

# Hyperglycemia and Incidence of Ischemic and Hemorrhagic Stroke—Comparison Between Fasting and 2-Hour Glucose Criteria

Marjukka Hyvärinen, MSc; Jaakko Tuomilehto, MD, PhD; Markku Mähönen, MD, PhD; Coen DA Stehouwer, MD, PhD; Kalevi Pyörälä, MD, PhD; Björn Zethelius, MD, PhD; Qing Qiao, MD, PhD; for the DECODE Study Group

**Background and Purpose**—We examined the impact of hyperglycemia on ischemic and hemorrhagic stroke incidence comparing criteria based on fasting plasma glucose (FPG) and 2-hour plasma glucose (2-hour PG).

**Methods**—Data from 9 European cohorts comprising 18 360 individuals between 25 to 90 years of age were collaboratively analyzed. The maximum length of follow-up varied between 4.9 to 36.8 years. Hazards ratios (95% confidence intervals) for stroke incidence were estimated using Cox-proportional hazards model adjusting for known risk factors.

**Results**—In individuals without a prior history of diabetes, the multivariate-adjusted hazards ratio for ischemic stroke corresponding to 1 SD increase in FPG was 1.12 (1.02 to 1.22) and in 2-hour PG 1.14 (1.05 to 1.24). Adding 2-hour PG to the model with FPG significantly improved the prediction of the model for the incidence of ischemic stroke ( $\chi^2=4.72$ ,  $P=0.03$ ), whereas FPG did not improve the 2-hour PG model prediction ( $\chi^2=0.25$ ,  $P=0.62$ ). A significantly increased hazard ratio was also observed for previously diagnosed diabetes (2.26 [1.51 to 3.38]) and for screen-detected diabetes defined by FPG (1.48 [1.08 to 2.02]) and 2-hour PG (1.60 [1.18 to 2.16]). None of the criteria predicted hemorrhagic stroke.

**Conclusions**—Diabetes defined by either of the criteria predicted the future risk of ischemic stroke but not the hemorrhagic stroke. The prediction is stronger for elevated 2-hour PG than for FPG levels. (*Stroke*. 2009;40:1633-1637.)

**Key Words:** fasting plasma glucose ■ 2-h plasma glucose ■ ischemic stroke ■ hemorrhagic stroke ■ incidence

Diabetes is an independent well-known risk factor for stroke.<sup>1</sup> Several studies have addressed the issue of diabetes and different subtypes of stroke.<sup>2,3,4</sup> Some<sup>2,5</sup> but not all<sup>6</sup> studies have found an increased risk of ischemic stroke but no association<sup>3</sup> or a decreased risk of hemorrhagic stroke in individuals with diabetes.<sup>4</sup>

The pathophysiology between ischemic stroke and hemorrhagic stroke differs.<sup>7</sup> Atherosclerosis is a known risk factor for stroke,<sup>8</sup> and it is often advanced in individuals with hyperglycemia<sup>9</sup> or diabetes.<sup>10</sup> Atherosclerosis has been found to be more strongly associated with postchallenge glucose levels than fasting glucose levels.<sup>11</sup> Yet, studies have also indicated that elevated serum fasting<sup>12</sup> and nonfasting<sup>5</sup> glucose levels increase the risk of ischemic stroke. The association between diabetes and hemorrhagic stroke is controversial.<sup>3,4,13</sup> However, diabetes often coexists with hypertension,<sup>14</sup> which has been reported to have an association with cerebral hemorrhage.<sup>15</sup>

The aim of the present study is to investigate the relationship between the incidence of ischemic and hemorrhagic stroke and hyperglycemia and to compare the differences between fasting and 2-hour plasma glucose criteria.

## Participants and Methods

### Study Population

This is a subdata analysis of the DECODE study including 9 cohorts from Finland and Sweden and consisting of 18 360 participants with 9985 men and 8375 women. Individuals participating at the baseline survey were followed up until 2006 and 2004 for the Finnish and the Swedish cohorts, respectively. The data on stroke mortality and morbidity were collected from National Causes of Death Register and the National Hospital Discharge Registry and ascertained by using a computerized record linkage of individual ID numbers of each of the individuals participating in the study. The age range of the study population varied from 25 to 90 years. The maximum length of follow-up varied between 4.9 to 36.8 years in between the different cohorts with a median length of follow-up of 12.9 years.

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From the Department of Public Health (M.H., J.T., Q.Q.), University of Helsinki, Finland; the Diabetes Prevention Unit, Department of Chronic Disease Prevention (J.T., M.M., Q.Q.), National Institute for Health and Welfare, Helsinki, Finland; the Department of Medicine (C.D.A.S.), Maastricht University Medical Centre, The Netherlands; the Department of Medicine (K.P.), University of Kuopio, Finland; and the Department of Public Health/Geriatrics (B.Z.), Uppsala University Hospital, Sweden.

Correspondence to Marjukka Hyvärinen, MSc, Department of Public Health, University of Helsinki, PL 41, Mannerheimintie 172, FIN-00014 Helsinki, Finland. E-mail marjukka.hyvarinen@helsinki.fi

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**Table 1. Demographic and Follow-Up Information of the Study Populations**

Study	n	Women (%)	Median (Range), Years		Stroke, n (%)			
			Age	Follow-Up	Ischemic	Hemorrhagic	Unspecified	All-Causes
Finland, East-West	382		76.1 (69.8–89.5)	8.82 (0.11–17.11)	66 (17.3)	2 (0.5)	3 (0.8)	71 (18.6)
FINRISK-1987	2637	1416 (53.7)	54.0 (35.9–64.2)	17.94 (0.01–19.95)	182 (6.9)	47 (1.8)	6 (0.2)	235 (8.9)
FINRISK-1992	1866	1021 (54.7)	54.0 (39.6–64.2)	14.12 (0.34–14.99)	55 (2.9)	29 (1.6)	2 (0.1)	86 (4.6)
FINRISK-2002	3701	1998 (54.0)	57.8 (28.0–74.0)	4.79 (0.26–4.94)	28 (0.8)	10 (0.3)		38 (1.0)
Helsinki Policemen Study	1120		44.6 (30.0–69.0)	28.07 (0.89–36.80)	127 (11.3)	21 (1.9)	12 (1.1)	160 (14.3)
Vantaa	584	325 (55.7)	65.1 (64.2–66.2)	12.52 (3.29–13.94)	50 (8.6)	16 (2.7)	3 (0.5)	69 (11.8)
Sweden, MONICA	3455	1742 (50.4)	48.7 (25.0–78.0)	11.53 (0.03–20.61)	60 (1.7)	18 (0.5)	13 (0.4)	91 (2.6)
Uppsala	1132		71.0 (69.4–73.6)	9.37 (0.08–12.36)	92 (8.1)	23 (2.0)	2 (0.2)	117 (10.3)
Malmö Preventive Project	3483	3483 (100.0)	54.8 (48.2–57.6)	15.33 (0.79–19.98)	97 (2.8)	30 (0.9)	4 (0.1)	131 (3.8)
Total	18360	9985 (54.4)	55.2 (25.0–89.5)	12.93 (0.01–36.80)	757 (4.1)	196 (1.1)	45 (0.2)	998 (5.4)

Individuals with a prior history of diabetes were classified as previously diagnosed diabetes. Further classification was made on the basis of fasting plasma glucose (FPG) and 2-hour plasma (2-hour PG) glucose criteria for individuals who had not previously been diagnosed as diabetic according to the WHO 2006 criteria.<sup>16</sup> For FPG levels  $\geq 7.0$  mmol/L and 2-hour PG levels  $\geq 11.1$  mmol/L individuals were classified as newly diagnosed diabetes, and individuals with intermediate hyperglycemia with FPG levels of 6.1 to 6.9 mmol/L or with 2-hour plasma glucose levels of 7.8 to 11.0 mmol/L as impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), respectively. Individuals with FPG levels of  $< 6.1$  mmol/L were classified as normal fasting glucose (NFG), and with 2-hour PG levels of  $< 7.8$  mmol/L as normal glucose tolerance (NGT).

### Definition of the First Stroke Events

First (incident) stroke events consisted of acute stroke events in individuals without a history of stroke before the baseline survey. Incidence of stroke was coded according to the International Classification of Diseases (8th, 9th, and 10th revisions) with codes 430 to 431, 433 to 434, 436 and I60 to I61, I63 to I64 for nonfatal and fatal stroke, and further classified into subtypes of stroke coding 433, 434, and I63 for ischemic stroke and 430 to 431 and I60 to I61 for hemorrhagic stroke and cases that could not be specified into unspecified stroke. Individuals, who had emigrated, whose vital status could not be confirmed, or individuals with a prior history of CVD (including stroke) at the baseline survey were excluded from the data analysis.

The local Ethics Committees had approved each individual study plan, and the data analysis plan was approved by the Ethics Committee of the National Public Health Institute, Finland.

### Statistical Methods

The data analysis was carried out using SPSS for Windows version 15.0. General linear model of the univariate analysis of variance was used to estimate the means according to FPG and 2-hour PG classes adjusting for age, center, and sex. Hazard ratios with 95% confidence intervals for stroke incidence were estimated for different glucose categories and also for a 1-SD increase in 2-hour PG (mmol/L) and FPG (mmol/L) criteria using Cox proportional hazards model. The FPG or 2-hour PG has been divided by their standard deviations to make them comparable. The analysis was adjusted for age, center, mean arterial pressure (MAP, as an alternative systolic blood pressure was also tested, and the results are shown in the text in the Result section), body mass index (BMI), total serum cholesterol, smoking status, and sex. MAP was defined as  $[(2 \times \text{diastolic}) + \text{systolic}] / 3$  and BMI was calculated by using weight in kilograms divided by the square of height in meters and smoking status was categorized as current smoker, ex-smoker, or nonsmoker. Chi-

squared log-likelihood ratio test were used to evaluate whether the 2 glucose criteria differ in their prediction of the new events of stroke.

Considering the variations in follow-up length, events rates, and risk factor levels between studies, particularly among the old Finnish policemen study, a stratified Cox regression analysis with “study” as Strata was also fitted and the results are shown and compared with those from the model where “study” was considered as a covariate. A sensitivity analysis truncating the follow-up length at 15 years was performed to check to what extent the difference in follow-up length could affect the results.

### Results

The demographic data at baseline and the number of subjects in each cohort are shown in Table 1. Of the total 998 (5.4%) incident stroke events observed, 757 (4.1%) were ischemic, 196 (1.1%) were hemorrhagic, and 45 (0.2%) unspecified strokes (Table 1). The characteristics of subjects according to different glucose categories are shown in Table 2. Individuals with both diagnosed and undiagnosed diabetes were older and had higher BMI compared to individuals without diabetes (Table 2). Among 1254 screen detected diabetic individuals, 368 (29%) met only the FPG criterion, 536 (43%) only the 2-hour PG criterion, and 350 (28%) qualified for the both diagnostic criteria for diabetes.

Multivariate-adjusted hazard ratios corresponding to a 1-SD increase in both FPG and 2-hour PG significantly predicted the incidence of ischemic stroke and overall stroke, but not hemorrhagic stroke subtype (Table 3). The log-likelihood ratio test showed that inclusion of 2-hour PG to the model with FPG improved the prediction of ischemic stroke ( $\chi^2 = 4.72$ ,  $P = 0.03$ ) and all stroke subtypes ( $\chi^2 = 4.93$ ,  $P = 0.03$ ). In contrast, the inclusion of FPG to the model with 2-hour PG did not improve the prediction either of ischemic stroke ( $\chi^2 = 0.25$ ,  $P = 0.62$ ) or overall ( $\chi^2 = 0.79$ ,  $P = 0.37$ ) stroke incidence (Table 3). Similar results were obtained from stratified Cox-regression analyses, which gave hazard ratios of 1.11 (1.02 to 1.22; 95% CI) and 1.14 (1.05 to 1.24; 95% CI) for ischemic stroke corresponding to a 1-SD increase in FPG and 2-hour PG, respectively. The stratified Cox regression analysis also showed that addition of the 2-hour PG to the model with FPG improved the model prediction ( $\chi^2 = 4.97$ ,  $P = 0.03$ ), but adding the FPG to the model with

**Table 2. Characteristics of Subjects at Baseline and Stroke Events Accumulated According to Fasting and 2-Hour Glucose Criteria**

	Fasting Plasma Glucose (mmol/L)			2-Hour Plasma Glucose (mmol/L)			Known DM
	<6.1	6.1–6.9	≥7.0	<7.8	7.8–11.0	≥11.1	
n (%)	13601 (74.1)	3168 (17.3)	718 (3.9)	12573 (68.5)	4028 (21.9)	886 (4.8)	873 (4.8)
Age	54.6 (0.1)	55.8 (0.2)	58.3 (0.3)	53.6 (0.1)	58.0 (0.1)	59.8 (0.2)	60.4 (0.3)
Body mass index, kg/m <sup>2</sup>	26.3 (0.0)	27.6 (0.1)	29.8 (0.2)	26.4 (0.0)	27.0 (0.1)	29.1 (0.2)	29.3 (0.2)
Cholesterol, mmol/L	6.04 (0.01)	6.10 (0.02)	6.17 (0.04)	6.03 (0.01)	6.12 (0.02)	6.12 (0.04)	5.81 (0.04)
Systolic blood pressure, mm Hg	137 (0.2)	141 (0.3)	146 (0.7)	138 (0.2)	139 (0.3)	147 (0.7)	147 (0.7)
Diastolic blood pressure, mm Hg	83 (0.1)	84 (0.2)	87 (0.4)	83 (0.1)	84 (0.2)	86 (0.4)	83 (0.4)
Smoking, n (%)	3206 (23.6)	913 (28.8)	195 (27.2)	3245 (25.8)	887 (22.0)	182 (20.5)	181 (20.7)
Stroke, n (%)							
All-causes	654 (4.8)	198 (6.3)	56 (7.8)	626 (5.0)	215 (5.3)	67 (7.6)	90 (10.3)
Ischemic stroke	494 (3.6)	150 (4.7)	46 (6.4)	475 (3.8)	163 (4.0)	52 (5.9)	67 (7.7)
Hemorrhagic stroke	137 (1.0)	38 (1.2)	5 (0.7)	127 (1.0)	42 (1.0)	11 (1.2)	16 (1.8)
Unspecified stroke	23 (0.2)	10 (0.3)	5 (0.7)	24 (0.2)	10 (0.2)	4 (0.5)	7 (0.8)

Data are given as means (SE) adjusted for age, study, and sex, or as n (%) as noted.

2-hour PG did not improve the model prediction ( $\chi^2=0.21$ ,  $P=0.65$ ).

Replacing the MAP with systolic blood pressure in the Cox regression analysis did not change the results substantially with hazard ratios of 1.11 (1.01 to 1.22; 95% CI) and 1.14 (1.05 to 1.23; 95% CI) for ischemic stroke corresponding to a 1SD increase in FPG and 2-hour PG. The analysis with systolic blood pressure consistently showed that 2-hour PG was a better predictor ( $\chi^2=4.30$ ,  $P=0.04$ ) than FPG ( $\chi^2=0.25$ ,  $P=0.62$ ) for ischemic stroke.

As compared with individuals with normal glucose levels, the hazard ratios for the ischemic stroke were higher for individuals with previously diagnosed diabetes and screen-detected diabetes defined by either FPG or 2-hour PG criteria (Table 4). The elevated FPG as well as the 2-hour PG did not predict the hemorrhagic stroke. The results of the sensitivity analysis, for which the follow-up length was truncated at 15 years, were in accordance with the present findings.

**Table 3. Hazard Ratios (95% Confidence Intervals) for the Incidence of Overall and Subtypes of Stroke Corresponding to a 1-SD Increase in Fasting (FPG) and 2-Hour Plasma Glucose (2-Hour PG) Levels (mmol/L)**

	Stroke Incidence		
	Ischemic	Hemorrhagic	All-Causes
No. of events	69	180	908
FPG	1.12 (1.02–1.22)	1.07 (0.88–1.30)	1.12 (1.04–1.21)
2-hour PG	1.14 (1.05–1.24)	1.06 (0.90–1.27)	1.14 (1.06–1.22)
$\chi^2$ for FPG, 1 df ( $p$ )*	0.25 (0.62)	0.17 (0.68)	0.79 (0.37)
$\chi^2$ for 2-hour PG, 1 df ( $p$ )*	4.72 (0.03)	0.09 (0.76)	4.93 (0.03)

\*The  $\chi^2$  indicates the changes in the model prediction when the variable indicated was removed from the model with both FPG and 2-hour PG simultaneously. Subjects with previously diagnosed diabetes are excluded.

1 SD is 1.2 for FPG and 2.7 for 2-hour PG.

Adjusted for age, study, BMI, total cholesterol, smoking, MAP, and sex.

## Discussion

The present study, based on 9 northern European cohorts with a median length of follow-up of 12.9 years, indicated that in individuals without previous diagnosis of diabetes the risk of ischemic stroke increased with increasing FPG and 2-hour PG levels, but 2-hour PG contributed to the risk more strongly than FPG. The risk of ischemic stroke was clearly increased in individuals with previously diagnosed or screen-detected diabetes. There was, however, no relationship between the degree of hyperglycemia and the risk of hemorrhagic stroke.

Some,<sup>17</sup> but not all,<sup>6</sup> studies have reported an increased risk of ischemic stroke in individuals with diagnosed diabetes. Increased risk of ischemic stroke has also been found in individuals with elevated serum fasting<sup>12</sup> and nonfasting<sup>5</sup> glucose levels and in individuals with diabetes defined by FPG<sup>1</sup> or 1-hour postload glucose levels.<sup>2</sup> Atherosclerosis, assessed by carotid artery stenosis or by carotid intima-media thickness, has been shown to increase the incidence of ischemic stroke<sup>8</sup> and to be more clearly associated with elevated postchallenge glucose levels than with fasting glucose levels.<sup>11</sup> Studies comparing different degrees of hyperglycemia defined by FPG and 2-hour PG criteria and the incidence of stroke are, however, scarce. With a large sample size, the comparison between the 2 glucose criteria with the subtypes of stroke was investigated in the present study, and the elevated 2-hour PG appeared to be slightly stronger than FPG with regard to the prediction of the ischemic stroke in the whole study population.

The association between the incidence of hemorrhagic stroke and diabetes is controversial.<sup>3,4,13</sup> Studies have found an increased risk<sup>13</sup> of hemorrhagic stroke in individuals with diabetes diagnosed by fasting glucose levels, no association in individuals with overt diabetes<sup>18</sup> or with diabetes defined by 1-hour postload glucose measurement,<sup>3</sup> or a decreased risk<sup>4</sup> in individuals with overt diabetes. The etiology and pathophysiology of the ischemic and hemorrhagic stroke are different,<sup>7</sup> which might also indicate different risk factors for

**Table 4. Hazard Ratios (95% Confidence Intervals) for Stroke Incidence According to Fasting Plasma Glucose (mmol/L) and 2-Hour Plasma Glucose (mmol/L) Categories**

Stroke Type	Fasting Plasma Glucose Category				2-Hour Plasma Glucose Category			
	<6.1	6.1 to 6.9	≥7.0	Known DM	<7.8	7.8 to 11.0	≥11.1	Known DM
Ischemic	1	1.18 (0.97–1.43)	1.48 (1.08–2.02)	2.20 (1.48–3.29)	1	1.14 (0.93–1.38)	1.60 (1.18–2.16)	2.26 (1.51–3.38)
Hemorrhagic	1	1.14 (0.78–1.67)	0.61 (0.25–1.52)	2.23 (0.96–5.18)	1	1.05 (0.72–1.55)	1.29 (0.67–2.45)	2.32 (0.99–5.42)
All-causes	1	1.18 (1.00–1.40)	1.36 (1.02–1.80)	2.26 (1.59–3.22)	1	1.14 (0.96–1.35)	1.57 (1.20–2.04)	2.33 (1.64–3.33)

the 2 stroke subtypes. In the present study, no relationship of hemorrhagic stroke with the elevated FPG or 2-hour PG was found.

The strength of the present study includes the long length of follow-up and the collaborative data analysis, which increased statistical power and made it possible to run data analyses in details. The national death and hospital discharge registers in Finland<sup>19,20</sup> and Sweden<sup>21</sup> provide complete follow-up information for outcomes. Additionally, the accuracy of the stroke diagnoses in the Hospital Discharge Register and Causes of Death Register when comparing the stroke events to the data provided by the population-based stroke registers in Finland<sup>19,20</sup> and Sweden<sup>21</sup> has been found to be fairly good. There are, however, variations in study design, laboratory assays, the follow-up length, and the event rates in between the studies. This may cause the problem when classifying people into categories. In this study, however, no other measures rather than glucose were studied. To overcome this limitation, glucose variables have been analyzed in both the categorical form and the linear form after standardized to a 1-SD increase. In addition, we have fitted the “study cohort” as a covariate in the data analysis, performed data analysis based on each single study instead of pooling all studies together and run a multivariate adjusted stratified Cox-regression analysis as well. All the results are shown in the manuscript; the main results and conclusion remain, however, unchanged regardless of what data analysis strategies were applied. To replace the MAP with systolic blood pressure in the data analysis did not alter the results either.

Regardless of the relatively large sample size, the low number of hemorrhagic stroke has impaired the precise estimates of the impact of hyperglycemia on hemorrhagic stroke. Also, the follow-up length for many of the cohorts is still short with the low stroke events accumulated, particularly when the strict criteria for acute stroke was applied. This made it impossible to analyze the data separately for men and women; therefore, whether the effect is the same for men as for women is still not known and needs to be further explored in the future.

In summary, this study showed that in individuals without previous diagnosis of diabetes the risk of ischemic stroke increased with increasing FPG and 2-hour PG levels, 2-hour PG contributing to the risk more strongly than FPG. Diabetes, both previously diagnosed and screen-detected, was associated with clearly increased risk of ischemic stroke. No relationship between hyperglycemia and the risk of hemorrhagic stroke was found.

## Appendix

The DECODE Study (Diabetes Epidemiology: Collaborative analysis Of Diagnostic Criteria in Europe) was started in 1997 on the initiative of the European Diabetes Epidemiology Group.

Studies and investigators in this collaborative study are:

### Finland East-West

A. Nissinen,<sup>1</sup> J. Pekkanen,<sup>1</sup> J. Tuomilehto,<sup>1,2,3</sup> 1. Department of Health Promotion and Chronic Disease Prevention, National Public Health Institute, Helsinki; 2. Department of Public Health, University of Helsinki, Helsinki; 3. South Ostrobothnia Central Hospital, Seinäjoki.

### The National FINRISK 87 and 92 Cohorts

J. Tuomilehto,<sup>1,2,3</sup> P. Jousilahti,<sup>2</sup> J. Lindström.<sup>2</sup> 1. Department of Public Health, University of Helsinki, Helsinki; 2. Department of Health Promotion and Chronic Disease Prevention, National Public Health Institute, Helsinki; 3. South Ostrobothnia Central Hospital, Seinäjoki.

### The National FINRISK 2002

J. Tuomilehto, T. Laatikainen, M. Peltonen, J. Lindström. Department of Health Promotion and Chronic Disease Prevention, National Public Health Institute, Helsinki.

### Helsinki Policemen Study

M. Pyörälä, K. Pyörälä. Department of Medicine, University of Kuopio.

### Vantaa Study

R. Tilvis,<sup>1</sup> S. Sairanen,<sup>1</sup> J. Tuomilehto.<sup>2,3,4</sup> 1. Division of Geriatrics, Department of Medicine, University of Helsinki, Helsinki; 2. Department of Health Promotion and Chronic Disease Prevention, National Public Health Institute, Helsinki; 3. Department of Public Health, University of Helsinki, Helsinki; 4. South Ostrobothnia Central Hospital, Seinäjoki.

### Sweden Malmö Preventive Project

PM. Nilsson, G. Berglund. Department of Clinical Sciences, Lund University, University Hospital, Malmö.

### Northern Swedish MONICA

M. Eliasson, B. Stegmayr. Department of Public Health and Clinical Medicine, Umeå University, Umeå.

### The Uppsala Longitudinal Study of Adult Men (ULSAM)

B. Zethelius. Department of Public Health/Geriatrics, Uppsala University Hospital, Uppsala.

### Secretariat

Q. Qiao,<sup>1</sup> K. Borch-Johnsen,<sup>2</sup> J. Tuomilehto.<sup>1</sup> 1. Diabetes Unit, Department of Health Promotion and Chronic Disease Prevention, National Public Health Institute, Helsinki and Department of Public Health, University of Helsinki, Helsinki, Finland; 2. Steno Diabetes Center, Gentofte, Denmark.



## Data Analysis

M. Hyvärinen,<sup>1</sup> Q. Qiao,<sup>1,2</sup> L. Zhang,<sup>1,2</sup> W. Gao.<sup>1,2</sup> 1. Department of Public Health, University of Helsinki, Helsinki, Finland; 2. Diabetes Unit, Department of Health Promotion and Chronic Disease Prevention, National Public Health Institute, Helsinki, Finland.

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## Disclosures

None.

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