

Fasting glucose level and the risk of  
incident cardiovascular disease, stroke  
and all-cause mortality among  
nondiabetic Koreans

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Directed by Professor Duk-Chul Lee

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## <TABLE OF CONTENTS>

ABSTRACT -----	1
I. INTRODUCTION -----	2
1. Impaired fasting glucose and the risk of cardiovascular disease and mortality -----	2
2. Low fasting glucose and the risk of cardiovascular disease and mortality -----	3
3. The purpose of this study -----	4
II. MATERIALS AND METHODS -----	5
1. Study participants -----	5
2. Data collection -----	6
3. Statistical analysis -----	7
III. RESULTS -----	8
1. General characteristics of the study participants -----	8
2. Incidence and mortality of cardiovascular disease -----	10
3. Incidence and mortality of ischemic heart disease -----	13
4. Incidence and mortality of stroke -----	15
5. All-cause mortality -----	20
IV. DISCUSSION -----	21
1. Impaired fasting glucose and cardiovascular disease -----	21
2. Low fasting glucose and cardiovascular disease -----	24
3. Sex difference and ischemic stroke -----	25
4. Limitations of this study -----	26
V. CONCLUSION -----	27
REFERENCES -----	28
ABSTRACTS (IN KOREAN) -----	31

## LIST OF FIGURES

Figure 1. Fasting glucose level and incidence of cardiovascular disease -----	11
Figure 2. Fasting glucose level and incidence of ischemic heart disease -----	13
Figure 3. Fasting glucose level and incidence of stroke -----	17
Figure 4. Fasting glucose level and all-cause mortality -----	21

## LIST OF TABLES

Table 1. Baseline characteristics of the study population -----	8
Table 2. General characteristics in categories of fasting serum glucose level -----	9
Table 3. Incidence and mortality of cardiovascular disease in total cohort -----	11
Table 4. Incidence and mortality of cardiovascular disease in men---	12
Table 5. Incidence and mortality of cardiovascular disease in women -----	12
Table 6. Incidence and mortality of ischemic heart disease in total cohort -----	13
Table 7. Incidence and mortality of ischemic heart disease in men --	14
Table 8. Incidence and mortality of ischemic heart disease in women -----	14
Table 9. Incidence and mortality of stroke in total cohort -----	16
Table 10. Incidence and mortality of stroke in men -----	18
Table 11. Incidence and mortality of stroke in women -----	19
Table 12. Fasting glucose level and all-cause mortality in total cohort -----	20

<ABSTRACT>

Fasting glucose level and the risk of incident cardiovascular disease,  
stroke and all-cause mortality among nondiabetic Koreans

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It is well established that diabetes increases the risk of cardiovascular disease and mortality. However, the relationships between mortality and both nondiabetic hyperglycemia and low fasting glucose level have been less clear. To assess this relationship, a prospective cohort study of more than one million Koreans was conducted over 10 years. A total of 1,213,829 Korean people who had not been diagnosed with specific medical conditions were grouped according to their baseline fasting serum glucose level. Each of the relationships between fasting glucose level and the risk of cardiovascular disease incidence and mortality, stroke incidence and mortality, and all-cause mortality exhibited J-shaped curves after multivariate adjustment for age, body mass index, systolic blood pressure, total cholesterol, ALT, alcohol drinking, smoking status and physical activity. There was no evidence of a J-shaped curve for ischemic heart disease. The incidence or mortality of ischemic heart disease increased from at fasting glucose level above 110 mg/dl, but no significant change was shown at the low blood sugar level. In conclusion, fasting sugar level below 70 mg/dl increases the risk of cardiovascular incidence (HR 1.06, 1.02-1.09) and mortality (HR 1.19, 1.10-1.27), thrombotic stroke incidence (HR 1.11, 1.05-1.18) and mortality (HR 1.26, 1.06-1.49), and all-cause mortality (HR 1.07, 1.04-1.10). Fasting glucose level between 100 to 109 mg/dl also increases the risk of cardiovascular disease, thrombotic stroke, and all-cause mortality, but the risk of 100 to 109 mg/dl is lower than the risk of 110 to 125 mg/dl. The HR was higher in women than men especially in ischemic stroke. Both low glucose level and impaired fasting glucose should be considered as a predictor of cardiovascular risk and more attention should be paid to women's abnormal fasting glucose level than men's.

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Key words: glucose, cardiovascular disease, stroke, cerebral infarction,

ischemic heart disease, mortality, risk factors

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I. INTRODUCTION

1. Impaired fasting glucose and the risk of cardiovascular disease and mortality

In 1997 the American Diabetes Association (ADA) lowered diagnostic criteria of fasting plasma glucose (FPG) level for diabetes mellitus from 140 mg/dl to 126 mg/dl on the grounds that the prevalence and incidence of diabetic retinopathy begin to increase at approximately a FPG of 125 mg/dl.<sup>1</sup> ADA also recommended using a new category of impaired fasting glucose (IFG) for fasting plasma glucose level 110 to 125 mg/dl in 1997. Then, ADA lowered the criteria for IFG from 110 to 100 mg/dl in 2003 in an effort to better identify individuals at future diabetes

risk and also to improve selection of individuals at risk for coronary heart disease.<sup>1, 2</sup>

Diabetes mellitus is a well established risk factor of all-cause and cardiovascular disease mortality.<sup>3</sup> Also, nondiabetic hyperglycemia has become increasingly recognized as a risk factor for cardiovascular disease.<sup>3, 4</sup> However, the roles of impaired fasting glucose and impaired glucose tolerance in the elevation of cardiovascular disease risk or mortality have not been clear.<sup>5-8</sup> Several studies showed that impaired glucose tolerance (IGT) is a risk factor for cardiovascular disease (CVD) mortality.<sup>9, 10</sup> The Australian Diabetes, Obesity and Lifestyle Study (AusDiab) found known diabetes mellitus and impaired fasting glucose (IFG) to be independent predictors for CVD mortality after adjustment for age, sex and other traditional CVD risk factors, but IGT was not.<sup>3</sup> The Atherosclerosis Risk in Communities (ARIC) Study showed neither isolated IFG nor isolated IGT was associated with a more adverse cardiovascular disease risk profile.<sup>7</sup>

## 2. Low fasting glucose and the risk of cardiovascular disease and mortality

Additional questions of interest examine 1) what constitutes a normal glucose value<sup>11</sup> and 2) the safety or danger of having

low fasting glucose.<sup>12</sup> The large Israeli prospective study revealed that higher fasting plasma glucose levels within the normoglycemic range (below 100 mg/dl) constitute an independent risk factor for type 2 diabetes among young men.<sup>13</sup> Wei et al. documented a U-shaped relation between fasting plasma glucose and mortality.<sup>14</sup> Participant of the study with low fasting plasma glucose levels had a high risk of cardiovascular disease and all-cause mortality.<sup>14</sup> The study of Taiwanese showed a J-shaped curve of relative risks for all-cause mortality by levels of fasting blood glucose on subjects with no history of diabetes.<sup>15</sup> The DECODE study published in 2003 found a J-curved risk of long-term mortality with the lowest total mortality in subjects with a FPG 81 to 90 mg/dl.<sup>16</sup> There are also another studies found the J-shaped relationship between glucose levels and mortality.<sup>12, 17</sup>

### 3. The purpose of this study

The aim of this study is to evaluate 1) the relationship between impaired fasting glucose and CVD and all-cause mortality and 2) the relationship between low fasting glucose level and CVD and all-cause mortality in the Korean population.

## II. MATERIALS AND METHODS

### 1. Study participants

We used the data from the previously published Korean Cancer Prevention Study (KCPS).<sup>18, 19</sup> The KCPS is a prospective cohort investigation of over one million Koreans who were insured by Korean Medical Insurance Corporation, the former National Health Insurance Corporation. The cohort included governmental employees, public and private school teachers, and their dependents. The insured were required to have biennial medical examinations. The examination was conducted at designated hospitals or clinics nationwide by medical staff in accordance with the guideline provided by the Korean Medical Insurance Corporation. The exam included height, weight and blood pressure measurement, hearing test, visual acuity, chest x-ray, urinalysis, CBC and routine blood chemistry after overnight fasting. Those examined were also asked to provide their medical history and respond to questionnaires inquiring lifestyle.

The cohort includes 1,329,525 Koreans (846,907 men and 482,618 women) aged 30 to 95 years. 784,870 (59%) subjects were enrolled in 1992 and 367,903 (27.7%) in 1993, 98,417 (7.4%) in 1994, and 78,335 (5.9%) in 1995. From these 1,329,525 participants, 27,192 subjects with missing information on anthropometric evaluation or with extremely low BMI (less than

16.0) or short stature (less than 130 cm) were excluded. Anyone who had ever been diagnosed with diabetes, hypertension, stroke, cancer, liver disease, respiratory disease, tuberculosis or any other specific diseases were also excluded from this study. A resultant 1,213,819 healthy Korean people were eligible for this study.

## 2. Data collection

The follow-up period was up to 10 years. The subjects' in-hospital medical records during this period were analyzed for their morbidity and mortality. The principal outcome variables were 1) ischemic heart disease (International Classification of Diseases, tenth revision, ICD-10 codes, I20 to I25), 2) cerebrovascular disease or stroke (ICD 10, I60 to I69), 3) cardiovascular disease (CVD) which includes ischemic heart disease(I20-I25), cerebrovascular disease (I60-I69), hypertensive heart disease (I10-15), other forms of heart disease likely related to atherosclerotic CVD (I44-I52), disease of arteries (I70-I74), and other sudden death, cause unknown (R96), and 4) all-cause mortality. The cerebrovascular disease (I60-69) included hemorrhagic stroke (I60-I62) and ischemic stroke (I63-I66). For those who had more than one event, we used only the first event for this analysis.

These outcomes were ascertained from diagnoses on the discharge summaries and from causes of death on death certificates. In Korea there are certified medical chart recorders who review and abstract the medical chart and assign discharge diagnosis in a standardized form using World Health Organization codes. The recorders also complete death certificates based on the information provided by physicians. Computerized search of death certificate data from the National Statistical Office in Korea was performed for each enrollee.

### 3. Statistical Analysis

Fasting serum glucose levels were categorized as less than 70, 70 to 84, 85 to 99, 100 to 109, 110 to 125, 126 to 139, and 140 or more mg/dl (<3.88, 3.88–4.66, 4.72–5.5, 5.55–6.05, 6.11–6.94, 7–7.72, and  $\geq 7.77$  mmol/L). We used fasting glucose 85 to 99 mg/dl group as a reference. We computed hazard ratios (HRs; the hazard for incidence and mortality in a specific fasting glucose group divided by the corresponding hazard in the reference group) using Cox proportional hazards modeling to adjust for age and other potential confounding factors such as body mass index, systolic blood pressure, total cholesterol, ALT, alcohol drinking, smoking status and physical activity. All analyses were performed with SAS statistical software, version

9.2.

### III. RESULTS

#### 1. General characteristics of the study participants

Of the total 1,213,829 healthy Koreans enrolled in the study, all of whom were over the age of 30, 770,556 were men and 443,273 were women. Their characteristics are described in Table 1.

Table 1. Baseline characteristics of the study population

Characteristic	Men (N=770,556)	Women (N=443,273)
Age (yr)	45.0±11.1	49.4±12.1
Body mass index	23.2±2.6	23.2±3.1
Systolic BP(mmHg)	124.5±16.0	121.5±19.1
Diastolic BP(mmHg)	81.0±11.0	78.2±12.6
Total cholesterol(mg/dl)	191.1±37.7	194.4±39.3
AST(IU/L)	26.3±16.6	22.4±10.0
ALT(IU/L)	25.8±19.9	19.3±12.0
Alcoholic drinking(%)		
No	23.2	85.7
Yes	76.8	14.3
Physical activity(%)		
No	71.5	83.4
Yes	28.6	16.6
Hypertension		
No	78.9	80.0
Yes	21.1	20.0
Smoking status (%)		
Never smoked	20.8	93.8
Former smoker	20.1	2.0
Current smoker	59.1	4.1

They are categorized into 7 groups according to their baseline fasting serum glucose level (table 2).

Table 2. General characteristics in categories of fasting serum glucose level

Fasting glucose (mg/dl)	<70	70-84	85-99	100-109	110-125	126-139	≥140	p for trend
Number of subjects	65,287 (5.4%)	409,137 (33.7%)	480,378 (39.6%)	140,735 (11.6%)	74,013 (6.1%)	14,743 (1.2%)	29,536 (2.4%)	
Age (yr)	45.6 ±12.1	45.2 ±11.5	46.4 ±11.5	48.2 ±11.6	49.8 ±11.5	53.2 ±11.3	54.0 ±10.6	0.001
BMI	22.7 ±2.7	22.9 ±2.7	23.3 ±2.8	23.6 ±2.8	23.9 ±2.9	24.1 ±3.0	24.0 ±2.9	0.001
Systolic BP	120.8 ±16.3	121.1 ±16.3	123.2 ±16.9	126.2 ±18.0	129.0 ±18.8	131.8 ±19.9	131.9 ±20.2	<.0001
Diastolic BP	78.3 ±11.3	78.6 ±11.3	79.9 ±11.5	81.7 ±11.9	83.1 ±12.2	84.4 ±12.7	84.3 ±12.6	<.0001
Cholesterol	186.1 ±38.2	187.9 ±36.5	192.7 ±37.1	197.5 ±39.2	200.9 ±41.8	203.3 ±44.4	209.7 ±50.6	<.0001
AST (IU/L)	24.0 ±14.8	23.7 ±12.6	24.6 ±13.0	26.4 ±16.2	23.4 ±20.0	30.0 ±26.4	29.3 ±25.9	0.038
ALT (IU/L)	21.6 ±17.6	22.0 ±16.5	23.1 ±16.6	25.3 ±19.1	27.3 ±21.5	29.1 ±23.8	29.5 ±25.7	<.0001
Alcoholic drinking								
No(%)	50.0	48.7	46.0	41.4	38.0	43.3	44.0	<.0001
Yes(%)	50.0	51.3	54.0	58.7	62.0	56.7	56.0	
Exercise								
No(%)	78.2	77.1	75.8	74.5	42.5	71.4	69.2	<.0001
Yes(%)	21.9	22.9	24.2	25.6	27.5	28.6	30.8	
Hypertension								
No(%)	84.0	83.6	80.0	73.8	68.0	61.7	61.4	<.0001
Yes(%)	16.1	16.5	20.0	26.2	32.0	38.4	38.6	
Smoking status								
Never smoked	48.7	49.5	48.0	44.0	40.6	43.5	43.1	<.0001
Former smoker	11.2	12.4	13.8	15.1	16.0	15.1	15.8	
Current smoker	40.1	38.1	39.2	41.0	43.4	41.4	41.2	

Most (78.7%) people's sugar level was below 100 mg/dl. Participants with fasting glucose of 85 to 99 mg/dl were 39.6%. 214,748 subjects (17.8%) had impaired fasting glucose (IFG) by 2003 ADA criteria. These criteria increased the number of IFG three-fold compared with that (6.1%) of 1997 ADA criteria. Table 2 shows that people whose fasting glucose levels are higher tend to be older and to have higher body mass index, blood pressure, total cholesterol and ALT levels. These groups show greater incidence of smoking and drinking. They also report to exercise more, which is not easy to understand. We believe it may be because they have more features of metabolic syndrome, and they realize the need for exercise more than their young and slim counterparts.

## 2. Incidence and mortality of cardiovascular disease

Cardiovascular disease (CVD) includes ischemic heart disease, hypertensive heart disease, other heart disease probably related with atherosclerosis, cerebrovascular disease, and disease of arteries. CVD also includes sudden death of unknown cause, which is usually of cardiac origin. The CVD incidence and mortality increased at low glucose level (CVD mortality for <70 mg/dl, HR 1.19 with 95% CI 1.10–1.27). The IFG also showed increased CVD incidence and mortality. The HR of glucose 100 to

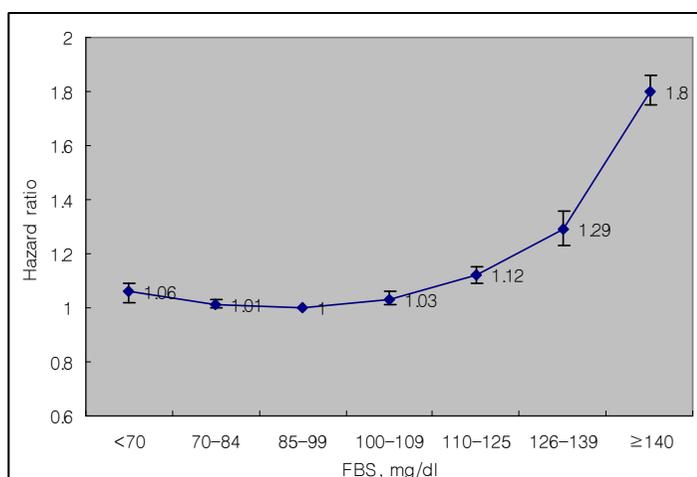
109 mg/dl group for cardiovascular mortality was 1.06 with 95% CI 1.01 to 1.12, and that of glucose 110 to 125 mg/dl was 1.16 with 95% CI 1.09 to 1.22. The HR increases as the glucose level rises, which results in the J-shaped curve (Fig 1).

Table 3. Incidence and mortality of cardiovascular disease in total cohort

Fasting Glucose	Incidence		Mortality	
	Case	HR (95%CI)**	Case	HR (95%CI)**
<70	3763	1.06(1.02-1.09)	956	1.19(1.10-1.27)
70-84	22551	1.01(1.00-1.03)	4833	1.04(1.00-1.08)
85-99	29170	1.00	6182	1.00
100-109	10247	1.03(1.01-1.06)	2379	1.06(1.01-1.12)
110-125	6581	1.12(1.09-1.15)	1594	1.16(1.09-1.22)
126-139	1752	1.29(1.23-1.36)	485	1.34(1.22-1.48)
≥140	4728	1.80(1.75-1.86)	1229	1.78(1.67-1.90)

\*\*Adjusted for age, BMI, SBP, total cholesterol, ALT, alcohol drinks, smoking status, and physical activity

Fig 1. Fasting glucose and HR for cardiovascular disease incidence



When we analyzed men and women separately, both showed the same results except for the CVD incidence rate at low glucose level in women was not significantly high (Table 4, 5). In men the CVD incidence and mortality showed J-shaped curve. In women only CVD mortality showed J-shaped curve.

Table 4. Incidence and mortality of cardiovascular disease (CVD) in men

Fasting Glucose (mg/dl)	Incidence			Mortality		
	Case	Rate per 100,000 PY*	HR (95%CI)**	Case	Rate per 100,000 PY*	HR (95%CI)**
<70	2330	563	1.06 (1.02-1.11)	610	178	1.15 (1.05-1.26)
70-84	13560	542	1.01 (0.99-1.03)	3005	165	1.02 (0.97-1.07)
85-99	17985	553	1.00	3922	162	1.00
100-109	6726	602	1.04 (1.01-1.06)	1537	178	1.03 (0.97-1.09)
110-125	4468	667	1.10 (1.07-1.14)	1067	190	1.11 (1.03-1.19)
126-139	1102	800	1.25 (1.18-1.33)	308	239	1.26 (1.12-1.42)
≥140	3074	1049	1.72 (1.66-1.79)	820	292	1.72 (1.59-1.85)

\* Age-adjusted rate

\*\* Adjusted for age, BMI, SBP, total cholesterol, ALT, alcohol drinks, smoking status, and physical activity

Table 5. Incidence and mortality of cardiovascular disease (CVD) in women

Fasting Glucose (mg/dl)	Incidence			Mortality		
	Case	Rate per 100,000 PY*	HR (95%CI)**	Case	Rate per 100,000 PY*	HR (95%CI)**
<70	1433	522	1.04 (0.98-1.10)	346	169	1.25(1.11-1.40)
70-84	8991	523	1.02 (0.99-1.05)	1828	155	1.09(1.02-1.16)
85-99	11185	637	1.00	2260	145	1.00
100-109	3521	553	1.02 (0.98-1.06)	842	166	1.11(1.02-1.20)
110-125	2113	645	1.13 (1.08-1.18)	527	180	1.22(1.10-1.34)
126-139	177	761	1.35 (1.24-1.46)	650	245	1.47(1.26-1.72)
≥140	409	1077	1.91 (1.81-2.01)	1654	286	1.87(1.68-2.09)

\* Age-adjusted rate

\*\* Adjusted for age, BMI, SBP, total cholesterol, ALT, alcohol drinks, smoking status, and physical activity

### 3. Incidence rate and mortality from ischemic heart disease

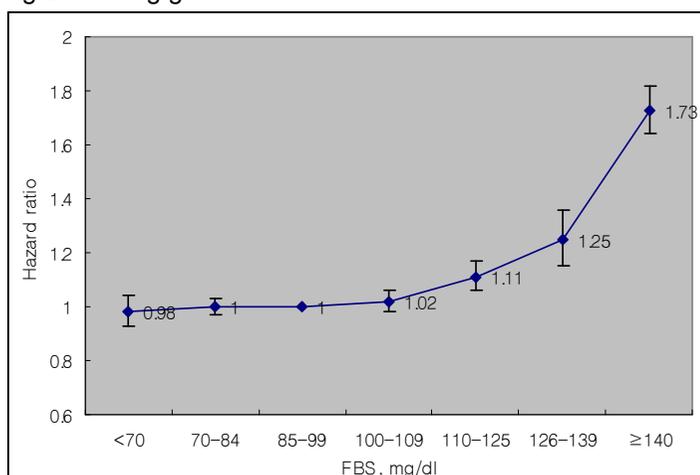
Among CVD, ischemic heart disease was analyzed. The risk of ischemic heart disease and its mortality went up from fasting glucose above 100 mg/dl. However, the ischemic heart disease incidence and mortality did not rise at the low fasting glucose level (Table 6).

Table 6. Incidence and mortality of ischemic heart disease in total cohort

Fasting glucose (mg/dl)	Incidence		Mortality	
	Case	HR (95%CI)**	Case	HR (95%CI)**
<70	1280	0.98(0.93-1.04)	206	1.09(0.94-1.27)
70-84	8212	1.00(0.97-1.03)	1160	1.07(0.99-1.15)
85-99	10710	1.00	1438	1.00
100-109	3659	1.02(0.98-1.06)	570	1.11(1.01-1.23)
110-125	2349	1.11(1.06-1.17)	397	1.28(1.15-1.44)
126-139	591	1.25(1.15-1.36)	118	1.55(1.28-1.87)
≥140	1629	1.73(1.64-1.82)	330	2.11(1.87-2.39)

\*\*Adjusted for age, BMI, SBP, total cholesterol, ALT, alcohol drinks, smoking status, and physical activity

Fig 2. Fasting glucose level and HR for ischemic heart disease incidence



The results from men and women did not show significant difference in the incidence and mortality of ischemic heart disease (Table 7 and 8).

Table 7. Incidence and mortality of ischemic heart disease in men

Fasting serum glucose	Incidence			Mortality		
	Case	Rate per 100,000 PY*	HR (95%CI)**	Case	Rate per 100,000 PY*	HR (95%CI)**
<70	872	195	1.01 (0.94-1.09)	145	38	1.04 (0.87-1.24)
70-84	5488	200	1.02 (0.99-1.06)	848	40	1.07 (0.97-1.17)
85-99	7146	253	1.00	1050	78	1.00
100-109	2646	219	1.05 (1.00-1.10)	424	45	1.10 (0.98-1.24)
110-125	1688	239	1.09 (1.04-1.15)	300	48	1.25 (1.09-1.42)
126-139	394	275	1.21 (1.09-1.34)	86	68	1.53 (1.22-1.91)
≥140	1080	350	1.57 (1.47-1.68)	227	74	1.90 (1.64-2.20)

\* Age-adjusted rate

\*\*Adjusted for age, BMI, SBP, total cholesterol, ALT, alcohol drinks, smoking status, and physical activity

Table 8. Incidence and mortality of ischemic heart disease in women

Fasting serum glucose	Incidence			Mortality		
	Case	Rate per 100,000 PY*	HR (95%CI)**	Case	Rate per 100,000 PY*	HR (95%CI)**
<70	408	134	0.91 (0.82-1.02)	61	27	1.24 (0.94-1.64)
70-84	2724	143	0.95 (0.90-1.00)	312	25	1.09 (0.94-1.27)
85-99	3564	152	1.00	388	24	1.00
100-109	1013	149	0.93 (0.87-1.00)	146	29	1.09 (0.90-1.32)
110-125	661	198	1.14 (1.04-1.24)	97	31	1.29 (1.03-1.61)
126-139	197	225	1.30 (1.13-1.51)	32	55	1.54 (1.07-2.21)
≥140	549	356	2.01 (1.83-2.20)	103	69	2.62 (2.09-3.29)

\* Age-adjusted rate

\*\*Adjusted for age, BMI, SBP, total cholesterol, ALT, alcohol drinks, smoking status, and physical activity

#### 4. Cerebrovascular disease

Total cerebrovascular disease, hemorrhagic stroke and ischemic stroke were analyzed with the same method. Total stroke mortality increased at low glucose group (<70 mg/dl) and hyperglycemic group (above 100 mg/dl). Stroke incidence increased at low glucose group (<70 mg/dl) and at a glucose level above 110 mg/dl. The incidence and mortality of ischemic stroke increased at low glucose group (<70 mg/dl) and hyperglycemic group above 100 mg/dl, showing J-shaped curve. The incidence and mortality of hemorrhagic stroke were increased only at glucose level above 140 mg/dl (Table 9). Men and Women showed differences in mortality of thrombotic stroke. The incidence of ischemic stroke increased at glucose below 70 mg/dl and above 100 mg/dl in men. But the mortality from ischemic stroke in men was high only at glucose above 140 mg/dl (Table 10). In women the incidence rate and mortality both increased at sugar above 100 mg/dl. Also low glucose level increased the risk of ischemic stroke mortality in women (Table 11).

Table 9. Incidence and mortality of stroke in total cohort

Fasting serum glucose	Incidence		Mortality	
	Case	HR (95%CI)**	Case	HR (95%CI)**
<b>Total Stroke</b>				
<70	1992	1.11(1.06-1.17)	635	1.19(1.09-1.30)
70-84	11272	1.02(0.99-1.04)	3146	1.03(0.98-1.08)
85-99	14575	1.00	4064	1.00
100-109	5225	1.04(1.01-1.07)	1544	1.05(0.99-1.11)
110-125	3405	1.13(1.09-1.18)	1031	1.13(1.05-1.21)
126-139	995	1.40(1.31-1.49)	312	1.29(1.15-1.45)
≥140	2681	1.95(1.87-2.04)	801	1.76(1.63-1.90)
<b>Hemorrhage Stroke</b>				
<70	575	1.07(0.98-1.17)	230	1.07(0.93-1.23)
70-84	3281	0.98(0.94-1.03)	1287	1.02(0.95-1.10)
85-99	4327	1.00	1657	1.00
100-109	1418	0.96(0.90-1.02)	558	0.94(0.85-1.03)
110-125	881	1.00(0.93-1.07)	393	1.07(0.95-1.20)
126-139	217	1.17(0.95-1.43)	107	1.17(0.95-1.43)
≥140	419	1.31(1.13-1.51)	228	1.31(1.13-1.51)
<b>Thrombotic Stroke</b>				
<70	1249	1.11(1.05-1.18)	154	1.26(1.06-1.49)
70-84	7060	1.02(0.99-1.06)	727	1.03(0.94-1.14)
85-99	9170	1.00	952	1.00
100-109	3426	1.07(1.03-1.12)	441	1.26(1.12-1.42)
110-125	2340	1.22(1.17-1.28)	271	1.26(1.10-1.44)
126-139	738	1.59(1.47-1.72)	77	1.36(1.07-1.72)
≥140	2143	2.41(2.30-2.53)	278	2.61(2.28-3.00)

\*\*Adjusted for age, BMI, SBP, total cholesterol, ALT, alcohol drinks, smoking status, and physical activity

Fig 3. Fasting glucose level and HR for stroke incidence

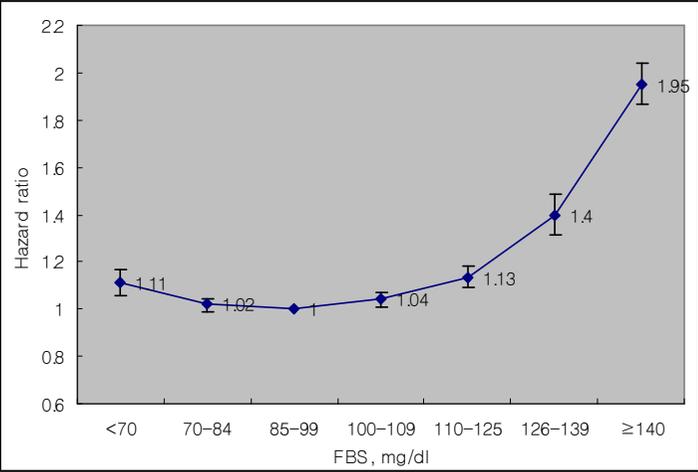


Table 10. Incidence and mortality of stroke in men

Fasting serum glucose	Incidence			Mortality		
	Case	Rate per 100,000 PY*	HR (95%CI)**	Case	Rate per 100,000 PY*	HR (95%CI)**
<b>Total Stroke</b>						
<70	1195	295	1.09 (1.03-1.16)	390	115	1.15 (1.03-1.28)
70-84	6604	276	1.00 (0.97-1.03)	1869	105	1.00 (0.94-1.07)
85-99	8870	283	1.00	2481	104	1.00
100-109	3351	307	1.03 (0.99-1.07)	957	112	1.00 (0.93-1.08)
110-125	2302	349	1.12 (1.07-1.17)	664	120	1.07 (0.98-1.17)
126-139	616	428	1.32 (1.22-1.44)	193	143	1.19 (1.02-1.38)
≥140	1766	578	1.89 (1.79-1.99)	532	188	1.72 (1.56-1.89)
<b>Hemorrhage Stroke</b>						
<70	328	78	1.00 (0.89-1.13)	143	37	1.06 (0.89-1.27)
70-84	1906	74	0.94 (0.89-1.00)	779	35	1.02 (0.93-1.12)
85-99	2680	80	1.00	1010	34	1.00
100-109	933	81	0.95 (0.88-1.03)	374	36	0.96 (0.85-1.08)
110-125	628	92	1.02 (0.93-1.11)	271	42	1.12 (0.98-1.28)
126-139	139	102	1.01 (0.85-1.20)	67	50	1.08 (0.83-1.40)
≥140	293	98	1.04 (0.82-1.18)	162	53	1.39 (1.17-1.64)
<b>Thrombotic Stroke</b>						
<70	785	197	1.12 (1.04-1.21)	97	28	1.15 (0.93-1.44)
70-84	4237	181	1.02 (0.98-1.06)	444	27	0.97 (0.85-1.10)
85-99	5639	184	1.00	619	28	1.00
100-109	2207	203	1.06 (1.01-1.12)	260	32	1.09 (0.94-1.26)
110-125	1572	233	1.19 (1.13-1.26)	170	32	1.10 (0.92-1.61)
126-139	452	307	1.49 (1.35-1.64)	46	33	1.19 (0.88-1.60)
≥140	1393	449	2.28 (2.15-2.43)	190	66	2.45 (2.07-2.90)

\* Age-adjusted rate

\*\*Adjusted for age, BMI, SBP, total cholesterol, ALT, alcohol drinks, smoking status, and physical activity

Table 11. Incidence and mortality of stroke in women

Fasting serum glucose	Incidence			Mortality		
	Case	Rate per 100,000 PY*	HR (95%CI)**	Case	Rate per 100,000 PY*	HR (95%CI)**
<b>Total Stroke</b>						
<70	797	293	1.14 (1.06-1.23)	245	119	1.26 (1.10-1.44)
70-84	4668	279	1.05 (1.01-1.09)	1277	106	1.08 (1.00-1.16)
85-99	5705	270	1.00	1583	99	1.00
100-109	1874	290	1.05 (1.00-1.11)	587	111	1.11 (1.01-1.22)
110-125	1103	317	1.13 (1.06-1.21)	367	122	1.21 (1.08-1.36)
126-139	379	420	1.49 (1.34-1.65)	119	151	1.45 (1.20-1.75)
≥140	915	559	2.00 (1.86-2.15)	269	176	1.80 (1.57-2.05)
<b>Hemorrhage Stroke</b>						
<70	247	85	1.17 (1.02-1.35)	87	36	1.09 (0.97-1.37)
70-84	1375	77	1.04 (0.97-1.12)	508	35	1.02 (0.91-1.15)
85-99	1647	76	1.00	647	35	1.00
100-109	485	76	0.97 (0.87-1.07)	184	29	0.89 (0.75-1.05)
110-125	253	72	0.93 (0.81-1.07)	112	34	0.96 (0.78-1.18)
126-139	78	86	1.12 (0.89-1.40)	40	50	1.34 (0.97-1.85)
≥140	126	76	0.98 (0.82-1.18)	66	43	1.16 (0.89-1.50)
<b>Thrombotic Stroke</b>						
<70	464	176	1.09 (0.99-1.21)	57	28	1.44 (1.08-1.91)
70-84	2823	172	1.04 (0.99-1.09)	283	25	1.16 (0.99-1.36)
85-99	3531	169	1.00	333	22	1.00
100-109	1219	183	1.08 (1.01-1.16)	181	34	1.58 (1.31-1.89)
110-125	768	220	1.24 (1.14-1.34)	101	34	1.55 (1.23-1.94)
126-139	286	314	1.73 (1.53-1.95)	31	44	1.63 (1.11-2.38)
≥140	750	446	2.55 (2.35-2.77)	88	55	2.77 (2.17-3.52)

\* Age-adjusted rate

\*\*Adjusted for age, BMI, SBP, total cholesterol, ALT, alcohol drinks, smoking status, and physical activity

## 5. All-cause mortality

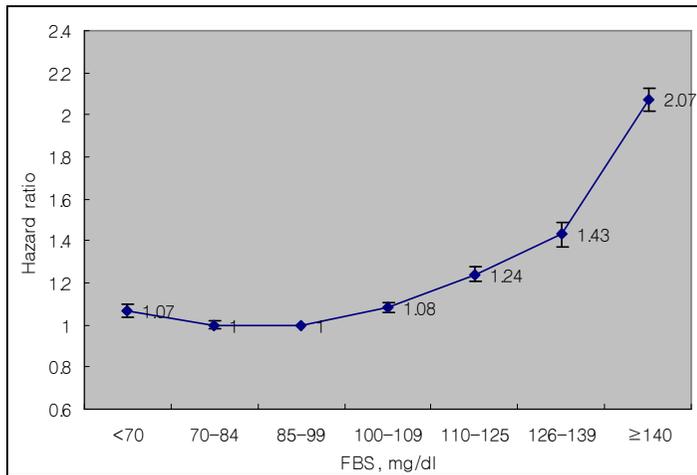
The relationship between all-cause mortality and fasting glucose level also showed J-shaped curve (Table 12). HR increased at the low glucose level (<70 mg/dl, HR 1.07, 95% CI 1.04-1.10) and started to increase from at glucose 100-109 mg/dl (HR 1.08, 95% CI 1.06-1.11). For the group with glucose above 140 mg/dl, HR was 2.07 (95% CI 2.02-2.13). Because the low glucose level can be resulted from certain cancer, we re-analyzed the previous result, which showed no increase of HR at glucose below 90 mg/dl.<sup>19</sup> Either glucose below 70 mg/dl (HR 1.02, 95% CI 0.97-1.07) or glucose 70-84 mg/dl (HR 0.99, 95% CI 0.96-1.02) group was not related with all-cancer mortality.

Table 12. All-cause mortality in total cohort

Fasting glucose	Mortality	
	Case	HR (95%CI)**
<70	4953	1.07(1.04-1.10)
70-84	25988	1.00(0.98-1.02)
85-99	33099	1.00
100-109	12333	1.08(1.06-1.11)
110-125	8424	1.24(1.21-1.28)
126-139	2396	1.43(1.37-1.49)
≥140	6606	2.07(2.02-2.13)

\*\*Adjusted for age, BMI, SBP, total cholesterol, ALT, alcohol drinks, smoking status, and physical activity

Fig 4. Fasting glucose level and HR for all-cause mortality



#### IV. DISCUSSION

##### 1. Impaired fasting glucose and CVD incidence and mortality

According to the findings reported by Nielson et al., nondiabetic hyperglycemic (fasting glucose 100 to 125 mg/dl) patients have a significantly greater risk for development of coronary artery disease.<sup>20</sup> The European Diabetes Epidemiology Group examined published data to assess the magnitude of the association between different thresholds (100 or 110 mg/dl) for IFG and diabetes.<sup>16</sup> They found that the magnitude of the association between diabetes and IFG is greater for IFG defined as fasting plasma glucose of 110 to 125 mg/dl (IFG110) than for the new category of fasting plasma glucose of 100 to 109 mg/dl (IFG100).<sup>16</sup> A meta-analysis of 38 prospective studies conducted

by Levitan et al. showed that both fasting glucose level and post-challenge blood glucose level were risk markers for CVD among apparently healthy individuals without diabetes.<sup>4</sup> This meta-analysis also showed a linear relationship between CVD risk and post-challenge blood glucose level and a possible threshold effect with fasting blood glucose level to be around 100 mg/dl.<sup>4</sup> Our findings are also consistent with Levitan's meta-analysis results. The fasting glucose level worked as a risk factor after adjusting confounding factors such as age, BMI, BP, total cholesterol, ALT, smoking, and physical activity. From fasting glucose 100 mg/dl the risk started to increase, although the increase of HR in group with fasting glucose 100 to 109 mg/dl was smaller than group with fasting glucose above 110 mg/dl. Another study with nondiabetic Italian Caucasians showed that IFG110 is associated with a worse metabolic and cardiovascular risk profile as compared with IFG100.<sup>21</sup> IFG110 was associated with higher risk of post-challenge glucose intolerance, lower levels of circulating IGF-1, and increased levels of inflammatory markers including white blood cell count and C-reactive protein.<sup>21</sup> Andreozzi's study implies that IFG110 was more related with the incidence of diabetes and inflammatory process of cardiovascular events than IFG100. In our result, the risk increased as the fasting glucose level increased. The change of

cutoff value for IFG has been challenged.<sup>16, 22</sup> Diagnostic criteria are beyond the scope of this study. Instead, we will discuss the clinical significance of the fasting glucose level 100 to 110 mg/dl. Recently, in the Chinese Multi-provincial Cohort Study<sup>23</sup>, Liu et al. reported that the normal fasting glucose group, impaired fasting glucose group and diabetes group with metabolic syndrome had increased CVD risk compared to those groups without metabolic syndrome. Therefore, Liu et al. concluded that the increased CVD risk in individuals with IFG or diabetes was largely driven by the coexistence of multiple metabolic disorders rather than hyperglycemia per se.<sup>23</sup> The Hoorn study also suggests high risk of cardiovascular mortality in individuals with impaired fasting glucose is explained by conversion to diabetes.<sup>22</sup> However, glucose is clearly responsible for the microvascular complications of diabetes and has a significant impact on the pathogenesis of atherosclerotic macrovascular disease.<sup>24</sup> The Rotterdam Study found IFG 110 to be associated with increased arterial stiffness in elderly people without diabetes mellitus.<sup>25</sup> The CATHAY study found that increased levels of glycemia (102 to 124 mg/dl) is adversely associated with arterial endothelial dysfunction and intima-media thickening.<sup>26</sup> With all of the results taken into consideration, non-diabetic hyperglycemia, i.e. impaired fasting glucose is an

independent risk factor of incident cardiovascular disease, ischemic heart disease, stroke and mortality and fasting glucose level 110 to 125 mg/dl tends to be more strongly related with the risk than fasting glucose level 100 to 109 mg/dl.

## 2. Low fasting glucose level and cardiovascular risk

Low fasting plasma glucose level was reported as a predictor of cardiovascular disease and all-cause mortality from a prospective cohort study of more than 40,000 people by Wei et al.<sup>14</sup> The lowest total mortality of that study was found in the subjects with a FPG in the interval 79 to 109 mg/dl. In the study by Balkau et al. the interval of the lowest total mortality was 94 to 103 mg/dl<sup>17</sup> and in the 2003 DECODE study was 81 to 90 mg/dl.<sup>16</sup> The findings by Wändell et al. showed that the lowest incidence mortality occurred in the interval of 113 to 121 mg/dl<sup>12</sup>, higher than other studies. In our study, the lowest total mortality count occurred within the 85 to 99 mg/dl interval. Although the numbers are arbitrary and varied, the trend of J-shaped curve with increasing risk at the lower glucose level is consistent.

Very low glucose level can be associated with CVD mortality in diabetic patients. But the studies mentioned above excluded diabetes patients or had very few cases of classic hypoglycemia with fasting glucose less than 50 mg/dl. It is not known how the

low fasting glucose level can be associated with CVD and all-cause mortality in nondiabetic people. Wei et al. hypothesized that long-term exposure to low fasting plasma glucose may serve as a risk factor of CVD mortality, perhaps through abnormal cardiac activity and thrombosis, especially in patients with atherosclerosis.<sup>14</sup> Tanne et al. reported a J-shaped relationship between fasting plasma glucose and incident ischemic cerebrovascular events in patients with pre-existing atherothrombotic disease.<sup>27</sup> Tanne et al. explained that hypoglycemia and rapid changes in plasma glucose have been shown to increase counter-regulatory hormones such as epinephrine and norepinephrine, which may induce vasoconstriction, platelet aggregation, and, thereby, ischemia.<sup>27</sup>  
<sup>28</sup> Further study will be needed to define the association of low fasting glucose level and CVD and all-cause mortality. Meanwhile, it would be worthwhile to pay more attention to low fasting glucose level in addition to nondiabetic hyperglycemia.

### 3. Sex differences and ischemic stroke

While elevated fasting glucose was associated with increase cardiovascular disease and mortality in both men and women, the hazard ratios were higher in women for all endpoints studied. The gender difference was particularly marked for ischemic stroke.

These findings are consistent with the well established interaction between gender and diabetes (women with diabetes have higher increases in cardiovascular risk compared to men with diabetes) and with the findings of the DECODE study, which showed a significant sex difference for cardiovascular mortality. Since women's nondiabetic hyperglycemia carries higher mortality risk than men's, probably a more aggressive intervention should be given to women's abnormal fasting glucose level.

#### 4. Limitations of this study

This study did not factor in the conversion to diabetes during follow-up and could not define the association between IFG and the risk of mortality as independent of the conversion to diabetes during follow-up. This study also did not include other parameters for metabolic syndrome such as triglyceride, HDL-cholesterol, and waist circumference and thus could not completely rule out the confounding effect of metabolic syndrome.

The outcomes were obtained from admission records and death certificates. Since their outpatient records were not included, the incidence of morbidity would be lower than actual incidence. For example, transient ischemic attack or mild angina that was

evaluated and treated in outpatient department would have been missed.

The cardiovascular disease in other studies usually accounted for all diseases of the circulatory system (ICD-10, I00 to I99) and sudden death of unknown origin, but the cardiovascular disease in our study did not include some of the diseases of the circulatory system (I00-I09, I26-I52, I77-79, I80-99). This also could have lowered the incidence and mortality of cardiovascular disease.

## V. CONCLUSION

A prospective cohort of more than one million Korean people for over the period of 10 years revealed that fasting glucose level is closely related with CVD incidence and mortality and all-cause mortality. The J-shaped curve was exhibited for each relationship, with the exception of the relationship between ischemic heart disease and fasting glucose level. The risk is high when fasting glucose level is below 70 mg/dl. The risk also starts to increase from a fasting glucose of 100 mg/dl. The increased risk for the fasting glucose interval of 100 to 109 mg/dl is smaller than that of 110 to 125 mg/dl. Both low glucose level and impaired fasting glucose should be considered as a predictor of cardiovascular disease risk.

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< ABSTRACT (IN KOREAN)>

한국인의 공복혈당과 심혈관계질환 및 전체사망률의 관계

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박찬신

당뇨가 심혈관계질환의 발생 및 사망률을 높이는 것은 잘 알려진 사실이다. 그러나 저혈당 및 공복혈당장애와 심혈관계질환의 발병 및 사망률의 관계는 명확하게 밝혀져 있지 않다. 따라서 이러한 관계를 조사하기 위하여 백만여 명의 한국인을 대상으로한 코호트 연구가 십 년 동안 행하여졌다. 특이한 병력이 없는 1,213,829 명의 한국인이 초기 공복혈당을 중심으로 분류되었다. 공복혈당과 심혈관계질환의 발병 및 사망률, 뇌졸중의 발병 및 사망률, 그리고 전체사망률이 모두 J 형 곡선의 관계를 나타내었다. 허혈성 심질환은 J 형 곡선을 나타내지 않았다. 허혈성심질환의 경우 공복혈당이 110 mg/dl 이상인 경우 발병을 및 사망률이 모두 증가하였으나 저혈당에서는 특별한 변화를 보이지 않았다. 결론적으로 공복혈당이 70 mg/dl 이하인 경우 심혈관계질환의 발병을 (HR 1.06, 1.02-1.09) 및 사망률 (HR 1.19, 1.10-1.27), 뇌졸중의 발병을 (HR 1.11, 1.06-1.17) 및 사망률 (HR 1.19, 1.09-1.30), 그리고 전체 사망률 (HR 1.07, 1.04-1.10)의 증가를 보였다. 공복혈당이 100-109 mg/dl 인 경우에도 심혈관계질환, 뇌졸중 및 전체 사망률이 증가하나 증가하는 위험도는 공복혈당 110-125 mg/dl 인 경우에 비하여 미약하였다. 공복혈당의 증가에 따른 심혈관계의 위험도의 상승은 남성에서보다 여성에서 더 현저하였으며 특히 허혈성 뇌졸중의 경우 여성에서 위험도의 증가가 높았다. 따라서 저혈당과 공복혈당장애 모두 심혈관계질환의 위험 요인으로 고려되어야 하며 여성의 비정상 공복혈당의 경우, 보다 적극적인 개입이 필요하다.

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핵심 되는 말: 공복혈당, 저혈당, 공복혈당장애, 심혈관계질환, 뇌졸중, 전체 사망률