 to 1.0)*
Δ Plasma total cholesterol (mmol/l)	−0.17 (−0.24 to −0.10)	−0.11 (−0.32 to 0.11)	−0.24 (−0.46 to −0.02)
Δ Plasma LDL cholesterol (mmol/l)	−0.15 (−0.21 to −0.08)	−0.19 (−0.39 to 0.01)	−0.13 (−0.33 to 0.08)
Δ Plasma HDL cholesterol (mmol/l)	0.03 (0.01 to 0.05)	0.12 (0.06 to 0.18)†	0.01 (−0.05 to 0.07)‡
Δ Plasma triglyceride (mmol/l)	−0.07 (−0.17 to 0.03)	−0.12 (−0.42 to 0.18)	−0.15 (−0.46 to 0.16)

* $P < 0.01$ vs. WC; † $P < 0.001$ vs. WC; ‡ $P < 0.001$ vs. AC.

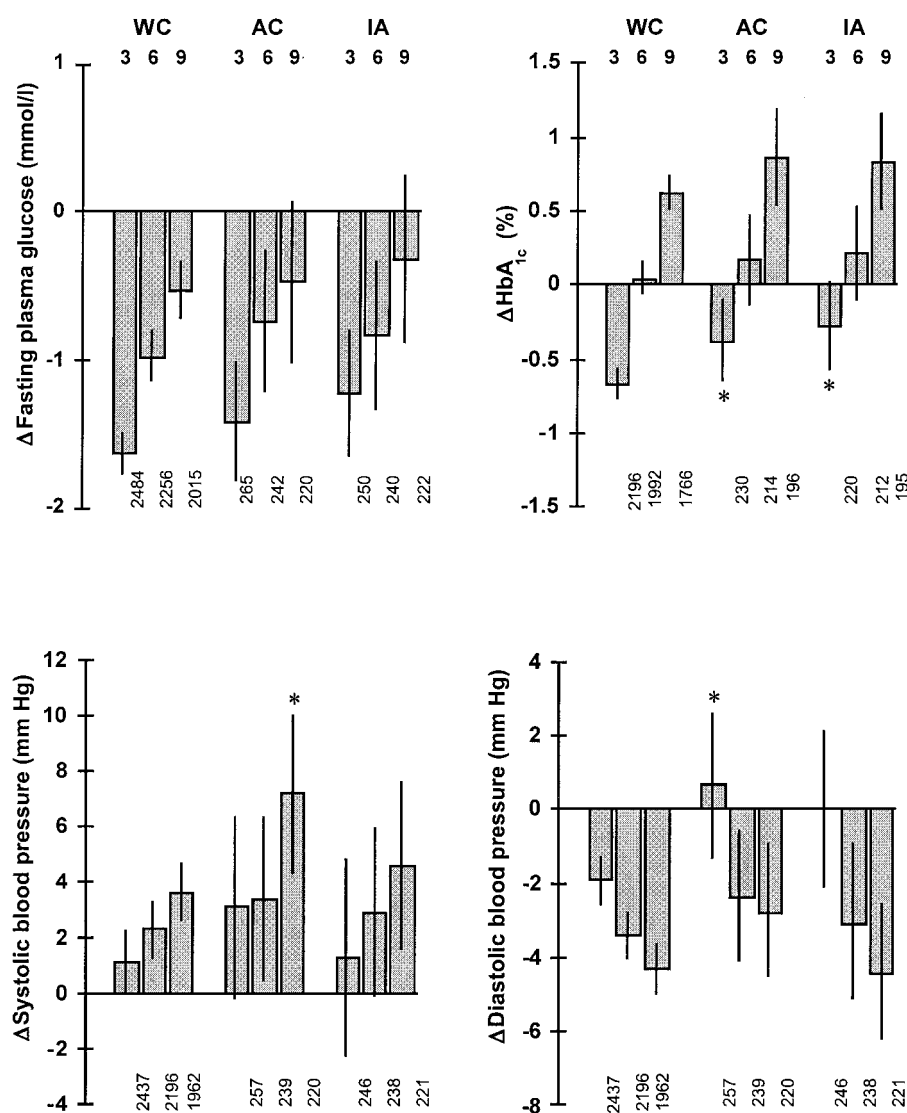


Figure 3—Mean (bars) and 99% CIs (lines) for cross-sectional changes in FPG, HbA_{1c}, SBP, and DBP from randomization to 3, 6, and 9 years in WC, AC, and IA patients. Data have been adjusted by analysis of covariance with Scheffe's test for contrasts adjusted for age in 10-year categories, sex, baseline value, BMI at baseline, and allocated blood glucose-lowering treatment, as well as change in weight over time. For SBP and DBP, adjustment has also been made for actual antihypertensive therapy. Numbers of patients at each time and in each group are shown below each bar. *Changes in AC and IA patients that were significantly different from those in WC patients at the same time point ($P < 0.01$).

mean SBP increased progressively over time. Apart from a significant difference in DBP between WC and AC patients at 3 years ($P < 0.001$), quantitative changes over 9 years were similar across the ethnic groups (see Fig. 3). The pattern of change in mean DBP was the inverse of SBP. Separate analyses of the cohort of patients with complete blood pressure data over 9 years were consistent with these findings.

Adjusted changes in lipid profiles are summarized in Fig. 4. Changes in total

cholesterol and LDL cholesterol were parallel; no significant differences were seen between the groups, except for change in LDL cholesterol at 3 years in WC patients compared with AC patients ($P = 0.006$). In WC patients, there was an initial increase in both total and LDL cholesterol at 3 years and a significant progressive reduction thereafter, whereas in both AC and IA patients, there was no initial increase and a subsequent decrease between 3 and 9 years.

Highly significant differences between adjusted changes in HDL cholesterol and triglyceride in AC patients compared with both WC and IA patients at each time point (both $P < 0.001$) were confirmed in the cohort with complete 9-year data. HDL cholesterol increased progressively in AC patients on annual samples taken between randomization and year 3 (Fig. 2), mean 0.16 mmol/l (95% CI 0.12–0.20), and this level was maintained thereafter (Figs. 2 and 4). WC patients had a similar, but proportionately lower, mean increase in HDL cholesterol of 0.05 mmol/l (0.04–0.07) at 6 months after randomization; this level was also maintained. IA patients showed no significant changes in HDL cholesterol from baseline. Plasma triglyceride in WC patients was close to baseline throughout (Fig. 4). In IA patients at 3 years, there was an increase in plasma triglyceride ($P < 0.001$ vs. WC patients) followed by a return to baseline. In AC patients, plasma triglyceride decreased by 0.3 mmol/l (0.1–0.5) at 3 years and was maintained subsequently ($P < 0.001$ vs. WC and IA patients). Fewer than 2% of patients were taking lipid-lowering medications during follow-up. No significant difference in the prevalence of such therapy was seen between ethnic groups at any time ($P > 0.18$).

In overweight patients, unadjusted changes in variables of interest were parallel to those summarized in Table 2 for the whole group. Body weight increased most in WC patients: mean 4.2 kg (95% CI 3.4, 4.9) vs. 2.6 kg (0.3, 4.8) and 1.7 kg (1.2, 4.5) in AC and IA patients, respectively ($P < 0.01$). There was a significantly greater increase in HDL cholesterol in AC patients, 0.13 mmol/l (0.04, 0.22), compared with both WC patients, 0.00 mmol/l (–0.03, 0.03), and IA patients, 0.00 mmol/l (–0.11, 0.12) mmol/l ($P < 0.001$). This pattern was also seen after adjustment of data, as for the whole group and for the 9-year cohort (data not shown).

CONCLUSIONS— This analysis of UKPDS data gives a detailed prospective evaluation of the relationship among self-reported ethnicity, metabolic variables, and blood pressure in type 2 diabetes. Previous studies, including both newly diagnosed patients (9) and those with longer duration of disease (2,18–21), have assessed cross-sectional data and

found ethnic differences in vascular risk factors. However, the UKPDS data allow a prospective comparison by self-reported ethnicity of newly diagnosed patients randomly allocated to different therapies and followed for a significant period of time. This analysis shows that there are important ethnic differences in body weight, lipid profiles, and blood pressure, but not glycemic control, during the first 9 years after diagnosis of type 2 diabetes.

The significant differences in age, sex, and BMI among the ethnic groups reported in the original cross-sectional study of UKPDS recruits (9) were replicated in the present analysis (Table 1). Adjustment for these baseline variables has allowed the investigation of whether ethnicity per se, as well as treatment allocation, had an independent influence on changes over time in metabolic control and blood pressure. Although WC patients had the greatest weight loss during the run-in period, their weight increase after randomization was significantly more than in the other two groups. Therefore, adjustment for change in weight was included.

Consistent with previous data (9), IA patients were the most insulin-resistant but had the greatest pancreatic β -cell function, whereas AC patients were the most insulin-sensitive but had the least insulin secretory capacity. Nevertheless, changes in FPG and HbA_{1c} over 9 years of follow-up were generally similar after adjusting for age, sex, BMI, baseline value, treatment allocation, and change in body weight (Fig. 3). An earlier analysis of 6-year data found that AC patients treated with metformin had the greatest reduction in HbA_{1c} (22), but this was not replicated in the larger 9-year data set after adjusting for potential confounders. These data strongly suggest that progression of glycemia in type 2 diabetes is independent of ethnicity.

Mean SBP increased similarly in all ethnic groups, although there was a greater increase in AC patients compared with WC patients at 9 years. Mean diastolic levels decreased progressively; there was a greater reduction in WC patients compared with AC patients at 3 years. The widening pulse pressure may represent a combination of ageing and loss of vascular compliance through the development of macrovascular disease. Although fewer IA patients were hypertensive, changes in blood pressure were

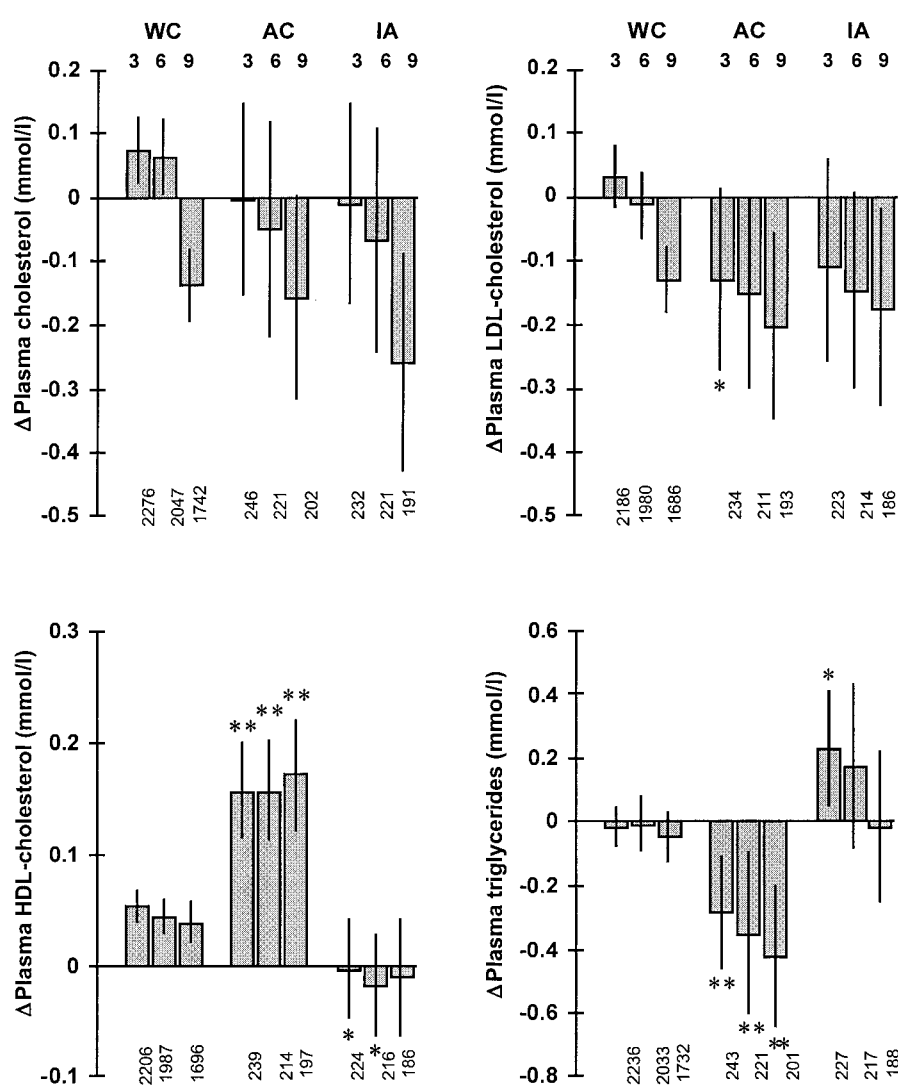


Figure 4—Mean (bars) and 99% CIs (lines) for cross-sectional changes in plasma lipid profiles from randomization to 3, 6, and 9 years in WC, AC, and IA patients. Data have been adjusted by analysis of covariance for age in 10-year categories, sex, baseline value, BMI at baseline, allocated blood glucose-lowering treatment, and change in weight over time. Numbers of patients at each time and in each group are given below the bars. *Significant changes in AC and IA greater than WC patients ($P < 0.01$); **changes in AC patients significantly different ($P < 0.001$) from WC or IA.

similar. The proportion of untreated hypertensive patients in all groups decreased by ~50%, and an increasing percentage of treated patients were prescribed one or more antihypertensive drug.

Small but generally beneficial changes in total and LDL cholesterol were noted during the first 9 years after diagnosis of diabetes. These changes were unlikely to be related to lipid-lowering therapy, because fewer than 2% of patients ever received it. However, progressively favorable changes in diet, including reduction in saturated fat intake, have

been observed in contemporaneous studies (23). Consistent with a number of previous cross-sectional studies in diabetes (9,24,25) and in the general population (26,27), AC patients had the lowest baseline plasma triglyceride and highest HDL cholesterol concentrations. These differences became more marked during the first 3 years of diabetes and then plateaued for no discernible reason.

Several studies have demonstrated lower cardiovascular mortality among AC patients with type 2 diabetes compared with WC patients (20,28,29). In UKPDS patients (28), the hazard ratio for fatal or

nonfatal myocardial infarction remained significantly lower for AC patients (0.4 [95% CI 0.2–0.7]) after adjusting for conventional risk factors, including lipid parameters, at baseline. It is possible that the sustained increase in HDL cholesterol and reduction in plasma triglyceride observed in AC patients contributes to the reduced incidence of cardiovascular disease (28). A greater, if transient, reduction in LDL cholesterol was observed in AC patients compared with WC patients in the present study and might also have contributed. Based on previous UKPDS data from WC patients (30), the mean difference of >0.1 mmol/l in HDL cholesterol between AC and WC patients seen throughout might equate to a $>15\%$ reduction in coronary risk.

By contrast, the similarity between metabolic and blood pressure profiles over 9 years in WC and IA patients shown seems contrary to the well-documented increased incidence of renal disease in IA patients with type 2 diabetes (10,31). Because IA patients start from significantly lower baseline blood pressure levels, the percentage of patients treated for hypertension was the lowest of the groups at each time point. However, considering the apparent propensity for progressive diabetic nephropathy among IA patients, the need for aggressive lowering of blood glucose and blood pressure may be greater than for other ethnic groups.

The present study did not consider possible ethnic differences in management factors, such as clinic attendance, compliance with treatment, or possible selection bias. Nevertheless, considering the similarities in FPG and HbA_{1c} profiles in all groups across the 9 years of follow-up, it is unlikely that the effectiveness of primary and specialist care and adherence to drug regimens were different. Therefore, although the ethnic differences in blood pressure and lipid profiles found during the first 9 years after diagnosis of type 2 diabetes could have potential clinical implications, our data suggest that the blood glucose-lowering therapies included in the UKPDS can be used without reference to ethnicity.

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APPENDIX

Participating centers:

The Diabetes Trials Unit, Oxford Centre for Diabetes, Endocrinology and Metabolism, Oxford; Fremantle Hospital, University of Western Australia; Radcliffe Infirmary, Oxford; Royal Infirmary, Aberdeen; University Hospital, Birmingham; St. George's Hospital, Hammersmith Hospital, and Whittington Hospital, London; City Hospital and Royal Victoria Hospital, Belfast; North Staffordshire Royal Infirmary, Stoke-on-Trent; St. Helier Hospital, Carshalton; Norfolk and Norwich Hospital, Norwich; Lister Hospital, Stevenage; Ipswich Hospital, Ipswich; Ninewells Hospital, Dundee; Northampton General Hospital, Northampton; Torbay Hospital, Torbay; Peterborough General Hospital, Peterborough; Scarborough Hospital, Scarborough; Derbyshire Royal Infirmary, Derby; Manchester Royal Infirmary, Manchester; Hope Hospital, Salford; Leicester General Hospital, Leicester; Royal Exeter & Devon Hospital, Exeter, U.K.

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