Nonfasting Serum Glucose and Insulin Concentrations and the Risk of Stroke

S. Goya Wannamethee, PhD; Ivan J. Perry, MD, PhD; A. Gerald Shaper, FRCP

Background and Purpose—Type 2 diabetes is an established risk factor for stroke, but the relations between asymptomatic hyperglycemia, hyperinsulinemia, and stroke incidence remain uncertain. We have examined the relationship between established diabetes, nonfasting serum glucose and serum insulin concentrations, and subsequent risk of stroke.

Methods—We performed a prospective study of 7735 men aged 40 to 59 years drawn from general practices in 24 British towns. Men with missing serum glucose values (n=50) and men on insulin injection (n=36) were excluded, leaving 7649 men available for analysis. Baseline nonfasting serum was analyzed for insulin with a specific enzyme-linked immunosorbent assay method in 18 of the 24 towns (n=5663 men).

Results—During the mean follow-up period of 16.8 years, there were 347 stroke cases (fatal and nonfatal) in the 7649 men. Men who developed diabetes during follow-up (n=320) and men with established type 2 diabetes at screening (n=98) both showed significantly increased risk of stroke, even after adjustment for cardiovascular risk factors, including blood pressure (adjusted relative risk [RR], 2.27; 95% CI, 1.23 to 4.20; RR, 2.07; 95% CI, 1.44 to 2.98, respectively). In men with no diagnosed diabetes at screening (n=7551), risk of stroke was increased significantly only in the top 2.5% of the nonfasting glucose distribution (≥8.2 mmol/L), and this persisted even after adjustment for cardiovascular risk factors, including hypertension (RR, 1.86; 95% CI, 1.11 to 3.13). Exclusion of the 320 men who developed diabetes during follow-up attenuated this risk so that it was no longer significant (RR, 1.56; 95% CI, 0.83 to 2.91). In the 5567 men with insulin measurements and no diagnosis of diabetes at screening, a J-shaped relationship was seen between nonfasting insulin and risk of stroke. Risk was significantly raised in the first quintile and in the fourth quintile and above compared with the second quintile, with all findings of marginal significance. Part of the increased risk at higher levels of insulin was due to men who developed diabetes in the follow-up period.

Conclusions—This study confirms the importance of established type 2 diabetes as an independent risk factor for stroke. The increased risk of stroke seen in hyperglycemic subjects and those with elevated serum insulin levels at screening reflected to some extent the high proportion of men who subsequently developed diabetes. (Stroke. 1999;30:1780-1786.)

Key Words: diabetes mellitus ■ glucose ■ insulin ■ stroke

It is well established that type 2 diabetes (non–insulin-dependent diabetes) is associated with a significantly increased risk of stroke,1–7 and several studies have indicated the excess risk to be independent of blood pressure.2,3,5,7,8 The development of type 2 diabetes is preceded by a prolonged period of insulin resistance with compensatory hyperinsulinemia and a gradual onset of hyperglycemia. Both hyperglycemia and hyperinsulinemia have been shown to be independently associated with increased risk of coronary heart disease (CHD).1,9–16 The role of hyperglycemia and hyperinsulinemia as risk factors for stroke is less well documented. Although some studies have shown hyperglycemia to be independently associated with risk of stroke in nondiabetics,1,3,7 some have found the association only in women,17 some have found no significant association in multivariate analysis,18 and others have found no association.19,20 The onset of diabetes may occur several years before its clinical diagnosis, and the issue of whether the increased risk of stroke in subjects with hyperglycemia seen in some studies reflects unrecognized diabetes or the early onset of diabetes has not been established. Much less is known about the relationship between insulin and stroke, and data from the few prospective studies linking insulin and stroke have been based on small numbers and have yielded inconsistent results.5,21,22 We have investigated the relationship between nonfasting hyperglycemia and hyperinsulinemia and risk of stroke events in a large prospective study of 7735 men followed up for an average of 16.8 years (the British Regional Heart Study) in whom there were >300 stroke cases. Information on the diagnosis of
diabetes at baseline and on incident cases during follow-up enables us to assess whether any relationships between hyperglycemia, hyperinsulinemia, and stroke are due to the development of clinical diabetes.

**Subjects and Methods**

The British Regional Heart Study is a large prospective study of cardiovascular disease comprising 7735 men aged 40 to 59 years selected from the age/sex registers of one group general practice in each of 24 towns in England, Wales, and Scotland. The criteria for selecting the town, the general practice, and the subjects as well as the methods of data collection have been reported. The overall response rate was 78%. Research nurses administered to each man a standard questionnaire that included questions on smoking habits, alcohol intake, physical activity, and medical history. The men were asked whether a physician had ever told them that they had angina or myocardial infarction (heart attack, coronary thrombosis), stroke, diabetes, and a number of other disorders. Several physical measurements were made, including height and weight, and blood samples (nonfasting) were taken for measurement of biochemical and hematological variables. All samples were kept at 4°C while being transferred overnight to the Wolfson Research Laboratories, Queen Elizabeth Hospital, Birmingham, UK, where estimations were completed by noon on the following day. Aliquots of serum from the men in the 7th to 24th towns visited (n=5663) were stored at −20°C.

Classification methods for smoking status, alcohol consumption, and physical activity have been reported. The men were classified according to their current smoking status into 6 groups: those who had never smoked cigarettes, ex–cigarette smokers, and 4 groups of current smokers (1 to 19, 20 to 21, 21 to 39, and ≥40 cigarettes per day). Heavy drinking was defined as drinking ≥6 units (1 UK unit=8 to 10 g alcohol) daily or on most days in the week. A physical activity score was derived for each man on the basis of frequency and type of activity, and the men were grouped into 6 broad categories on the basis of their total score. Body mass index (BMI), calculated as weight/height², was used as an index of relative weight.

**Blood Pressure**

The London School of Hygiene sphygmomanometer (a random-zero device) was used to measure blood pressure twice in succession with the subjects seated and with the arm supported on a cushion. The mean of the 2 readings was used in the analysis, and all blood pressure readings were adjusted for observer variation within each town. The men were also asked whether they were on regular antihypertensive treatment.

**Insulin and Glucose Measurement**

**Glucose**

Glucose was analyzed with a commercially available automated analyzer (Technicon SMA 12/60). Diurnal variation in serum glucose levels was modest, and no adjustments were made for the diurnal variation.

**Serum Insulin**

Serum insulin concentration was determined by a 2-site enzyme-linked immunosorbent assay with the use of commercially available monoclonal antibodies raised against human insulin (Novo Nordisk A/S) that do not cross-react with proinsulin. Analyses were performed in the Department of Medicine, University of Newcastle upon Tyne, UK, on nonfasting samples that had been stored at −20°C for 13 to 15 years. In this laboratory, no change in insulin levels was detected in repeated assays of 34 samples, stored at −20°C over an 8-year period (mean difference, 0.19 mU/L; P=0.5). There were significant diurnal variations in serum insulin levels, related presumably to meals, and adjustments were therefore made for the marked diurnal variation in serum insulin.

**Preexisting CHD, Stroke, and Diabetes**

The men were asked whether a physician had ever told them that they had angina or myocardial infarction (heart attack, coronary thrombosis), stroke, and a number of other disorders. The World Health Organization (WHO) (Rose) chest pain questionnaire was administered to all men at the initial examination, and a 3–orthogonal lead ECG was recorded at rest.

**Previous Stroke**

Evidence of a previous stroke was determined by the subject’s recall of such a diagnosis made by a physician. There were 52 such men in the study. They were not excluded from follow-up, and adjustments for preexisting stroke were made in Tables 1, 2, and 4.

**Coronary Heart Disease**

The men were separated into 3 groups according to the evidence of CHD at screening, as follows: (1) men with no evidence of CHD on WHO chest pain questionnaire or ECG and no recall of a physician’s diagnosis of CHD (n=5757); (2) men with evidence suggesting CHD short of a definite myocardial infarction; this group contained those with ECG evidence of possible or definite myocardial ischemia or possible myocardial infarction (asymptomatic), those with angina or a possible myocardial infarction on WHO (Rose) chest pain questionnaire, or those with recall of a physician’s diagnosis of angina (symptomatic) (n=1508); and (3) men with a previous definite myocardial infarction on ECG or who recalled a physician’s diagnosis of a myocardial infarction (“heart attack”) (n=423).

Men with preexisting CHD were categorized in groups 2 and 3 combined.

**Diabetes**

Diabetes mellitus prevalence at screening was based on recall of a physician’s diagnosis of the condition (n=121). Eighty-five men recalled non–insulin-dependent diabetes, of whom 1 subject had no glucose measurement and 36 men were on insulin injections.

**Follow-Up**

All men were followed up for all-cause mortality and for cardiovascular morbidity. All cardiovascular events occurring in the period up to December 1995 are included in the study, for an average follow-up of 16.75 years (range, 15.5 to 18.0 years), and follow-up has been achieved for 99% of the cohort. Information on death was collected through the established “tagging” procedures provided by the National Health Service registers in Southport (England and Wales) and Edinburgh (Scotland). All subjects resident in Great Britain are entered on a National Health Service Central Register. Those involved in research program can be tagged or marked on the register for the purpose of informing the investigator of any emigration, death, or change of registration site that might take place, providing that consent has been obtained. Nonfatal stroke events were those that produced a neurological deficit that was present >24 hours. Evidence regarding such episodes was obtained by reports from general practitioners, by approximately biennial reviews of the patients’ notes through to the end of the study period, and from personal questionnaires to surviving subjects at years 5 and 12 after the initial examination. Fatal stroke episodes were those coded on the death certificate as International Classification of Diseases codes 430 to 438. All death certificates in which it appeared that coding for stroke was not appropriate, or in which stroke was not the attributed cause of death certificate as stroke were reviewed. No information on the type of stroke was available.

**Identification of Incident Cases of Diabetes**

New cases of type 2 diabetes were ascertained by means of (1) a postal questionnaire sent to the men at year 5 of follow-up for each individual (98% response rate), (2) systematic reviews of primary care records in 1990, 1992, and 1994 looking specifically for cases of non-insulin-dependent diabetes mellitus, (3) an additional questionnaire to 6483 surviving members of the cohort resident in Britain in 1992 (91% response rate), and (4) review of all death certificates.
TABLE 1. Nonfasting Blood Glucose and Age-Adjusted Rates per 1000 Person-Years and Adjusted RR of Stroke in 7551 Men (336 Stroke Cases) With No History or Early Diagnosis of Diabetes

<table>
<thead>
<tr>
<th>Blood Glucose, mmol/L</th>
<th>n</th>
<th>Cases</th>
<th>Age-Adjusted Rate/1000 p-y</th>
<th>Adjusted RR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>&lt;4.9</td>
<td>1473</td>
<td>56</td>
<td>2.6</td>
<td>1.00</td>
</tr>
<tr>
<td>4.9–5.1</td>
<td>1770</td>
<td>77</td>
<td>2.9</td>
<td>1.12 (0.79, 1.58)</td>
</tr>
<tr>
<td>5.2–5.5</td>
<td>1276</td>
<td>45</td>
<td>2.3</td>
<td>0.89 (0.60, 1.32)</td>
</tr>
<tr>
<td>5.6–6.0</td>
<td>1497</td>
<td>75</td>
<td>3.2</td>
<td>1.22 (0.86, 1.73)</td>
</tr>
<tr>
<td>6.1–7.1</td>
<td>1141</td>
<td>54</td>
<td>3.1</td>
<td>1.20 (0.83, 1.75)</td>
</tr>
<tr>
<td>7.2–8.1</td>
<td>208</td>
<td>8</td>
<td>2.6</td>
<td>0.88 (0.42, 1.85)</td>
</tr>
<tr>
<td>≥8.2</td>
<td>186</td>
<td>21</td>
<td>7.8</td>
<td>2.70 (1.63, 4.45)</td>
</tr>
</tbody>
</table>

Values in parentheses are 95% CIs. p-y indicates person-years; A, age-adjusted; B, adjusted for age, smoking, BMI, alcohol intake, physical activity, preexisting CHD/stroke, antihypertensive treatment, and systolic blood pressure; and C, adjusted for B and excluding 320 men who developed diabetes during follow-up.

for any mention of diabetes. In the primary care record review, the records of each study participant (including discharge letters from hospitals) were examined for a number of specific diagnoses, including diabetes. Inconsistencies between the questionnaire data and the clinical records were resolved by means of further review of primary care records. A diagnosis of diabetes was not accepted on the basis of questionnaire data unless confirmed in the primary care records.

Statistical Methods
The Cox proportional hazards model was used to assess the independent contributions of serum glucose to the risk of stroke and to obtain the RRs adjusted for age and other risk factors.30 Age, systolic blood pressure, and BMI were fitted as continuous variables. Smoking (6 levels), physical activity (6 levels), alcohol intake (5 levels), diabetes (yes/no), preexisting stroke (yes/no), use of antihypertensive treatment (yes/no), and preexisting CHD on questionnaire/ECG (3 levels) were fitted as categorical variables. Direct standardization was used to obtain age-adjusted rates per 1000 person-years, with the study population used as the standard.

Results
All men on insulin injections for diabetes were excluded from the analysis (n=36). During the mean follow-up period of 16.8 years (range, 15.5 to 18.0 years), there were 347 major stroke events (fatal and nonfatal) in the 7649 men with data on blood glucose, a rate of 3.0/1000 person-years.

Serum Glucose and Stroke Risk
Men with history of type 2 diabetes at screening (n=84) and those diagnosed as diabetic in the calendar year of screening (n=14) were excluded from the analysis examining serum glucose and risk of stroke. The remaining men were initially divided into approximate fifths of the glucose distribution. Because of the possibility that risk is only raised at the upper extreme of the distribution,14 men in the top 95th to 97.5th and >97.5th percentiles of the glucose distribution were separated, and 7 groups were used (Table 1). Stroke risk (age adjusted) was raised significantly only in men at or above the 97.5 percentile of the distribution (≥8.2 mmol/L). Adjustment for potential confounders, eg, lifestyle characteristics, preexisting disease, and blood pressure, attenuated the relationship, but hyperglycemic subjects (≥8.2 mmol/L) still showed a significantly increased risk (category B in Table 1). Exclusion of 320 men who developed diabetes during follow-up reduced the increased risk in the hyperglycemics further (category C in Table 1), and the difference was no longer significant (adjusted RR, 1.56; 95% CI, 0.83 to 2.91).

Men With Diagnosed Type 2 Diabetes
The men were divided into 4 groups: (1) no diabetes: serum glucose <8.2 mmol/L with no diagnosed type 2 diabetes at screening or during follow-up; (2) hyperglycemic only (>97.5 percentile; ≥8.2 mmol/L): no diagnosis of type 2 diabetes at entry or during follow-up; (3) men who developed type 2 diabetes during the mean 16.8-year follow-up (range, 15.5 to 18.0 years); and (4) men with diagnosed type 2 diabetes at baseline or diagnosed in year of entry (n=98).

TABLE 2. Age-Adjusted Rates per 1000 Person-Years and Adjusted RR of Stroke in 7649 Men Classified With No Diabetes, Hyperglycemia, and Type 2 Diabetes

<table>
<thead>
<tr>
<th>No. of Strokes</th>
<th>Age-Adjusted Rates/1000 p-y</th>
<th>Adjusted RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>No diabetes (n=7093)</td>
<td>289</td>
<td>2.7</td>
</tr>
<tr>
<td>Hyperglycemia (n=138)</td>
<td>13</td>
<td>6.0</td>
</tr>
<tr>
<td>Developed diabetes (n=320)</td>
<td>34</td>
<td>6.4</td>
</tr>
<tr>
<td>Preexisting diabetes (n=98)</td>
<td>11</td>
<td>7.3</td>
</tr>
</tbody>
</table>

Values in parentheses are 95% CIs. p-y indicates person-years; A, age-adjusted; B, adjusted for age, smoking, BMI, alcohol intake, physical activity, preexisting CHD/stroke, and antihypertensive treatment; and C, adjusted for above and, in addition, for systolic blood pressure.
Table 2 shows the age-adjusted stroke rates per 1000 person-years and RRs for the 4 groups. Risk of stroke was significantly raised in men with type 2 diabetes at baseline and in those who developed type 2 diabetes during follow-up. In men who developed type 2 diabetes during follow-up, stroke was preceded by a diagnosis of type 2 diabetes in 17 of the 34 stroke cases, and 6 additional men were diagnosed as diabetic in the same year as the stroke event. Hyperglycemic men (≥97.5 percentile) who did not develop type 2 diabetes during the follow-up period also showed a significant increase in risk.

**Serum Glucose, Diabetes, and Blood Pressure and Insulin Levels**

Table 3 shows the mean level of BMI, serum glucose, systolic and diastolic blood pressure, and serum insulin levels for the 4 groups. Mean BMI and systolic pressure was significantly raised in hyperglycemic men and the 2 type 2 diabetes groups. Diastolic blood pressure was raised significantly only in the group of men who subsequently developed type 2 diabetes. Mean insulin levels were lowest in men without diabetes at screening or during the follow-up period and without hyperglycemia (≤8.2 mmol/L). They were highest in hyperglycemic men and intermediate in those who developed diabetes during follow-up or who were diabetic at screening.

**Adjustment for Systolic Blood Pressure**

The increased risk of stroke in the 2 type 2 diabetes groups persisted even after adjustment for confounders, including systolic blood pressure (Table 2). As noted earlier (Table 1), the increased risk in hyperglycemic subjects was attenuated and was no longer significant.

**Nonfasting Insulin and Risk of Stroke**

Insulin levels were available in 18 of the 24 towns, and analysis is confined to the 5567 men (248 cases) with data on insulin available and who had no diabetes at screening or diagnosis of diabetes in the calendar year of entry. The men were divided into quintiles of the insulin distribution, with men in the top 95th percentile further separated. Table 4 shows the age-adjusted rate per 1000 person-years and the adjusted RRs for the 6 insulin groups. A J-shaped relationship was seen between serum insulin and risk of stroke, with the lowest risk in the second quintile of the distribution. This group was used as the reference group. Thereafter, age-adjusted risk increased progressively. Adjustments for confounders (category B in Table 4) and systolic blood pressure (category C in Table 4) reduced the increased risk in the top 95th percentile, but the J-shaped relationship persisted, and a test for trend for the increasing risk from the 2nd quintile upward was of marginal significance (P=0.06). Exclusion of

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**Table 3. Mean BMI, Glucose, Systolic and Diastolic Blood Pressures, and Serum Insulin Levels by Presence of Hyperglycemia and Diagnosed Type 2 Diabetes**

<table>
<thead>
<tr>
<th></th>
<th>No Diabetes</th>
<th>Hyperglycemia</th>
<th>Developed Diabetes</th>
<th>Preexisting Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=7093)</td>
<td>(≥97.5 Percentile) (n=138)</td>
<td>(n=320)</td>
<td>(n=98)</td>
</tr>
<tr>
<td>Mean BMI, kg/m^2</td>
<td>25.4</td>
<td>26.0</td>
<td>27.7</td>
<td>27.0</td>
</tr>
<tr>
<td>Mean glucose, mmol/L</td>
<td>5.36</td>
<td>9.10</td>
<td>6.30</td>
<td>8.76</td>
</tr>
<tr>
<td>Mean SBP, mm Hg</td>
<td>144.5</td>
<td>159.4</td>
<td>152.2</td>
<td>154.1</td>
</tr>
<tr>
<td>Mean DBP, mm Hg</td>
<td>82.0</td>
<td>83.6</td>
<td>87.4</td>
<td>83.3</td>
</tr>
<tr>
<td>Mean insulin,* mU/L</td>
<td>11.9</td>
<td>35.9</td>
<td>19.7</td>
<td>15.3</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure.

*Insulin data available in 5637 men.

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**Table 4. Nonfasting Insulin and Age-Adjusted Rates per 1000 Person-Years and Adjusted RR of Stroke in 5567 Men With No History of Diabetes or Diagnosis in Calendar Year of Screening**

<table>
<thead>
<tr>
<th>Serum Insulin, mU/L</th>
<th>n</th>
<th>Cases</th>
<th>Age-Adjusted Rate/1000 p-y</th>
<th>Adjusted RR</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6.65</td>
<td>1113</td>
<td>53</td>
<td>3.3</td>
<td>1.42 (0.94, 2.15)</td>
<td>1.41</td>
</tr>
<tr>
<td>6.65–9.80</td>
<td>1118</td>
<td>39</td>
<td>2.3</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>9.81–14.46</td>
<td>1110</td>
<td>42</td>
<td>2.5</td>
<td>1.10 (0.71, 1.71)</td>
<td>1.16</td>
</tr>
<tr>
<td>14.47–23.15</td>
<td>1117</td>
<td>56</td>
<td>3.4</td>
<td>1.47 (0.98, 2.21)</td>
<td>1.51</td>
</tr>
<tr>
<td>23.16–46.59</td>
<td>827</td>
<td>42</td>
<td>3.5</td>
<td>1.51 (0.97, 2.32)</td>
<td>1.55</td>
</tr>
<tr>
<td>≥46.60</td>
<td>282</td>
<td>16</td>
<td>3.7</td>
<td>1.61 (0.90, 2.89)</td>
<td>1.63</td>
</tr>
</tbody>
</table>

Test for trend from quintile 2

P=0.04  P=0.04  P=0.06  P=0.15

Values in parentheses are 95% CIs; p-y indicates person-years; A, age-adjusted; B, adjusted for age, smoking, BMI, alcohol intake, physical activity, preexisting CHD/stroke, and antihypertensive treatment; C, adjusted for above and, in addition, for systolic blood pressure; and D, adjusted for C and excluding 222 men who developed diabetes during the follow-up of 17 years.
men who developed type 2 diabetes during follow-up made little difference to the increased risk in the lowest quintile (RR, 1.53; 95% CI, 1.00 to 2.33) but further reduced the risk in the higher levels of insulin concentration.

Discussion
It is well recognized that established diabetes mellitus is an important risk factor for the development of stroke,1–7 and this study confirms the positive relationship between established diabetes and risk of stroke. The risk of stroke in men who developed type 2 diabetes during follow-up was almost as high as in those with established diabetes at screening. There has been growing interest in the role of metabolic factors associated with the prediabetic state in the development of stroke. Hyperglycemia and hyperinsulinemia are both integral to the pathogenesis of type 2 diabetes, and both have been associated with increased risk of CHD,1,9–16 although the independent role of these factors has not been firmly established. The role of hyperglycemia and hyperinsulinemia as risk factors for stroke is even less certain.

Serum Glucose and Risk of Stroke
Previous studies that have examined the relationship between glucose intolerance or hyperglycemia and risk of stroke in nondiabetics have yielded inconsistent results.1,3,7,17–20 The Whitehall Study observed a significant increase in risk of stroke mortality in men in the 95th percentile of the 2-hour blood glucose distribution, independent of blood pressure and other cardiovascular risk factors.1 In the Honolulu Heart Study, a positive but nonsignificant relationship was seen between hyperglycemia and total stroke after adjustment for cardiovascular risk factors. When examined in relation to type of stroke, an independent relationship was seen between nonfasting glucose (top 10th decile) and thromboembolic stroke but not hemorrhagic stroke.7 In the pooled analysis of the Whitehall, Paris Prospective, and Helsinki Policemen studies, risk of stroke mortality was only significantly raised in subjects with 2-hour blood glucose at or above the 97.5th percentile of the distribution, but this was attenuated and became nonsignificant after adjustment for cardiovascular risk factors.18 The Paris Prospective Study observed a 2-fold increase in risk of stroke mortality in the top 2.5% of the fasting glucose distribution after adjustment, although the findings were not statistically significant.18 The Oslo Study observed increased risk in the top 95th percentile of the distribution, but the findings were not statistically significant, and those in the top 2.5% were not separated for analysis.19 The Midspan Study (Scotland) observed an independent relationship between hyperglycemia (≥95th percentile) and risk of stroke mortality in women, but no association was seen in men.17 The National Health and Nutrition Examination Survey (NHANES) (United States) observed no association between impaired glucose tolerance and prevalence of nonfatal stroke.20 In the present British Regional Heart Study, risk of stroke was only significantly raised in the upper 97.5th percentile of the distribution, and this was independent of cardiovascular risk factors, including blood pressure. Although we were not able to differentiate between types of

stroke, approximately 85% of strokes in the United Kingdom are due to ischemia, ie, they are thromboembolic.31 Although fasting samples or those taken after glucose load would have provided a more precise and reliable measure of glycemic status, the findings in our study, which are based on nonfasting glucose, are similar to those observed in the Whitehall Study1 and the pooled Whitehall, Paris Prospective, and Helsinki Policemen studies, which used fasting glucose or 2-hour glucose.18

In previous studies that have noted a significant positive finding, the increased risk appears to be at the extreme end of the distribution of the population, as seen in the present study. Most studies that have separated the upper extreme of the distribution have noted increased risk, although the findings have not always been statistically significant. Many of these studies are based on a small number of stroke cases. The discrepancy between studies may also relate to the large sample size required to detect a significantly increased risk at the extreme of the serum glucose distribution.1

Subclinical Diabetes
It has been suggested that serum elevated glucose may serve as a marker for an increased risk of subsequent diabetes and that the excess stroke risk in hyperglycemic subjects may be due simply to the inclusion of men with subclinical diabetes that has not yet become clinically manifest.1,18 In the present study we were able to identify incident cases during follow-up, and the findings support this suggestion. Exclusion of incident diabetes cases considerably attenuated the relationship seen in the hyperglycemic group, although a nonsignificant increase in risk was still seen. We have only excluded physician-diagnosed cases of diabetes, and it is likely that the effect seen in the upper 2.5% of the distribution would be even further attenuated if we could identify and exclude undiagnosed cases.

Those who developed diabetes during the follow-up period were at an increased risk of stroke, and their risk was only slightly lower than those with established diabetes at baseline. This is consistent with the fact that duration of diabetes also plays a role in the development of stroke.4 In those who subsequently developed diabetes, half of the cases were diagnosed in the same year or after the diagnosis of stroke. Since diabetes is normally present up to 10 years before clinical diagnosis, these subjects probably had subclinical diabetes before the stroke event rather than developing diabetes after a stroke event. Major cardiovascular risk factors, including hypertension and hyperlipidemia, predict diabetes in longitudinal analyses.32 Thus, it is not surprising that men who developed diabetes during follow-up were at substantially increased risk of stroke. It is hypothesized that the increased risk of CHD in diabetes is well established before the onset of clinically manifest disease, ie, that “the clock for CHD starts ticking before the onset of clinical diabetes.”33 Overall, the data suggest that, as is the case with CHD, risk of stroke is already substantially increased before the onset of clinically manifest or detected diabetes.

Serum Insulin and Risk of Stroke
The mean insulin levels in the 4 groups (Table 3) are in agreement with the observation that “the greatest hyperinsu-
linemia (although not the greatest insulin resistance) occurs early on in this process; coincident with the development of fasting hyperglycemia (clinical diabetes) levels become substantially lower."34 Given the extent to which established stroke risk factors such as hypertension and cigarette smoking are associated with insulin resistance,16 one would expect that hyperinsulinemia would predict stroke in univariate analysis. The question arises as to whether serum insulin concentrations are an independent risk factor for stroke. Only 3 prospective studies to date have examined the relationship between plasma insulin and the risk of stroke, and the evidence for an independent role of insulin in the development of stroke is inconclusive.5,21,22 The Kuopio (Finland) study in elderly men and women (36 cases) showed a positive association between plasma insulin and risk of stroke even after adjustment for hypertension and other factors.5 In the Helsinki Policemen Study (70 cases), hyperinsulinemia was associated with increased risk of stroke, but not independently of upper body obesity.21 In the Honolulu Heart Program, a U-shaped relationship was seen between fasting insulin and the risk of stroke (59 definite or probable cases). The increased risk in the top tertile appeared to be mediated through other cardiovascular risk factors.22 The increased risk in the first tertile was unexplained, but residual confounding by smoking and other comorbid conditions was suggested. These studies are severely limited by the small number of stroke events occurring. We have also observed a J-shaped relationship between nonfasting serum insulin and risk of stroke even after adjustment for cardiovascular risk factors, although the increased risk at higher levels was slightly attenuated after adjustment for blood pressure. It can be argued that if we had a measure of body fat distribution such as waist-hip ratio in addition to BMI in the current study, the observed relation with insulin would be further attenuated.

The explanation for the increased risk in the first quintile is less clear. It is noteworthy, however, that an identical J-shaped relation between serum insulin concentration and the incidence of diabetes is observed in this cohort of men.35 Exclusion of men who developed diabetes during the follow-up period reduced the positive trend seen from the second quintile onward, but risk remained increased in the first quintile compared with the second quintile, albeit nonsignificantly. Inevitably our adjustment for incident cases of diabetes by exclusion of physician-diagnosed cases will be incomplete, since a high proportion of cases of type 2 diabetes are undiagnosed for prolonged periods. It remains uncertain as to whether serum insulin is an independent risk factor for stroke. It will be difficult to resolve the issue in multivariate analysis, given the extent to which hyperinsulinemia is intercorrelated with other stroke risk factors, particularly measures of obesity and its distribution.

Bias
The use of nonfasting serum insulin measurements, adjusted for time of sampling, has almost certainly increased the amount of random error in the data compared with the use of insulin measured under fasting conditions. All measurements of insulin in epidemiological studies are beset by problems of high within-subject variability relative to between-subject variability, and it is likely that differences in this regard are small between fasting postload and nonfasting samples (adjusted for time of sampling). Despite this constraint, however, we have described, in an earlier publication from this study, a significant nonlinear association between nonfasting insulin and CHD that is consistent with findings from other major insulin-CHD studies.16 The associations between nonfasting insulin and CHD outcome and cardiovascular risk factors, such as BMI, lipids, and blood pressure, reported in this cohort16,36 are consistent with those reported with fasting and postload insulin in other studies.37 Correlation coefficients between insulin and biological risk factors in the present study16 have been shown to be virtually identical to those reported from a population-based study in eastern Finland in which fasting and 2-hour plasma insulin values were measured.37 Furthermore, the relationships between insulin and CHD and risk factors were similar irrespective of time of sampling. This strongly suggests that the use of nonfasting insulin in the present investigation has not been associated with systematic measurement error.

Conclusion
This study confirms the importance of established diabetes as an independent risk factor for the development of stroke, although the roles of hyperglycemia and hyperinsulinemia in this process are weak. Those apparently nondiabetic at screening who manifested diabetes during the average 17-year follow-up were at increased risk of a magnitude similar to those with diabetes at screening. Stroke risk was only increased in the top 2.5% of the serum glucose distribution, and this reflected the high proportion of men who subsequently developed diabetes in this group. A weak J-shaped relationship was seen between nonfasting insulin and risk of stroke, with the increased risk in the lowest insulin quintile remaining unexplained. The increased risk at higher levels of serum insulin was due in part to the men who developed diabetes in the follow-up period. Whether insulin is an independent risk factor for stroke remains uncertain.

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