Hyperglycemia and Stroke Mortality

Comparison between fasting and 2-h glucose criteria

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For the DECODE Study Group*

OBJECTIVE — We investigated stroke mortality in individuals in different categories of glycaemia and compared hazard ratios (HRs) corresponding to a 1-SD increase in 2-h plasma glucose and fasting plasma glucose (FPG) criteria.

RESEARCH DESIGN AND METHODS — We examined data from 2-h 75-g oral glucose tolerance tests taken from 13 European cohorts comprising 11,844 (55%) men and 9,862 (45%) women who were followed up for a median of 10.5 years. A multivariate adjusted Cox proportional hazards model was used to estimate HRs for stroke mortality.

RESULTS — In men and women without a prior history of diabetes, multivariate adjusted HRs for stroke mortality corresponding to a 1-SD increase in FPG were 1.02 (95% CI 0.83–1.25) and 1.52 (1.22–1.88) and those in 2-h plasma glucose 1.21 (1.06–1.38) and 1.31 (1.06–1.61), respectively. Addition of 2-h plasma glucose to the model with FPG significantly improved prediction of stroke mortality in men ($\chi^2 = 10.12; P = 0.001$) but not in women ($\chi^2 = 0.01; P = 0.94$), whereas addition of FPG to 2-h plasma glucose improved stroke mortality in women ($\chi^2 = 4.08; P = 0.04$) but not in men ($\chi^2 = 3.29; P = 0.07$).

CONCLUSIONS — Diabetes defined by either FPG or 2-h plasma glucose increases the risk of stroke mortality. In individuals without a history of diabetes, elevated 2-h postchallenge glucose is a better predictor than elevated fasting glucose in men, whereas the latter is better than the former in women.

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Revascular death was used as an end point and coded according to the ICD with codes 430–438 (8th and 9th revisions) and codes 160–169 (10th revision). The methods to recruit participants for the DECODE cohorts have been described previously (8,9). Briefly, the database was collected from researchers who had performed epidemiological studies using standard 2-h 75-g oral glucose tolerance tests in Europe. Individual data from different participating European cohorts were sent to the Diabetes and Genetic Epidemiology Unit of the National Public Health Institute in Helsinki, Finland, for data analysis. Each study had been approved by the local ethics committees, and the ethics committee of the National Public Health Institute approved the data analysis plan.

### Statistical methods

A general linear model of univariate ANOVA was used to estimate the means adjusted for age and center. The Cox proportional hazards model was used to calculate hazard ratios (HRs) and their 95% CIs for stroke mortality in the different FPG and 2-h plasma glucose levels. The models were adjusted for age, center, hypertension status (≥140/90 mmHg or treatment), BMI, total serum cholesterol, smoking status, and sex. BMI was calculated as weight in kilograms divided by height in meters squared, and smoking status was classified as current smoker, ex-smoker, or nonsmoker. Cumulative mortality curves were plotted using the same multivariate Cox proportional hazards analysis. \( \chi^2 \) log-likelihood ratio tests were used to determine the difference between the FPG and 2-h plasma glucose criteria. SPSS (version 15; SPSS, Chicago, IL) was used for data analysis.

### RESULTS

- **The number of participants, their demographic data at baseline, and the number of stroke events in each DECODE cohort that accumulated during the follow-up years are shown in Table 1. Mortality from stroke was higher in diabetic than in nondiabetic individuals.**

### Table 1—Demographic data at baseline and number of stroke events during the follow-up in each study

| Country                  | Study Name          | Men (n) | Women (n) | Age (years) mean ± SD | Men (n) | Women (n) | Age (years) mean ± SD | Stroke | Women | Age (years) mean ± SD | Maximum follow-up years |
|--------------------------|---------------------|---------|-----------|-----------------------|---------|-----------|-----------------------|--------|-------|-----------------------|------------------------|
| Finland, East-West*      |                     | 405     | —         | 76.2 ± 4.5            | 29 (7.2)| —         |                        |        |       |                        | 16.2                   |
| FINRISK-1987             |                     | 1,261   | 1,440     | 54.0 ± 5.8            | 25 (2.0)| 24 (1.7)  |                        |        |       |                        | 19.0                   |
| FINRISK-1992             |                     | 877     | 1,041     | 54.1 ± 6.0            | 6 (0.7) | 7 (0.7)   |                        |        |       |                        | 14.0                   |
| FINRISK-2002             |                     | 1,786   | 2,055     | 57.9 ± 7.8            | 3 (0.2) | 2 (1.2)   |                        |        |       |                        | 3.9                    |
| Helsinki Policemen Study*|                     | 1,136   | —         | 44.7 ± 8.0            | 79 (7.0)| —         |                        |        |       |                        | 36.8                   |
| Vantaa                   |                     | 271     | 335       | 65.2 ± 0.4            | 5 (1.8) | 9 (2.1)   |                        |        |       |                        | 13.9                   |
| Italy, Cremona           |                     | 799     | 1,003     | 58.4 ± 10.8           | 5 (0.6) | 2 (0.2)   |                        |        |       |                        | 6.9                    |
| The Netherlands, Hoorn Study |                 | 1,087   | 1,282     | 61.7 ± 7.3            | 12 (1.1)| 11 (0.9)  |                        |        |       |                        | 10.2                   |
| Zutphen Study*           |                     | 479     | —         | 75.8 ± 4.5            | 9 (1.9) | —         |                        |        |       |                        | 4.8                    |
| Sweden, MONICA          |                     | 1,733   | 1,760     | 48.9 ± 13.4           | 18 (1.0)| 8 (0.5)   |                        |        |       |                        | 20.6                   |
| Uppsala*                |                     | 1,164   | —         | 71.0 ± 0.6            | 27 (2.3)| —         |                        |        |       |                        | 12.4                   |
| U.K., Goodinge          |                     | 448     | 570       | 54.6 ± 10.3           | 8 (1.8) | 1 (0.2)   |                        |        |       |                        | 9.7                    |
| Newcastle               |                     | 398     | 376       | 54.8 ± 12.5           | 5 (1.3) | 4 (1.1)   |                        |        |       |                        | 10.6                   |
| Total                   |                     | 11,844  | 9,862     | 56.8 ± 11.3           | 231 (2.0)| 68 (0.7)  |                        |        |       |                        | 36.8                   |

Data are n, means ± SD, or n (%), unless otherwise indicated. *The study includes only men.

Discriminated fatal stroke events in men, whereas that based on FPG was a better predictor in women.

The HRs corresponding to a 1-SD increase in 2-h plasma glucose or FPG are shown in Table 3. The log-likelihood ratio test showed that addition of 2-h plasma glucose to the model with FPG significantly improved the prediction of the model (\( \chi^2 = 10.45; P = 0.001 \)) in all individuals and in men (\( \chi^2 = 10.12; P = 0.001 \)) but not in women (\( \chi^2 = 0.01; P = 0.94 \)). Addition of FPG to the model with 2-h plasma glucose improved the prediction of stroke mortality in women but not in men (Table 3). Interaction of sex with FPG was found to be significant (\( P = 0.05 \)) but not with 2-h plasma glucose (P = 0.53).

Because waist circumference and triglycerides were not measured in all cohorts included in the current data analysis, they were not adjusted in the final model. Their effects were, however, tested in a subgroup of 9,010 (42%) men and 8,900 (41%) women with measurement of waist and a subgroup of 10,379 (48%) men and 8,235 (38%) women with triglycerides. Adjustment for either waist or triglycerides did not change the results for 2-h plasma glucose in men or FPG in women, but it attenuated the hazards for 2-h plasma glucose in women and FPG in men. The HRs adjusting for waist corresponding to a 1-SD increase in 2-h plasma glucose were 1.23 (95% CI 0.99–1.52) in men and 1.07 (0.78–1.48) in women; those corresponding to a 1-SD increase in FPG were 1.08 (0.86–1.35) in men and 1.38 (0.95–2.00) in women. HRs adjust-
ing for triglycerides were for 2-h plasma glucose 1.24 (1.03–1.50) in men and 0.98 (0.65–1.49) in women, whereas for FPG 0.87 (0.69–1.10) and 1.50 (0.90–2.48), respectively. Further adjustment for either waist or triglycerides in the subgroups did not change the main results based on the whole study population.

**CONCLUSIONS** — We confirmed in this analysis that diabetes defined by either FPG or 2-h plasma glucose criteria conveyed increased stroke mortality. Individuals with IFG defined according to the FPG criteria alone had a stroke mortality lower than those with diabetes but higher than those with NFG in women but not in men, whereas the opposite was found for IGT and NGT. Stroke mortality was higher in men with IGT than in men with NGT, but such a difference was not seen in women.

Overt diabetes (1,10) as well as diabetes defined based on 1-h postload glucose (11), FPG levels (12,13), or nonfasting glucose levels (7,14) have been reported to predict an increased risk of stroke. Yet, studies that have conducted a 2-h oral glucose tolerance test and compared the stroke risk between 2-h postload hyperglycemia and fasting hyperglycemia are rare. Moreover, because the category IFG has only recently been introduced (15), studies estimating the stroke risk in individuals with IFG compared with those with IGT are very few. The DECODE Study Group (8) previously found that the risk of stroke death was higher in women with IFG than with IGT (8), but as a result of the low number of stroke deaths, a direct comparison between FPG and 2-h plasma glucose was not made separately for men and women. With the increasing number of stroke deaths accumulated in the DECODE cohorts, the glucose-stroke relationship was reinvestigated in detail in the present data analysis. With regard to CHD mortality,
when we analyzed the data with men and women together, the findings of the present study (results not shown) were in accordance with the previous findings (8). Also, in the present study, when men and women were pooled, the 2-h plasma glucose–stroke relation was still stronger than the FPG-stroke relation. However, when the data were analyzed separately,
we found that in men, the 2-h plasma glucose criteria better predicted stroke mortality than the FPG criteria, but in women the role was reversed. When the data are analyzed with men and women together, the majority of the stroke deaths come from men, and the results of the men drive the direction of the analysis; thus, the sex differences in FPG and 2-h plasma glucose criteria better predict stroke mortality than the FPG criteria, but in women the role was reversed. When the data are analyzed with men and women together, the majority of the stroke deaths come from men, and the results of the men drive the direction of the analysis; thus, the sex differences in FPG and 2-h plasma glucose criteria better predict stroke mortality than the FPG criteria, but in women the role was reversed.
glucose criteria with regard to stroke risk remain undetected.

Diabetes increases the risk of CHD events (16). The risk is more markedly increased in diabetic women than in diabetic men (17). This was also found in the current study population of all ages: the ratio of male CHD mortality to female CHD mortality in subjects with normal glucose levels (both NFG and NGT) and with diabetes (diagnosed or undiagnosed) was 5.94 and 2.53, respectively.

The underlying pathophysiology of IFG and IGT are different. IFG is predominantly associated with hepatic insulin resistance and decreased first-phase insulin secretion, whereas IGT is associated with peripheral insulin resistance and impairment of both early- and late-phase insulin responses (18). A population study in Mauritius reported that men have lower levels of β-cell function and higher prevalence of IFG than women and women have lower insulin sensitivity and higher prevalence of IGT than men (19). Thus, the stroke mortality in relation to the two glucose categories may also differ between the two sexes, which could partly explain the differences found between men and women in the present study.

Abdominal adiposity, measured as waist circumference or as waist-to-hip ratio, has been found to increase the risk of ischemic stroke in both men and women (20) or in men only (21). Plasma triglyceride levels have also been shown to have an association with increased risk of stroke in some (22) but not all studies (23) or have been found to have an increased stroke risk only in women (24). Because the two variables, waist circumference and triglycerides, were not measured in all of the cohorts used in the present study, adjustments for these variables were not done in the final data analysis. However, when their effect was tested in a subgroup of individuals, the results did not change, indicating that the 2-h plasma glucose category improves the prediction of stroke mortality in men compared with FPG category alone, whereas the latter is better than the former in women.

Overt diabetes is more closely related to ischemic stroke than to hemorrhagic stroke (25). Regardless of the relatively large sample size, the follow-up duration for many of the cohorts in the present study is still short, with few stroke events accumulated, and as a result of the small number of stroke events in women, we could not further classify people into ischemic or hemorrhagic stroke. This is one of the limitations of the current study. In addition, in the DECODE study, some cohorts included men only, and thus cohorts for men and women in the present analysis were to some extent different. One may speculate that the sex-specific glucose-stroke relationship is study-dependent. However, when we limit the data analysis to the studies comprising both men and women, the results were not changed. The strength of the present study is that all the cohorts used in the study had data available for both FPG and 2-h glucose levels. This is the first study to investigate the question of glucose levels and the risk of stroke in a study group where all participants had a 2-h 75-g oral glucose tolerance test. The collaborative data analysis gives more statistical power than if the analysis had been performed individually by the different centers, and thus avoids the spurious results caused by a small study. To try to take into account the difference between studies, in all pooled data analysis, “cohort” was adjusted for.

In summary, the present study confirmed that diabetes defined by either fasting or postchallenge glucose is a predictor of stroke mortality in both sexes. In people without diabetes, elevated 2-h postchallenge glucose is a better predictor than elevated fasting glucose in men, whereas fasting plasma glucose is better than 2-h postchallenge glucose in women.

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