# Fasting Glucose and All-Cause Mortality by Age in Diabetes: A Prospective Cohort Study

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## OBJECTIVE

**To examine associations between fasting glucose and mortality and to identify the levels associated with lowest mortality by age in diabetes.**

## RESEARCH DESIGN AND METHODS

**A total of 359,645 Korean adults with known prevalent diabetes participated in health screening during 2001–2004 and were followed up until 2013.**

## RESULTS

**U-curve associations were found. Fasting glucose levels associated with the lowest mortality were ~90–130 mg/dL, except for in those aged 18–44 years (~80–95 mg/dL). Multivariable-adjusted hazard ratios of fasting glucose <65, 65–74, 75–84, 140–169, 170–199, and ≥200 mg/dL were 1.46, 1.12, 1.09, 1.12, 1.31, and 1.78, respectively, compared with 85–99 mg/dL.**

## CONCLUSIONS

**Optimal fasting glucose range for survival is higher in adults with than without known prevalent diabetes, except, perhaps, younger adults. Tight glucose control may lessen premature death in younger adults with diabetes. Hypoglycemia (<65 mg/dL) was associated with higher mortality than was fasting glucose 170–199 mg/dL, while fasting glucose 65–84 mg/dL had risks comparable with those at levels 140–169 mg/dL in diabetes.**


Fasting glucose levels are a fundamental element of managing diabetes in patients to achieve good glycemic control. Precise estimates of the age-specific relative risks of death associated with fasting glucose may help determine better glucose targets for management of diabetes. However, little is known about the associations of the full range of fasting glucose with all-cause mortality and the optimal range for survival according to age in diabetes.

## RESEARCH DESIGN AND METHODS

More detailed information about the Korean Metabolic Risk Factor (KOMERIT) study has previously been published (1–3). This study included 12,845,017 adults who participated in routine health screenings during 2001–2004 by the National Health Insurance Service, which provides mandatory insurance coverage for 97% of the Korean population. After exclusion of individuals with missing information or extreme anthropometric measures, 12,815,006 participants, of whom 369,645 had known prevalent diabetes, were follow up until 2013 for survival (1). This study was approved by the institutional review board of Catholic Kwandong University (Gangneung, Republic of Korea).


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Fasting serum glucose and total cholesterol were assayed using enzymatic methods (3). Blood pressure and BMI (measured as weight in kilograms divided by the square of height in meters) were measured. Information on smoking history, alcohol use, and known prevalent diabetes status at baseline was collected via questionnaire.

Fasting glucose concentrations were categorized into 10 groups. A restricted cubic spline transformation of fasting glucose with 5 knots was used to evaluate nonlinear associations (Supplementary Data). HRs were calculated using Cox proportional hazards models stratified by age at baseline after adjustment for age at baseline, sex, smoking status, alcohol use, physical activity, BMI, systolic blood pressure, and total cholesterol with use of the same method as in our previous study (3), and this previous study provided more detailed information on the corresponding associations in individuals without known diabetes. All *P* values were two-sided. All analyses were performed with SAS, version 9.4 (SAS Institute, Cary, NC).

## RESULTS

During a mean 10.5 years of follow-up, 62,034 adults with known diabetes died. At baseline, the mean ± SD age was 56.8 ± 12.1 years and the mean fasting glucose level was 148.5 ± 71.1 mg/dL (Supplementary Table 1).

Men with diabetes had 3.04 mg/dL (0.167 mmol/L) higher mean fasting glucose levels than women with diabetes (149.78 vs. 146.75 mg/dL). The sex difference in mean glucose levels peaked at 32–35 years, when men had a level ~15 mg/dL higher than women (Supplementary Fig. 1).

In people with diabetes, U-curve associations between fasting glucose and all-cause mortality were found with a nadir at 100–109 mg/dL in categorical analysis and 107 mg/dL in spline analysis (Supplementary Table 2 and Fig. 1). In populations with diabetes, multivariable-adjusted hazard ratios (HRs) of mortality associated with fasting glucose levels of <65, 65–74, 75–84, 140–169, 170–199, and ≥200 mg/dL were 1.46, 1.12, 1.09, 1.12, 1.31, and 1.78, respectively, compared with 85–99 mg/dL, in comparison with 1.20, 1.06, 1.02, 1.51, 1.74, and 2.29 in people without known diabetes. In the 18–44 years age-group, in persons with diabetes, the HRs associated with 100–109, 110–125, and 126–139 mg/dL were 1.35, 1.48, and 1.96, respectively, compared with 85–99 mg/dL. In persons with diabetes aged 65–99 years, fasting

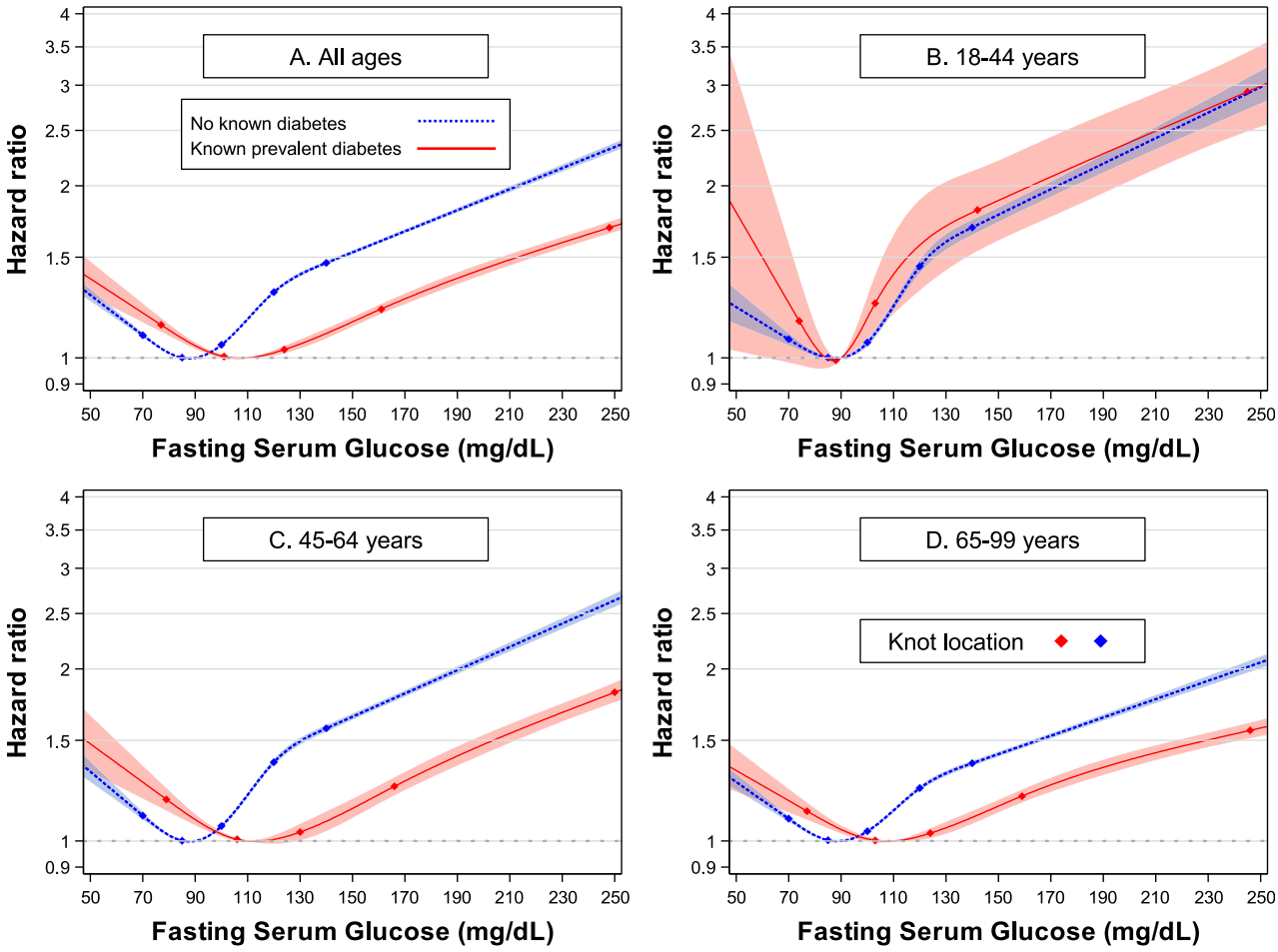


**Figure 1**—HRs for mortality by age according to known prevalent diabetes status at baseline. Restricted cubic splines of fasting serum glucose with 5 knots were used with reference values of 90 mg/dL for people without prevalent diabetes and people with prevalent diabetes aged 18–44 years and 110 mg/dL for people with prevalent diabetes aged ≥45 years. HRs and 95% CIs were calculated using Cox proportional hazards models stratified by baseline age (18–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75–84, and 85–99 years) after adjustment for age at baseline (continuous variable), sex, smoking status, alcohol use, physical activity, BMI, systolic blood pressure, and total cholesterol levels. To convert glucose from mg/dL to mmol/L, multiply by 0.0555.

glucose levels <100 mg/dL were associated with excess mortality compared with 100–109 mg/dL.

When the range with an excess risk <5% was considered the optimal range for survival, as described in Supplementary Data, the optimal ranges in persons with diabetes aged 18–44, 45–64, and 65–99 years were 65–99, 85–139, and 85–139 mg/dL in the categorical analysis and ~80–95, 95–135, and 90–130 mg/dL in the spline analysis, respectively.

## CONCLUSIONS

U-curve associations were found between fasting glucose and all-cause mortality in those with diabetes regardless of age. In individuals with prevalent diabetes, at younger ages (18–44 years old), overall associations and fasting glucose range for minimal mortality (~80–95 mg/dL) were similar to those of individuals without known prevalent diabetes. However, in middle-aged and elderly adults with prevalent diabetes, the range for lowest mortality shifted upward to ~90–130 mg/dL. The population with diabetes had more extreme HRs related to hypoglycemia (<65 mg/dL) than individuals without known diabetes. The risk of death associated with hypoglycemia generally exceeded that of levels 170–199 mg/dL, while low-normal levels (65–84 mg/dL) showed a risk comparable with that of fasting glucose 140–169 mg/dL. The finding of 3.0 mg/dL higher fasting glucose levels in men than in women was similar between individuals with and without known prevalent diabetes, despite the substantial difference in the pattern of the mean fasting glucose levels according to sex and age (3).

J- or U-curve associations between A1C and mortality have been reported in some (4,5), but not all (6,7), prior studies. However, few studies have shown U-curve associations of fasting glucose in diabetes, perhaps due to lack of studies with a sufficient number of subjects (8). The observed U-curve associations provide evidence supporting that patients with diabetes should be carefully monitored to avoid fasting glucose 65–84 mg/dL in addition to hypoglycemia (<65 mg/dL), considering the greater excess mortality for hypoglycemia <65 mg/dL than fasting glucose 170–199 mg/dL and a comparable risk between levels 65–84 and 140–169 mg/dL.

Our results further suggest that tight glucose control has more beneficial effects at younger ages than at older ages. Our age-specific findings were generally concordant not only with the Diabetes Control and Complications Trial (DCCT), the Epidemiology of Diabetes Interventions and Complications (EDIC) study, and the UK Prospective Diabetes Study (UKPDS) and its follow-up study that reported a reduction in all-cause mortality in the intensive glucose treatment group but also with other large clinical trials that reported no reduction in mortality associated with the intensive treatment (9–15). Younger mean age at enrollment in DCCT/EDIC (27.2 years) and UKPDS/the follow-up study (53 years) compared with other large trials (>60 years) may have substantially contributed to the beneficial effect of intensive glucose reductions (9–14). Further, the participants of UKPDS had incident diabetes, no vascular complications, and lower blood pressure and A1C than patients with type 2 diabetes in other trials. Similarly, persons with diabetes aged 18–44 years probably had fewer vascular complications, lower blood pressure and fasting glucose, and shorter diabetes duration than their older counterparts in our study. Relatively higher proportion of type 1 diabetes at 18–44 years, although <10% in Korea (1), might partially affect the findings.

Combined with the evidence from the DCCT/EDIC and UKPDS studies, our study provides further evidence that stringent glucose control could reduce overall mortality in younger patients with diabetes with the short duration of diabetes and little vascular damage.

The study has limitations, such as a lack of information on cause-specific mortality or other measures of glucose tolerance. Information relevant to diabetes, such as medication, duration, type, or complications, was not examined. Changes in fasting glucose, due to advancing age and glucose-lowering treatment, during follow-up were not allowed for. The ethnically homogenous population may affect the generalizability. Nonetheless, we observed U-curve associations regardless of age and sex, with a higher optimal range in older adults of both sexes; these findings enhance the generalizability of our results.

### Summary

The optimal fasting glucose ranges for survival were approximately 90–130 mg/dL in diabetes, except younger adults aged 18–44 years, who had similar optimal ranges to individuals without known diabetes. Stringent glucose control may ameliorate premature death risk more in younger than in older adults with diabetes. Avoidance of low-normal level (65–84 mg/dL) as well as hypoglycemia (<65 mg/dL) may improve survival in diabetes.

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**Author Contributions.** S.-W.Y. conceived the study concept and design, acquired data, performed statistical analyses, and wrote the first draft. S.-W.Y. and S.P. conducted the literature search. S.-W.Y., S.P., Y.-h.L., B.B., and J.-J.Y. analyzed and interpreted data. All authors contributed to critical revision of the manuscript. All authors read and approved the final submitted version of the manuscript. S.-W.Y. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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