제 26차 대한당뇨병학회 춘계학술대회, 2013. 5. 9-11. 제주

Fasting Glucose Level and Atherosclerotic Cardiovascular Diseases

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Graduate School of Public Health

Yonsei University, Seoul, Korea

Contents

- Background
- Japanese Funagata Diabetes Study
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Haffner et al., 1990

Original Contributions

Cardiovascular Risk Factors in Confirmed Prediabetic Individuals

Does the Clock for Coronary Heart Disease Start Ticking Before the Onset of Clinical Diabetes?

Steven M. Haffner, MD, MPH; Michael P. Stern, MD; Helen P. Hazuda, PhD; Braxton D. Mitchell, PhD; Judith K. Patterson, PhD

JAMA 1990;2893-2898

Haffner et al., 1990

Since pre diabetic individuals are hyper insulinemic, and since hyper insulinemia may be a cardiovascular risk factor,

we hypothesized that pre-diabetic individuals might have an atherogenic pattern of risk factors even before the onset of clinical diabetes.

JAMA 1990;2893-2898

Hu FB et al, 2002

Epidemiology/Health Services/Psychosocial Research

ORIGINAL ARTICLE

Elevated Risk of Cardiovascular Disease Prior to Clinical Diagnosis of Type 2 Diabetes

FRANK B. HU, MD[1,2,3]
MEIR J. STAMPFER, MD[1,2,3]
STEVEN M. HAFFNER, MD[4]
CAREN G. SOLOMON, MD[5]
WALTER C. WILLETT, MD[1,2,3]
JOANN E. MANSON, MD[2,3,6]

OBJECTIVE — To examine whether the risk of cardiovascular disease (CVD) is elevated before clinical diagnosis of type 2 diabetes in women.

RESEARCH DESIGN AND METHODS — A total of 117,629 female nurses aged 30–55 years who were free of diagnosed CVD at baseline were recruited in 1976 and followed for 20 years.

8-year follow-up of the San Antonio Heart Study (4), subjects who converted to diabetes during the follow-up had higher baseline levels of total and LDL cholesterol, triglycerides, and blood pressure and lower levels of HDL than those who remained nondiabetic, even after adjustment for obesity. The enhanced atherogenic risk profile in the prediabetic state may contribute to the subsequent increased risk of CVD. To our knowledge, no long-term prospective data exist on incidence of cardiovascular end points in

Diabetes Care 25:1129–1134, 2002

Hu FB et al, 2002

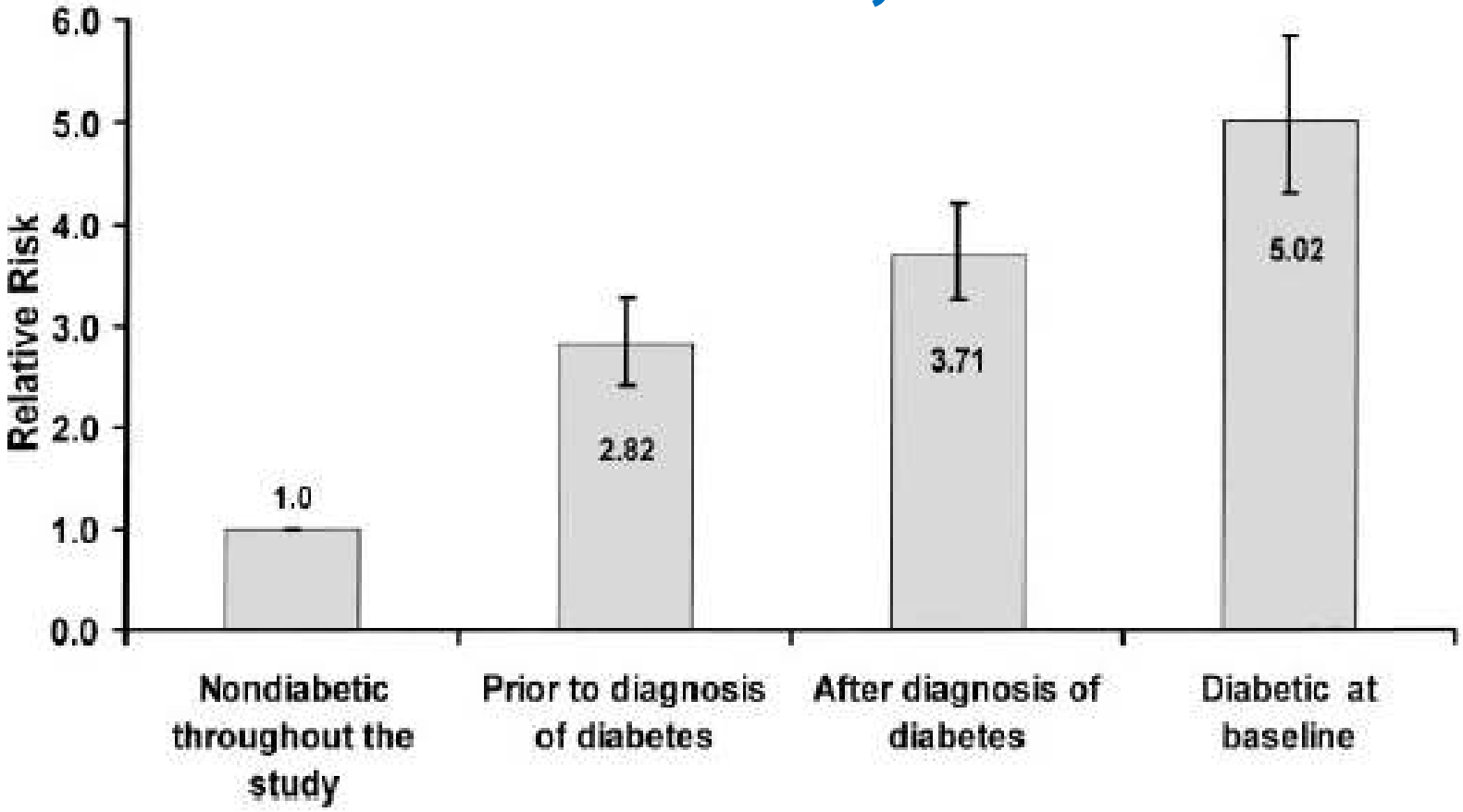

Figure 1—*Multivariate RRs and 95% CIs of MI or stroke according diabetes status: the NHS 1976–1996. Adjusted for the same variables in Table 2.*

***Diabetes Care* 25:1129–1134, 2002**

Hu FB et al, 2002

- **Indicated a substantially elevated risk of CVD before clinical diagnosis of type 2 diabetes in women.**
- **These findings suggest that aggressive management of cardiovascular risk factors is warranted in individuals at increased risk for diabetes.**

Diabetes Care 25:1129–1134, 2002

- **Japanese Funagata Diabetes Study**
  - **IGT, IFG**

Epidemiology/Health Services/Psychosocial Research

ORIGINAL ARTICLE

Impaired Glucose Tolerance Is a Risk Factor for Cardiovascular Disease, but Not Impaired Fasting Glucose

The Funagata Diabetes Study

MAKOTO TOMINAGA, MD
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HIDEO MANAKA, MD
KIMIKO IGARASHI, MD
TAKEO KATO, MD
AKIRA SEKIKAWA, MD, MPH

diabetes have recently been proposed by the Expert Committee of the American Diabetes Association (ADA) (1) and provisionally agreed to by a World Health Organization (WHO) consultation (2). These criteria, which use fasting plasma glucose levels

Tominaga et al., Diabetes Care 1999;22:920

Objective

To determine whether the new category of impaired fasting glucose (IFG) recently proposed by the Expert Committee of the American Diabetes Association is a risk factor for cardiovascular disease.

Tominaga et al., Diabetes Care 1999;22:920

Research Design

- Cohort population, Yamagata prefecture, Japan, 1990-1992
- 7 years follow-up
- Three groups
  - NGT (n=2016), IGT (n=382), Diabetes (n=253)
  - NFG, IFG, Diabetes
- Life-tables method
- Cox's proportional hazard model

Tominaga et al., Diabetes Care 1999;22:920

Results

	NGT	IGT	DM
N	2,016	382	253
Age, years	58.8	62.7	65.6
Fasting P. glucose	91	99	130
2h plasma glucose	101	158	266

Tominaga et al., Diabetes Care 1999;22:920

All cause death CVD death

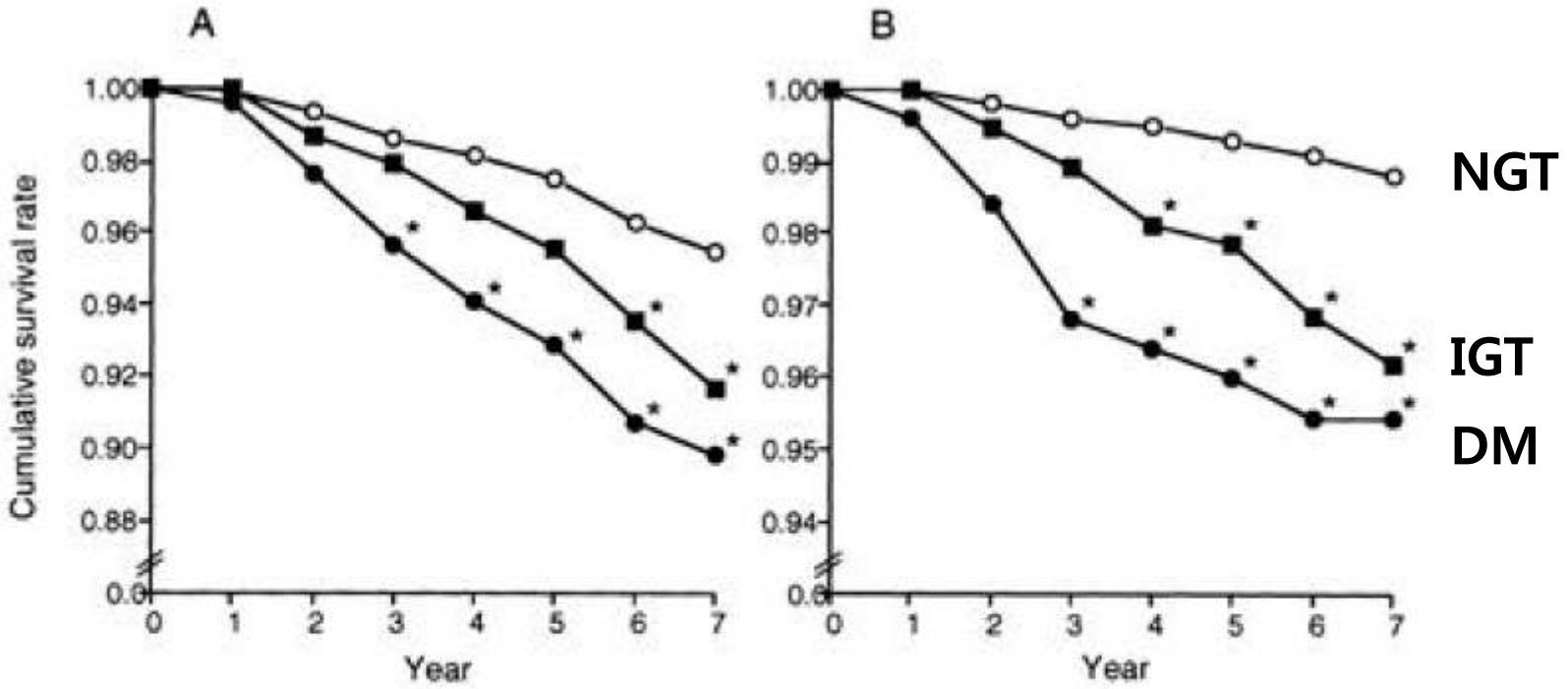

Figure 1—*Cumulative survival rate of the Funagata cohort population, classified into NGT, IGT, and diabetic groups according to the WHO criteria (1985). A: Cumulative survival rates from all causes of death, determined by the life-table method, of both the IGT (■) and the diabetic group (●) were signifi - cantly lower when compared with those of the NGT group (○). B: Cumulative survival rates from car - diovascular disease (coronary heart disease and stroke) of the IGT and diabetic groups were also significantly lower than that of the NGT group. *P < 0.05.*

Tominaga et al., Diabetes Care 1999;22:920

WHO criteria, 1985

	HR	95% CI	P value
Death from all cause			
Age	1.105	1.085-1.126	0.0001
IGT	1.313	0.837-2.059	0.2360
Diabetes	1.205	0.742-1.957	0.4506
Death from CVD			
Age	1.114	1.070-1.150	0.0001
IGT	2.219	1.076-4.577	0.0309
Diabetes	2.274	1.069-4.838	0.0329

Tominaga et al., Diabetes Care 1999;22:920

Results

- The hazard ratio of IGT to NGT on death from CVD:
- 2.219 (95% CI, 1.076-4.577)

Tominaga et al., Diabetes Care 1999;22:920

All cause death CVD death

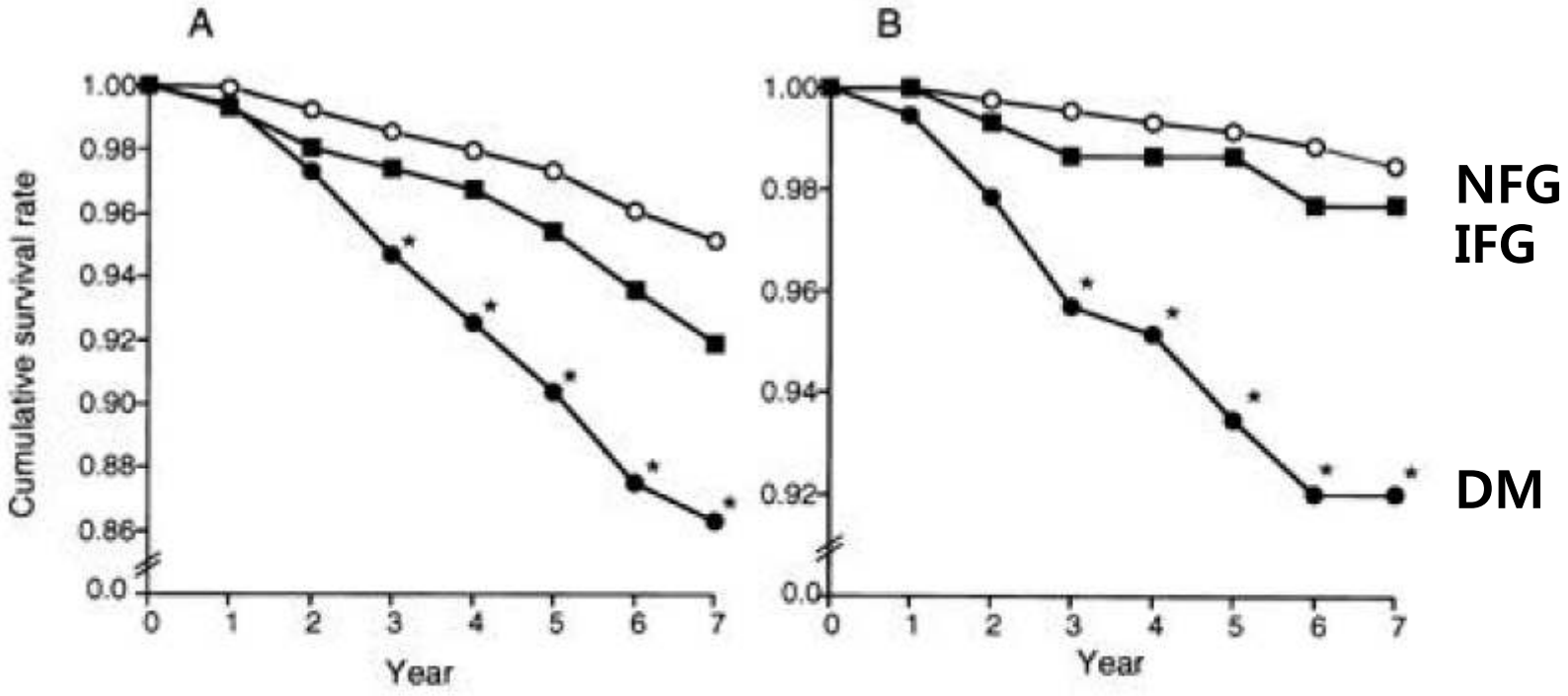

Figure 2—*Cumulative survival rate of the Funagata cohort population, classified into NFG, IFG, and diabetic groups according to the ADA recommendation (1997). A: The cumulative survival rate of the IFG group (■) from all causes of death was not different from that of the NFG group (○), although the cumulative survival rate of the diabetic group (●) was significantly lower than that of the NGT group. B: The cumulative rate of survival from cardiovascular disease in the IFG group was also not different from that of the NFG group. *P < 0.05.*

Tominaga et al., Diabetes Care 1999;22:920

ADA recommendation, 1997

	HR	95% CI	P value
Death from all cause			
IFG	1.236	0.643-2.378	0.5255
Diabetes	1.706	1.072-2.715	0.0241
Death from CVD			
IFG	1.136	0.345-3.734	0.8342
Diabetes	2.484	1.226-5.033	0.0116

Tominaga et al., Diabetes Care 1999;22:920

Results

- The hazard ratio of IFG to NFG on death from CVD:
- 1.136 (95% CI, 0.345-3.734)

Tominaga et al., Diabetes Care 1999;22:920

Conclusion

In conclusion, IGT, but not IFG, was a risk factor for death from cardiovascular disease.

Therefore, the two diagnostic criteria (WHO 1985 and ADA 1997) with and without OGTT should be used as routine clinical practices for the purposes of diagnosing overt diabetes or detecting risk factors for cardiovascular disease.

Tominaga et al., Diabetes Care 1999;22:920

Korean Data I

- **Korean Heart Study**
  - **Stage 1 IFG, Stage 2 IFG**

Epidemiology/Health Services Research
ORIGINAL ARTICLE

Impaired Fasting Glucose and Risk of Cardiovascular Disease in Korean Men and Women

The Korean Heart Study

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JAEWON CHOE, MD, PHD[1]
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SEONG-WOOK PARK, MD, PHD[4]
YOUNG DUK YUN, MD[5]
SOO-JIN BAEK, MS[5]
YEJIN MOK, MPH[6,7]
SUN HA JEE, PHD, MPH[6,7]

OBJECTIVE—The relationship between impaired fasting glucose (IFG) and risk of cardiovascular disease (CVD) or ischemic heart disease (IHD) varies widely according to sex and ethnicity. We evaluated the relationship between IFG and CVD or IHD among Korean men and women.

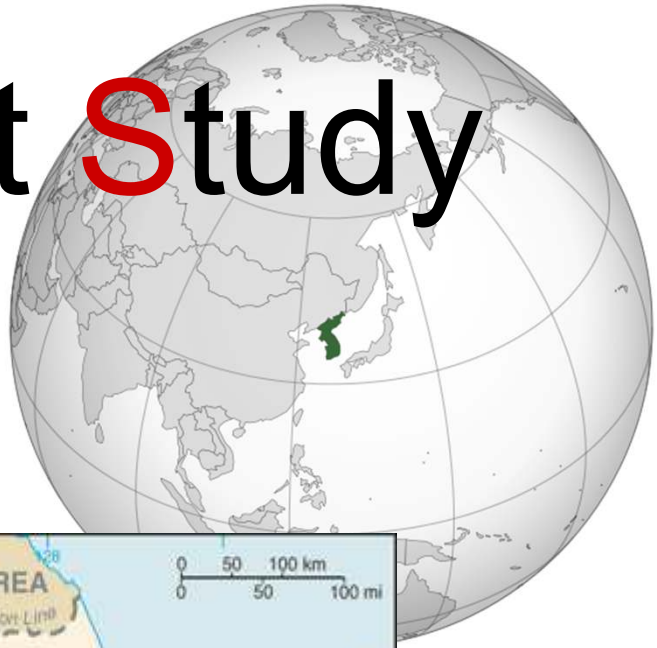
RESEARCH DESIGN AND METHODS—A total of 408,022 individuals who underwent voluntary private health examinations in 17 centers in South Korea were followed for 10 years. Data regarding CVD or IHD events were obtained from the Korean National Health Insurance database. IFG was categorized as grade 1 (fasting glucose 100–109 mg/dL) or grade 2 (110–125 mg/dL).

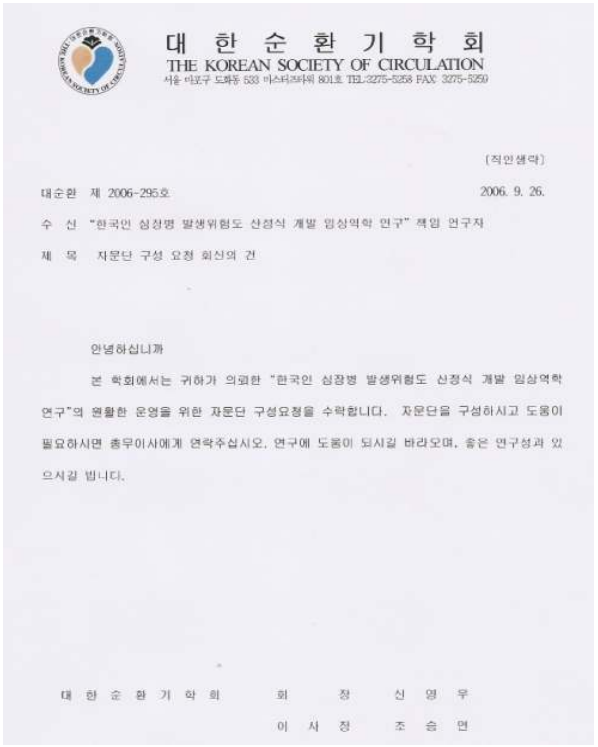
mortality (7,8). However, the association between impaired fasting glucose (IFG) and risk of CVD and/or IHD remains unclear (7–18). Although some studies have reported that IFG was associated with a greater risk of IHD/CVD in women than in men (17,19), others have reported similar risks for men and women (18).

There has also been considerable debate regarding the threshold glucose level associated with increased CVD risk. In 2003, the American Diabetes Association (ADA) lowered the fasting plasma glucose (FPG) cutoff point for IFG from 110 to 100 mg/dL (20). Some studies have reported that FPG levels of 110–125 mg/

Kim HK et al., Diabetes Care 2012

Korean Heart Study (KHS)





대 한 순 환 기 학 회
THE KOREAN SOCIETY OF CIRCULATION
서울 마포구 도화동 533 마스터즈타워 801호 TEL:3275-5258 FAX: 3275-5259

(직인생략)

대순환 제 2006-295호 2006. 9. 26.

수 신 "한국인 심장병 발생위험도 산정식 개발 임상역학 연구" 책임 연구자

제 목 자문단 구성 요청 회신의 건

안녕하십니까

본 학회에서는 귀하가 의뢰한 "한국인 심장병 발생위험도 산정식 개발 임상역학 연구"의 원활한 운영을 위한 자문단 구성요청을 수락합니다. 자문단을 구성하시고 도움이 필요하시면 총무이사에게 연락주십시오. 연구에 도움이 되시길 바라오며, 좋은 연구성과 있으시길 빕니다.

대 한 순 환 기 학 회 회 장 신 영 무
이 사 장 조 승 연

European Journal of Preventive Cardiology

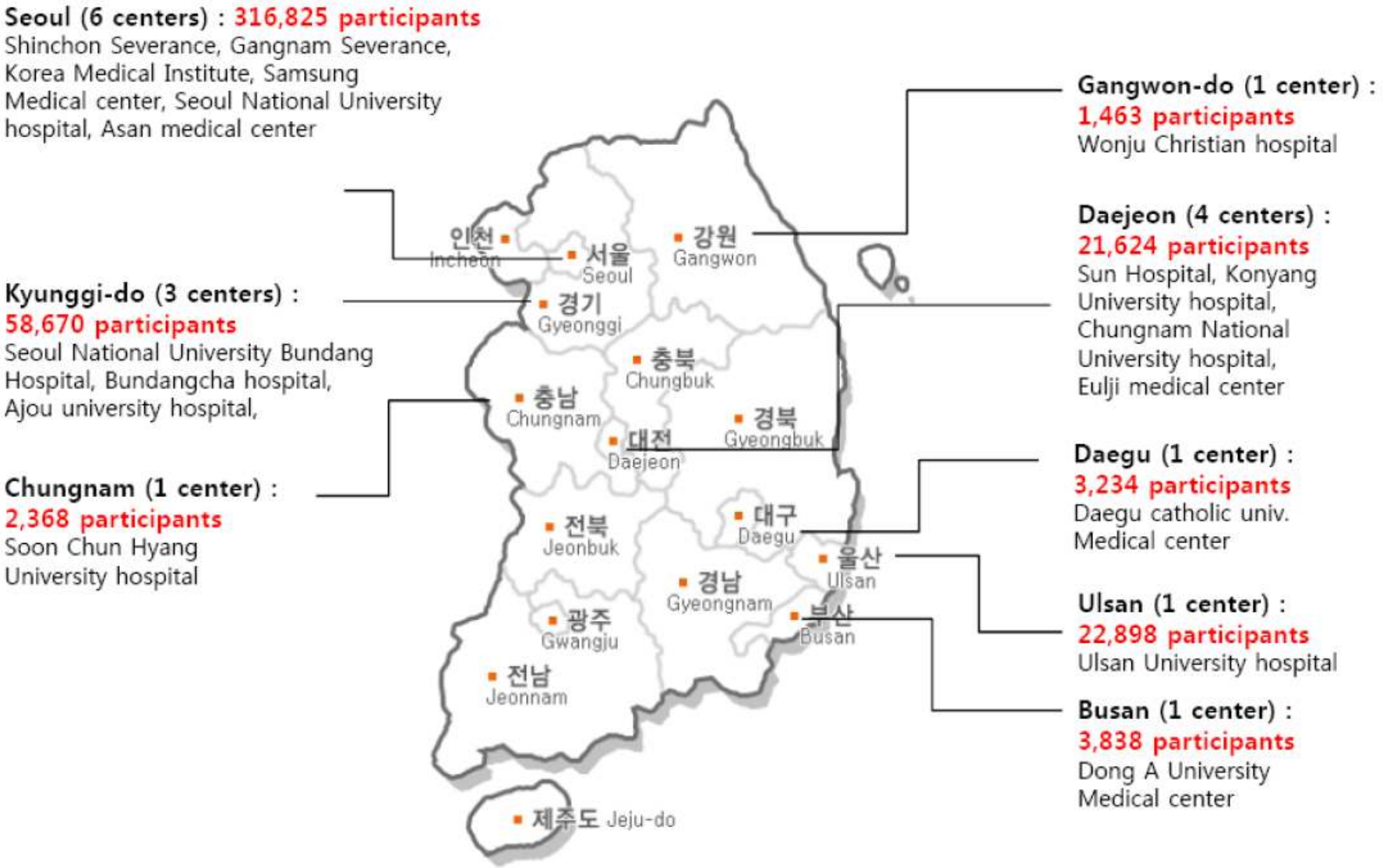
April 30, 2013

The Korean Heart Study: Rationale, Objectives, Protocol, and Preliminary Results for a New Prospective Cohort Study of 430,920 Men and Women

Running title: The Korean Heart Study

Sun Ha Jee,[1] G. David Batty,[2] Yangsoo Jang,[3] Dong Joo Oh,[4] Byung-Hee Oh,[5] Sang Hoon Lee,[6] Seong-Wook Park,[7] Ki-Bae Seung,[8] Heejin Kimm,[1] Sang Yeun Kim,[1] Yejin Mok,[1] Hyon-Suk Kim,[9] Duk Chul Lee,[10] Sung Hee Choi,[11] Moon Jong Kim,[12] Gyu Jang Lee,[13] Jidong Sung,[14] BeLong Cho,[15] Eung Soo Kim,[16] Byung-Yeon Yu,[17] Tae-Yong Lee,[18] Jong Sung Kim,[19] Yong-Jin Lee,[20] Jang-Kyun Oh,[21] Sung Hi Kim,[22] Jong-Ku Park,[23] Sang Baek Koh,[24] Sat Byul Park,[25] Soon Young Lee,[26] Cheol-In Yoo,[27] Moon Chan Kim,[28]Hong-Kyu Kim,[29] Joo-sung Park,[30] Young Duk Yun,[31] Soo Jin Baek,[31] Jonathan M Samet,[32] Mark Woodward,[33]

Figure 1. Location of health promotion centers participating in the Korean Heart Study (18 centers), 1996-2004



Design of the Korean Heart Study

Cohort study with about ~10 years follow-up

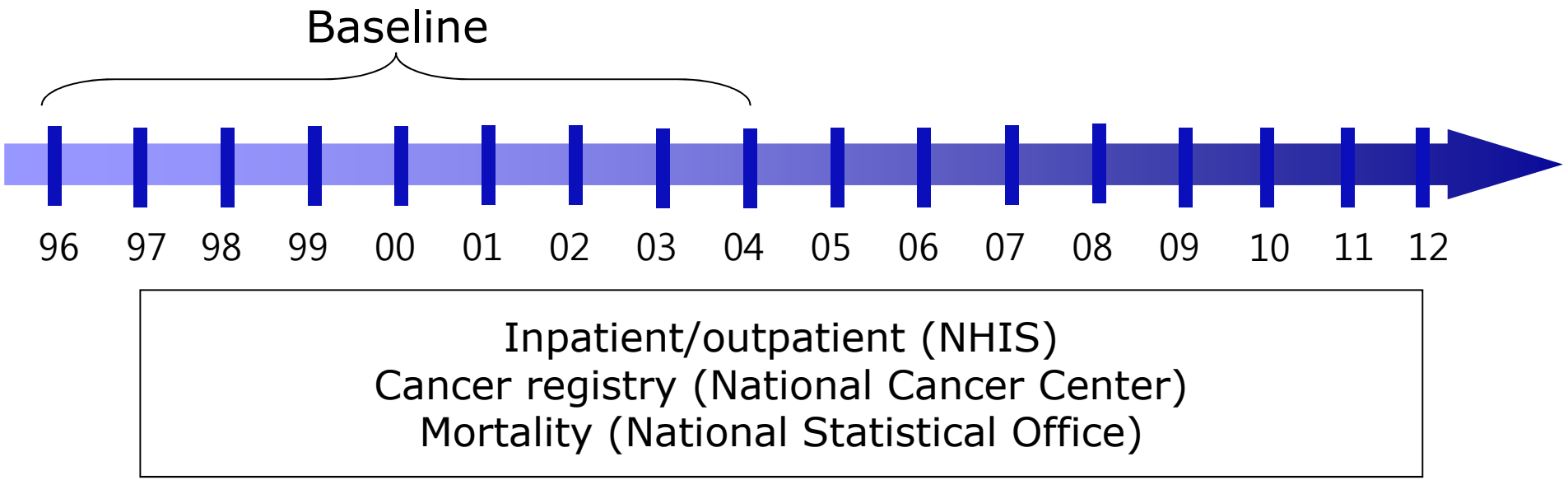
Number of participants : 430,920 aged 30 and older

From 18 Health Promotion Centers

Event follow-up:

Inpatient data from National Health Insurance Service (NHIS)

Mortality data from National Statistical Office



KHS IRB

[서식 12] 07-YUMC-01

임상연구 심의결과 통보서

수신	연구의뢰자	
	시험책임자	보건대학원 지 선 하

심사종류	■ 초심사 □ 종료보고서	□ 시정승인심사 □ 최종결과보고서	□ 연구계획변경심사 □ 연구계획취소심사	□ 중간보고서 □ 기타보고
접수번호(승인번호)	4-2007-0065		과제승인일자	2007.04.13
과제명	한국인의 심장병 발생위험도 모형 개발 사업			
	Protocol No.		Version No.	
시험자	시험책임자	소속	직위	성명
		보건대학원	부 교 수	지 선 하
연구관련	□ 임상연구 (□ 약물, □ 의료기기, □ 의료행위(시술, 수술, 진단방법) □ 유전자 치료연구 □ 배아줄기세포 연구 □ 세포치료연구 □ 기타) □ 관찰연구 (임상정보, 임상시료, 설문조사) □ 기타			
	임상연구	연구대상	일반명 :	상품명 :
		Phase	□ I □II(a,b) □III □IV ■ 학술연구(후향적 □ 생물학적 동등성 □ 기타)	
연구예정기간	시작일자	2007 년 05 월 01 일	종료예상일자	2009년 04 월 30 일
연구의뢰자	회사명 :		대표(직위) :	
심의내용	1. 후향적 연구 심의의뢰서 2. 계획서 요약 3. 연구 계획서 4. 증례 기록서 5. 피험자 서면동의 취득 불필요 사유서 6. 연구책임자 최근 이력 및 경력에 관한 문서 7. 연구비 소요내역서			
심의일자	2007년 04월 13일	IRB 회의	□ 제1IRB □ 제2IRB ■ 제3IRB □ 제4IRB □ 제5IRB	
참석자명단	김승민(3IRB 위원장), 박윤선(간사), 남경모, 유철주, 이경환(변호사), 민경대, 김찬윤, 경대룡, 정현철, 정기양, 김희순, 고수영(IRB행정) (총 13위원 중 12위원 참석) ※ 단, 시험책임자 및 시험담당자(해당 연구 관련자 포함)가 위원인 경우 해당위원은 관련 임상연구 심의에 참여하지 않음.			
심의결과	■ 승인 □ 시정승인 □ 보완 □ 반려 □ 승인된 임상시험의 중지			
	※ 권고사항은 임상시험 진행에 있어 차질이 없는 범위 내에서 승인 후 답변서 또는 수정을 요청하는 항식입니다.			

2007년 04월 13일

연세대학교 의과대학 세브란스병원

병원장 : 박 장 일 (인)

※ 연세대학교 의과대학 세브란스병원 임상연구심의위원회는 국제 임상시험 통일안(ICH-GCP) 및 임상시험관리기준(GCP)를 준수합니다.

연세대학교 의료원 세브란스병원 연구심의위원회

Yonsei University Health System, Severance Hospital, Institutional Review Board

서울특별시 서대문구 연세로 50 (우) 120-752

Tel.02 2228 0430~4 0450~4 Fax.02 2227 7888~9 Email irb@yuhs.ac

심 의 일 자 2013년 1 월 15 일

과제승인번호 4-2007-0065

세브란스병원 연구심의위원회의 심의 결과를 다음과 같이 알려 드립니다.

Protocol No. 없음

연 구 제 목 한국인 만성질환 역학연구

연 구 책 임 자 지선하 / 세브란스병원 보건대학원

의 뢰 자 세브란스병원

연구예정기간 2007-04-13 ~ 2022-12-31

지속심의 빈도 면제

과 제 승 인 일 2007-04-13

위 험 수 준 Level I 최소위험

심 의 종 류 질의답변,계획변경

심 의 내 용 -* 증례기록서 상의 병원 ID 부분 삭제함.
- 개인정보 보호를 위해 대상자 별 연구용 ID를 생성하고, 대상자의 질병발생기록과 연계 시 주민번호는 병원 ID 및 연구용 ID와 함께 별도의 로그지로 작성하여 국민건강보험공단 연구원으로 직접 제출.

* 연구계획서의 '연구자료관리' 부분에서 언급한 바와 같이 피험자의 개인정보보호를 위해서 환자의 식별번호를 없애고 개인정보는 코드화하여 관리하게 되며, 자료 담당 인력이외에는 주민등록번호 혹은 개인정보를 사용할 수 없도록 되어 있으며, 건강보험 공단 내에 서버 터미널을 통한 분석 시스템을 구축하여 외부로 나갈 수 없는 방안을 확보함.

심 의 결 과 승인, 피험자 동의 면제

심 의 의 견 -

※ 세브란스병원 연구심의위원회는 국제 임상시험 통일안(ICH-GCP) 및 임상시험 관리기준(KGCP)을 준수합니다. 연구책임자 및 연구담당자가 IRB 위원인 경우, 해당 위원은 해 연구의 심의과정에 참여하지 않았습니다.

연세대학교 의료원

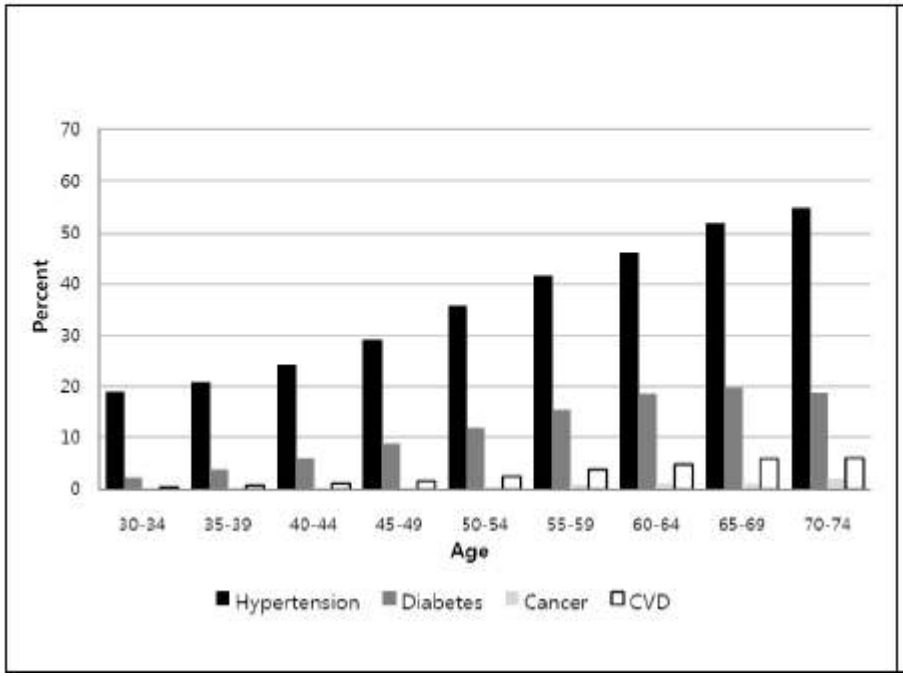
세브란스병원

연구심의위원회 위원장

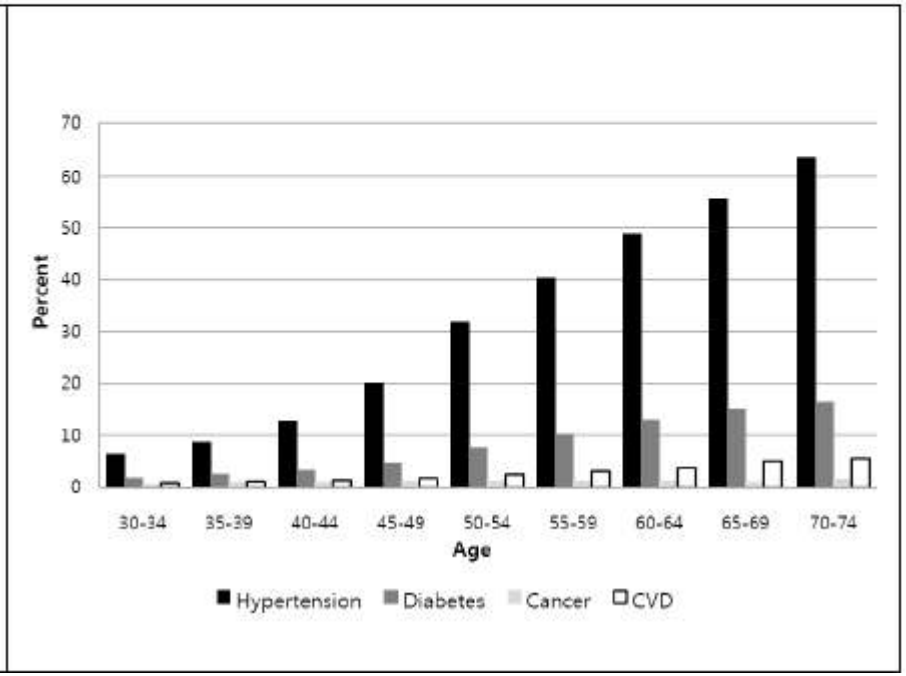
Baseline Characteristics

Figure 2. Health conditions at baseline (1996-2004) according to age in the Korean Heart Study (N=430,920)

Men

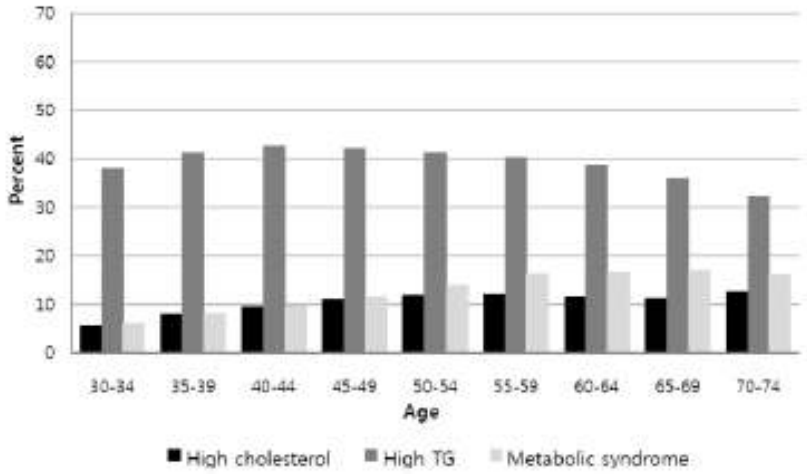


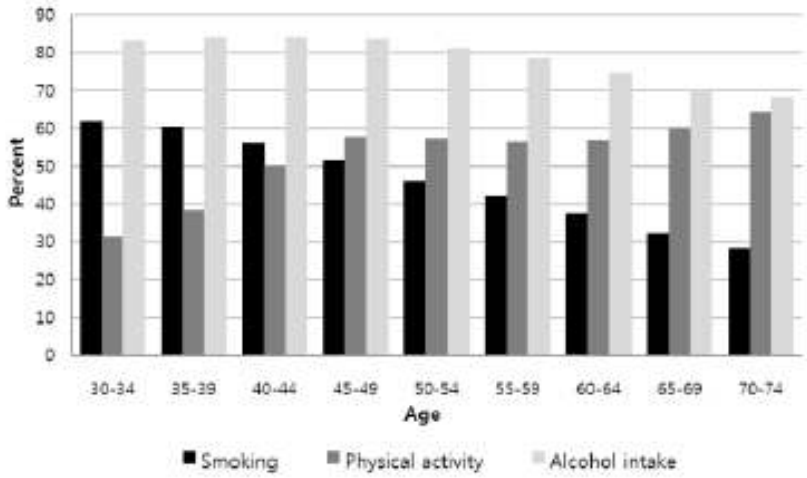
Women



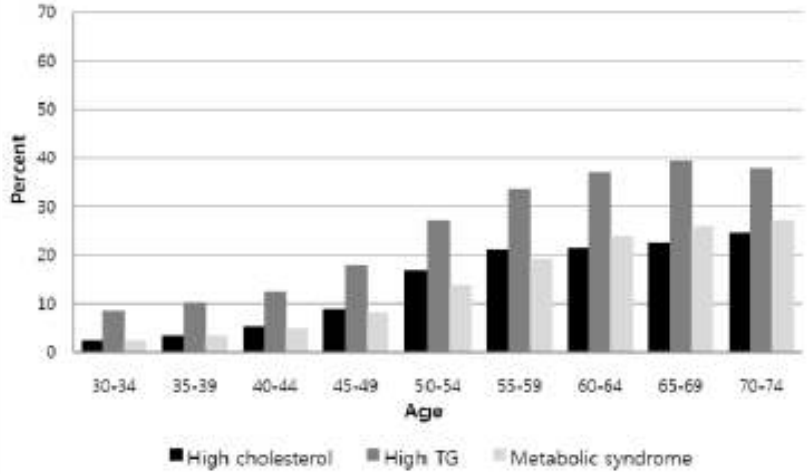
Baseline Characteristics

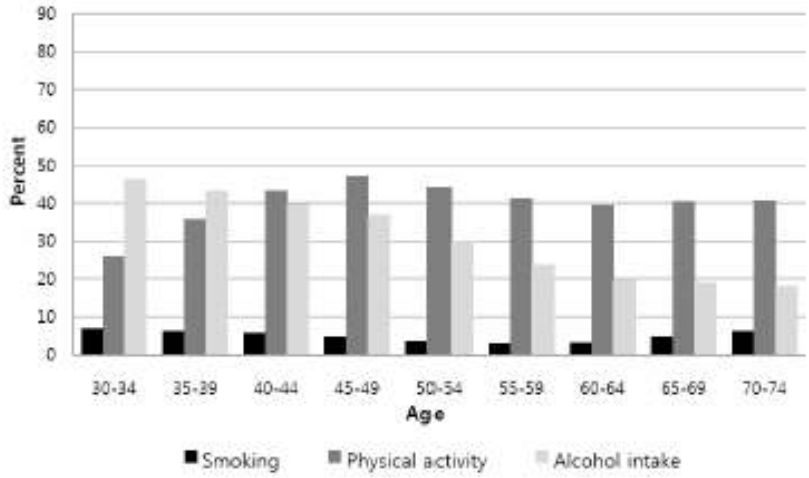
Men





Women





Original Article

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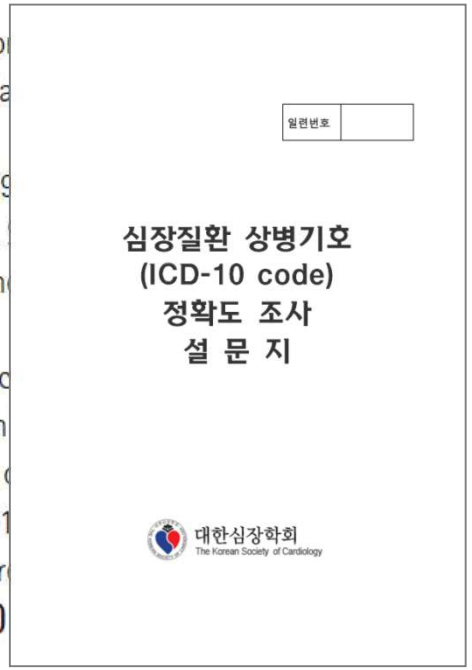
Print ISSN 1738-5520 • On-line ISSN 1738-5555

kcj
Korean Circulation Journal

Validity of the Diagnosis of Acute Myocardial Infarction in Korean National Medical Health Insurance Claims Data: The Korean Heart Study (1)

Heejin Kimm, MD, Ji Eun Yun, PhD, Sang-Hak Lee, MD, Yangsoo Jang, MD, and Sun Ha Jee, PhD
Institute for Health Promotion, Cardiovascular Genome Center, Yonsei University, Seoul, Korea

Background and Objectives: Medical insurance claims (MIC) data are one of the largest sources of outco
tional Classification of Diseases (ICD) codes. We evaluated the validity of the ICD codes from the Korean Na
the outcomes from acute myocardial infarction (AMI) in the Korean Heart Study.
Subjects and Methods: Baseline information was obtained from health examinations conducted from 19
tion regarding the incidence of AMI came from hospital admission discharge records from 1994 to 2007.
sent to 98 hospitals. In total, 107 cases of AMI with ICD codes of I21- (93 men, 26-73 years of age) were in
code accuracy and reliability (kappa) for AMI were calculated.
Results: A large number of AMI cases were from hospitals located in the Seoul area (75.9%). The accurac
to World Health Organization criteria (1997-2000, n=24, kappa=0.46) and 73.1% according to the European
College of Cardiology (ESC/ACC) criteria (2001-2007, n=83, kappa=0.74). An age of 50 years or older was the
of codes for AMI (odds ratio, 4.6; 95% confidence interval, 1.2-17.7) in patients diagnosed since January 2001
Conclusion: The accuracy for diagnosing AMI using the ICD-10 codes in Korean MIC data was >70%, and r
ever, more attention is required for recoding ICD codes in older patients. **(Korean Circ J 2012;42:10-15)**



Epidemiology/Health Services Research
ORIGINAL ARTICLE

Impaired Fasting Glucose and Risk of Cardiovascular Disease in Korean Men and Women

The Korean Heart Study

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CHUL-HEE KIM, MD, PHD[2]
EUN HEE KIM, MD[1]
SUNG JIN BAE, MD, PHD[1]
JAEWON CHOE, MD, PHD[1]
JOONG-YEOL PARK, MD, PHD[3]
SEONG-WOOK PARK, MD, PHD[4]
YOUNG DUK YUN, MD[5]
SOO-JIN BAEK, MS[5]
YEJIN MOK, MPH[6,7]
SUN HA JEE, PHD, MPH[6,7]

OBJECTIVE—The relationship between impaired fasting glucose (IFG) and risk of cardiovascular disease (CVD) or ischemic heart disease (IHD) varies widely according to sex and ethnicity. We evaluated the relationship between IFG and CVD or IHD among Korean men and women.

RESEARCH DESIGN AND METHODS—A total of 408,022 individuals who underwent voluntary private health examinations in 17 centers in South Korea were followed for 10 years. Data regarding CVD or IHD events were obtained from the Korean National Health Insurance database. IFG was categorized as grade 1 (fasting glucose 100–109 mg/dL) or grade 2 (110–125 mg/dL).

mortality (7,8). However, the association between impaired fasting glucose (IFG) and risk of CVD and/or IHD remains unclear (7–18). Although some studies have reported that IFG was associated with a greater risk of IHD/CVD in women than in men (17,19), others have reported similar risks for men and women (18).

There has also been considerable debate regarding the threshold glucose level associated with increased CVD risk. In 2003, the American Diabetes Association (ADA) lowered the fasting plasma glucose (FPG) cutoff point for IFG from 110 to 100 mg/dL (20). Some studies have reported that FPG levels of 110–125 mg/

Kim HK et al., Diabetes Care 2012

Objective

- **The relationship between impaired fasting glucose (IFG) and risk of CVD or IHD varies widely according to sex and ethnicity.**
- **We evaluated the relationship between IFG and CVD or IHD among Korean men and women.**

Kim HK et al., Diabetes Care 2012

Method

IFG was categorized as

- **Grade 1 (fasting glucose 100–109 mg/dL)**
- **Grade 2 (fasting glucose 110–125 mg/dL)**

10 years follow-up

Cox's proportional hazard model

Kim HK et al., Diabetes Care 2012

Baseline characteristics 1996-2004 (N=384,795)

	Normogly-cemia	Prediabetes		Diabetes
		100-109	110-125	
N	289,511	49,921	17,975	27,388
Sex (male), %	58.7	68.1	71.3	69.1
Age, years	44.7	47.7	50.1	52.0
Smoking, %	33.6	34.7	34.9	34.8
Alcohol,%	61.9	67.8	69.4	65.5
BMI, kg/m^2	23.4	24.4	25.0	24.6
SBP, mmHg	119	126	130	129
T cholesterol	191	201	207	205
HDL, mg/dL	51	50	49	48
LDL, mg/dL	115	122	125	124
FBS, mg/dL	87	104	116	146

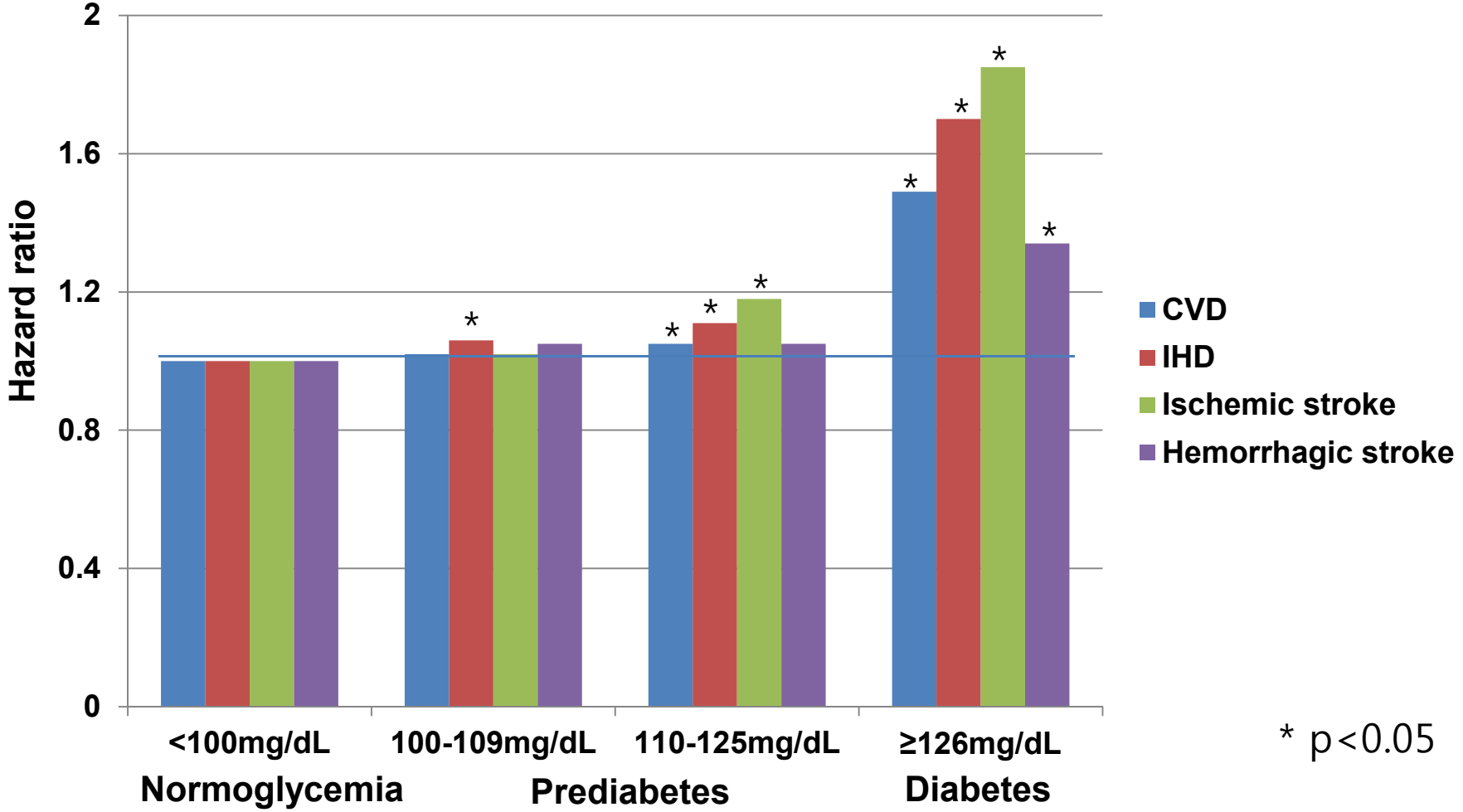
Kim HK et al., Diabetes Care 2012

Incidence rates of CVD per 100,000 person years

Categories	Rates	IRR
Normoglycemia (<100)	744	1.0
Grade 1 IFG (100-109)	1,084	1.45
Grade 2 IFG (110-125)	1,416	1.90
Diabetes (≥126 or Med.)	2,203	2.96

Kim HK et al., Diabetes Care 2012

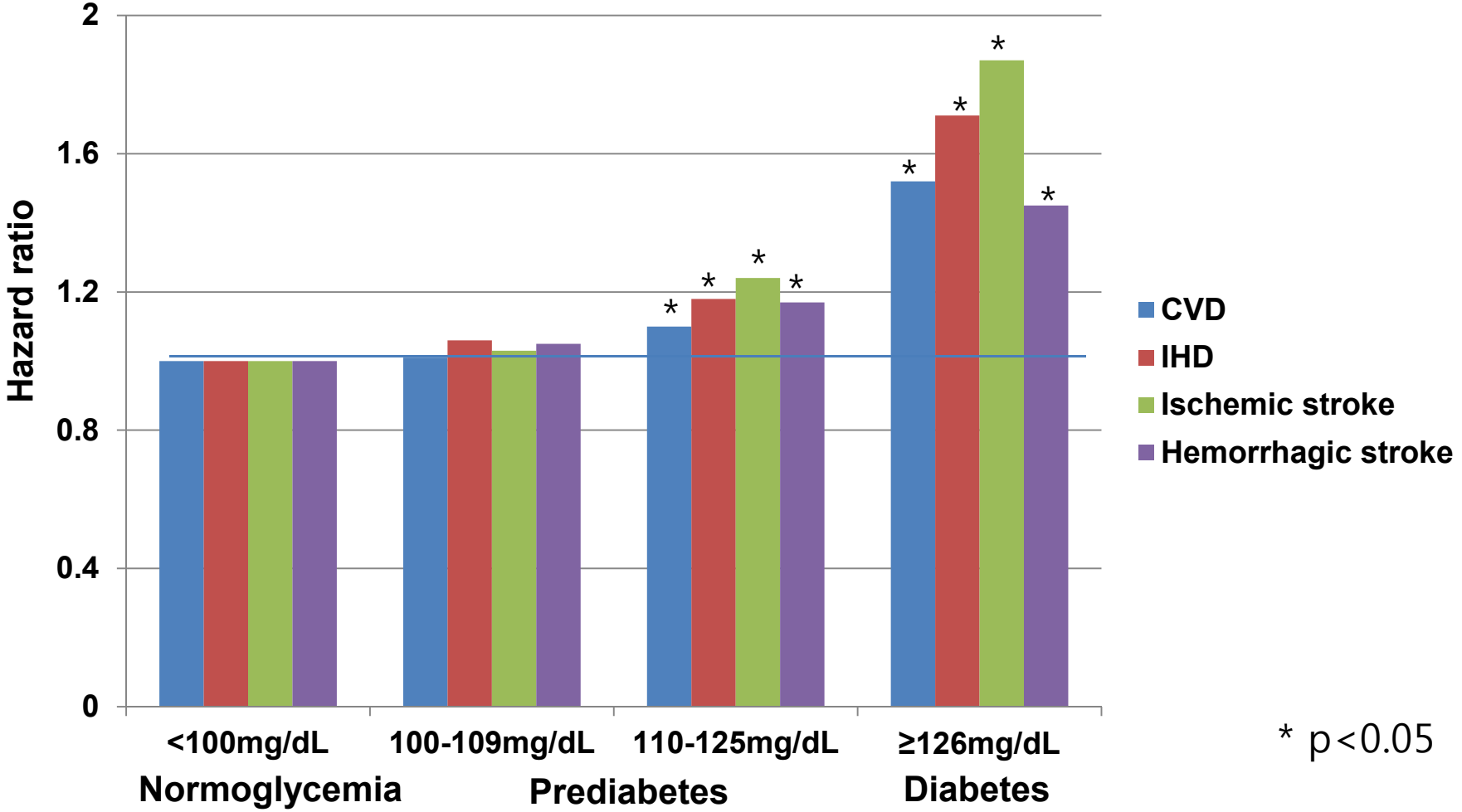
HRs of CVDs by different traits of dysglycemia (Total)



* p<0.05

Kim HK et al., Diabetes Care 2012

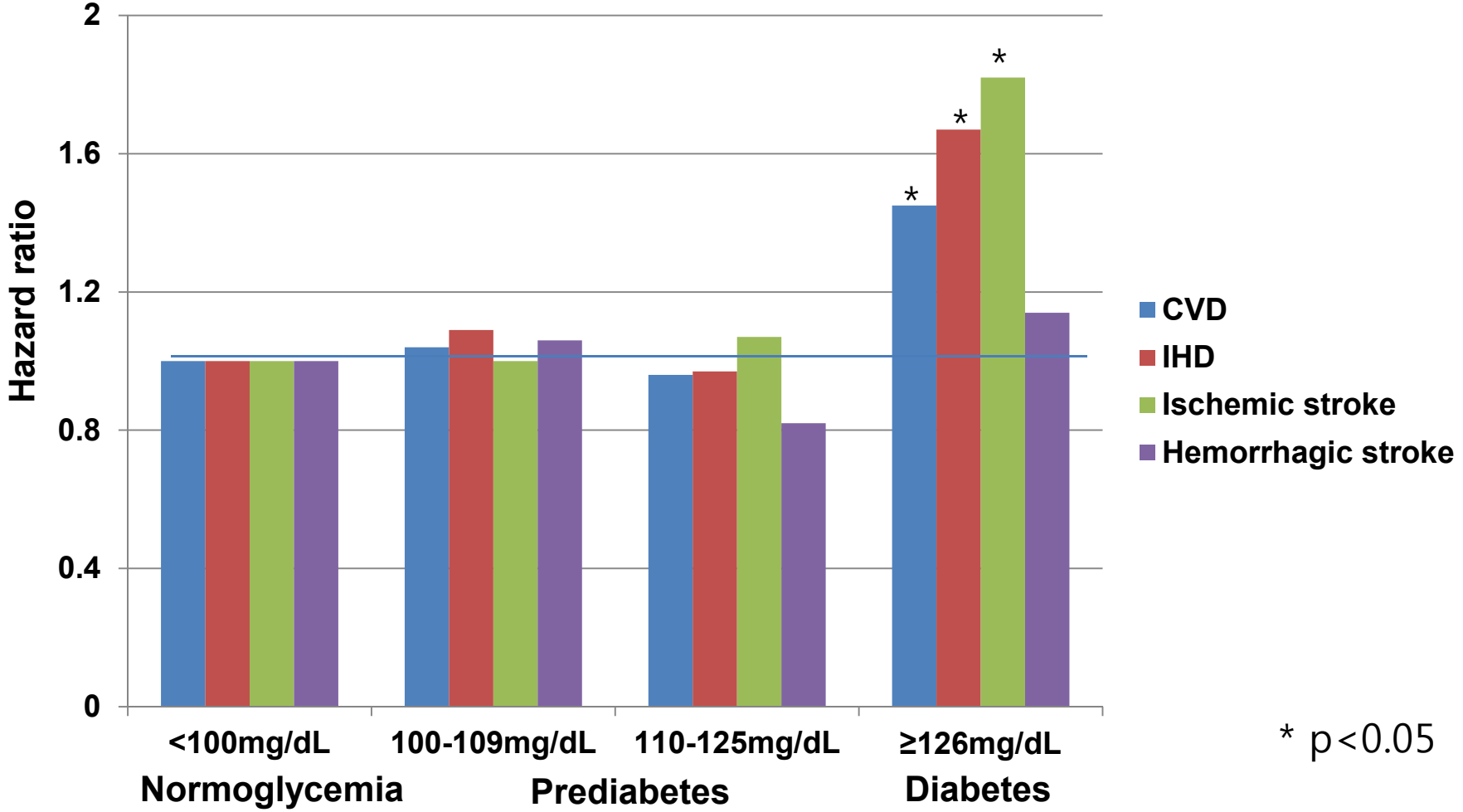
HRs of CVDs by different traits of dysglycemia (Men)



* p<0.05

Kim HK et al., Diabetes Care 2012

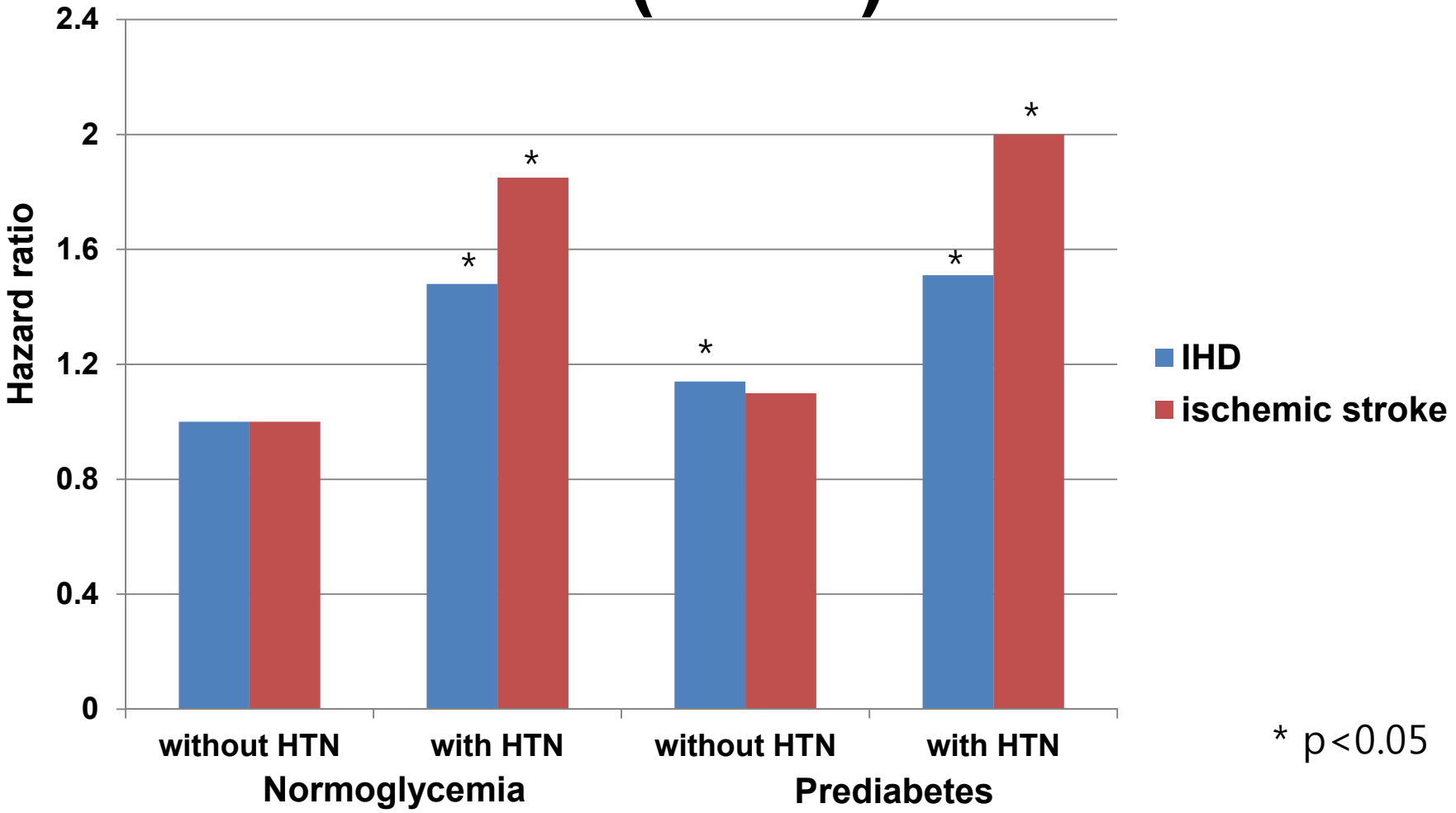
HRs of CVDs by different traits of dysglycemia (Women)



* p<0.05

Kim HK et al., Diabetes Care 2012

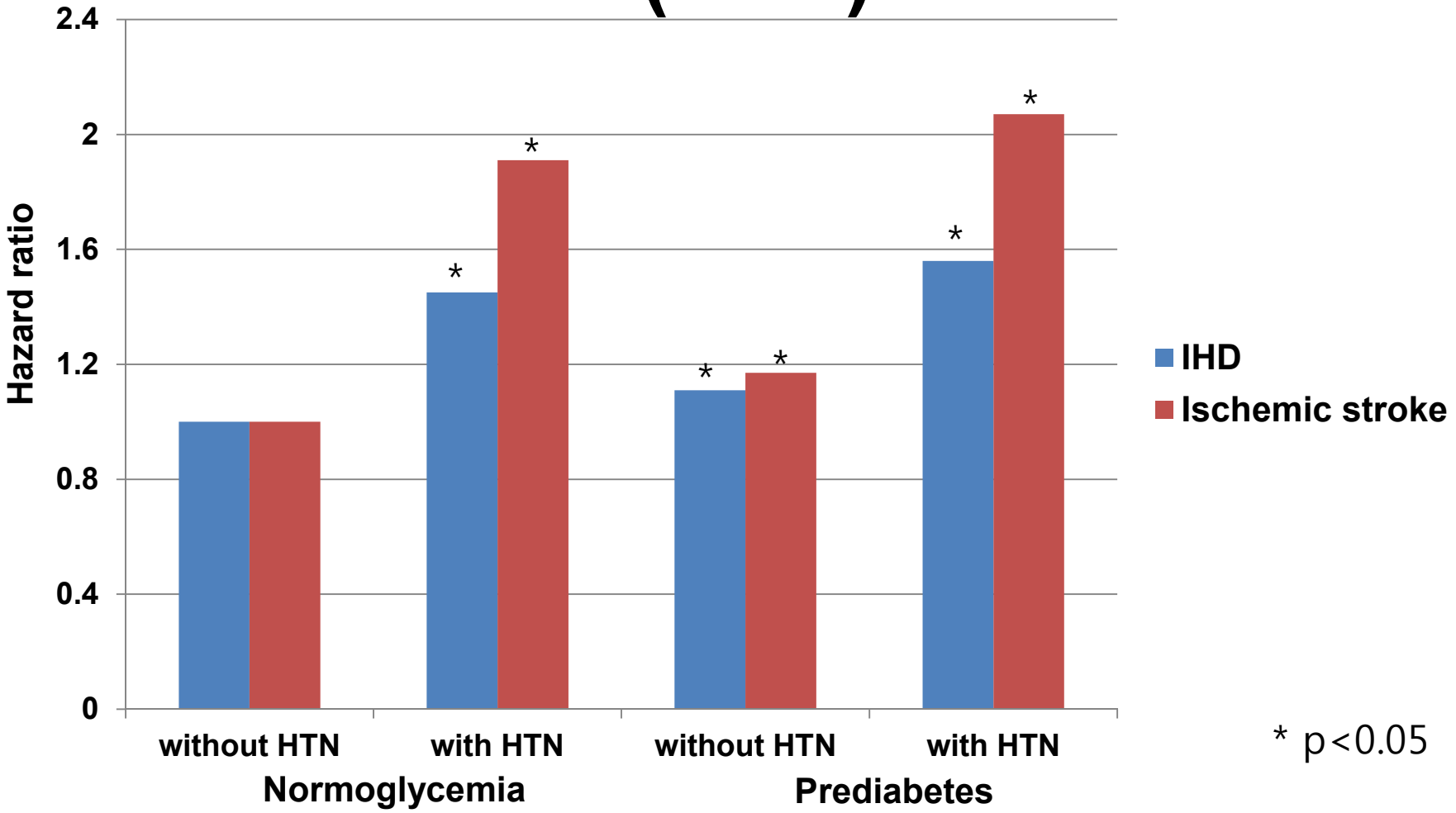
HRs of IHD and ischemic stroke of prediabetes with or without HTN (Total)



* p<0.05

Kim HK et al., Diabetes Care 2012

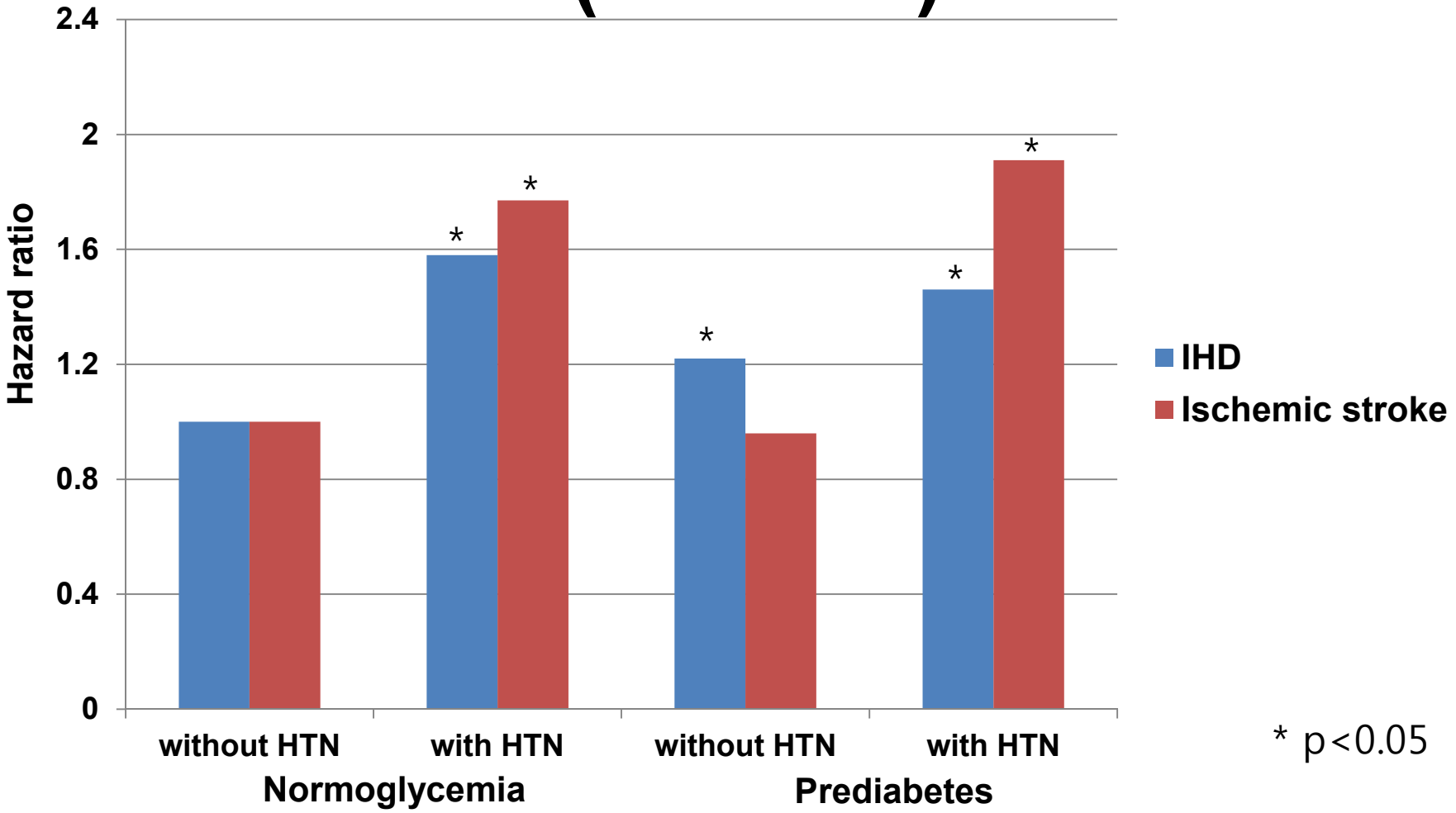
HRs of IHD and ischemic stroke of pre-diabetes with or without HTN (Men)



* p<0.05

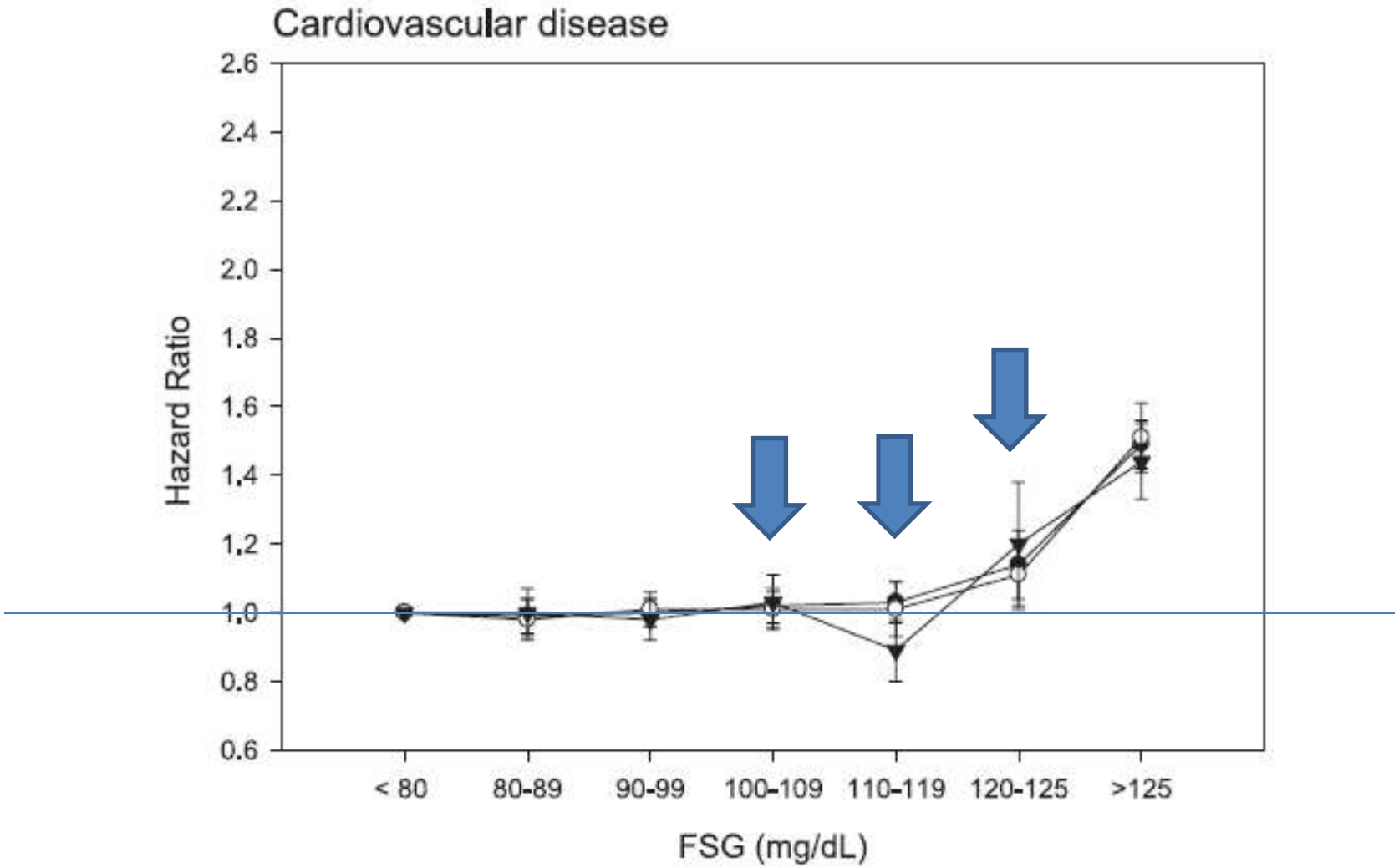
Kim HK et al., Diabetes Care 2012

HRs of IHD and ischemic stroke of pre-diabetes with or without HTN (Women)



* p<0.05

Kim HK et al., Diabetes Care 2012



Kim HK et al., Diabetes Care 2012

Conclusion

- Our study showed that IFG, defined as FSG levels of 100–125 mg/dL, is associated with increased risk of CVD (including IHD and ischemic stroke) in the Korean population.
- This association is independent of other conventional risk factors in men but not in women.
- Further studies are needed to identify subgroups with IFG for whom prevention efforts in reducing cardiovascular events are cost-effective.

Kim HK et al., Diabetes Care 2012

Comments

- 코호트 추적기간이 짧다.
- Stage 1 IFG (100-109) ?
- Pre diabetes의 중요성 인지…
- Pre diabetes 군의 heterogeneity ?

Korean Data II

- **Korean Adiponectin Cohort Study**
  - **Adiponectin as predictor of diabetes among people with IFG (pre diabetes)**

Adiponectin as predictor for diabetes among pre-diabetic groups

Hyon-Suk Kim, Jaeseong Jo, Jung Eun Lim, Young Duk Yun, Soo Jin Baek, Tae-Yong Lee, Kap Bum Huh & Sun Ha Jee

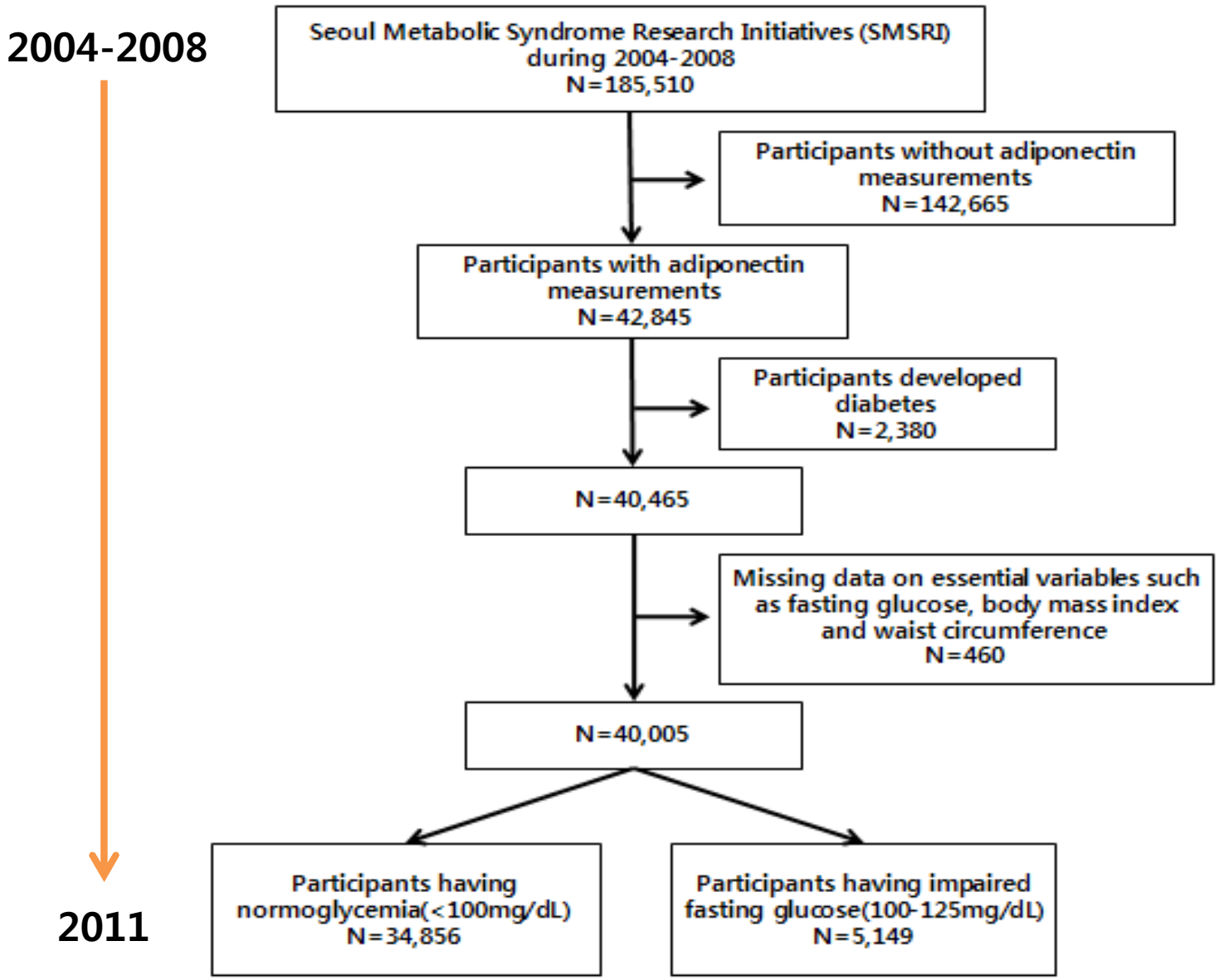
Endocrine
International Journal of Basic and Clinical Endocrinology

ISSN 1355-008X

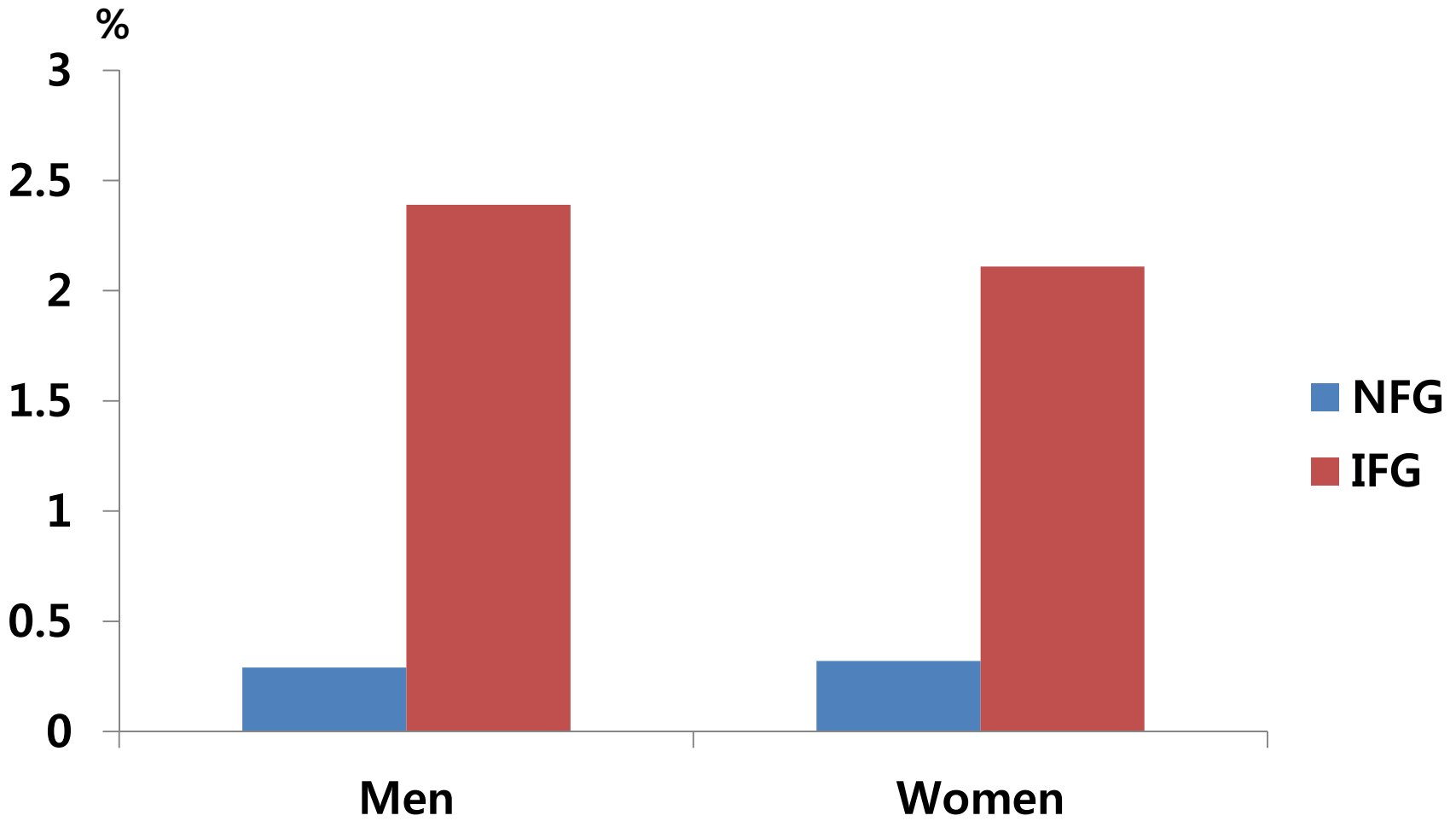
Endocrine
DOI 10.1007/s12020-013-9890-5

Kim SH et al., Endocrine, 2013 Feb.

Korean Adiponectin Cohort Study



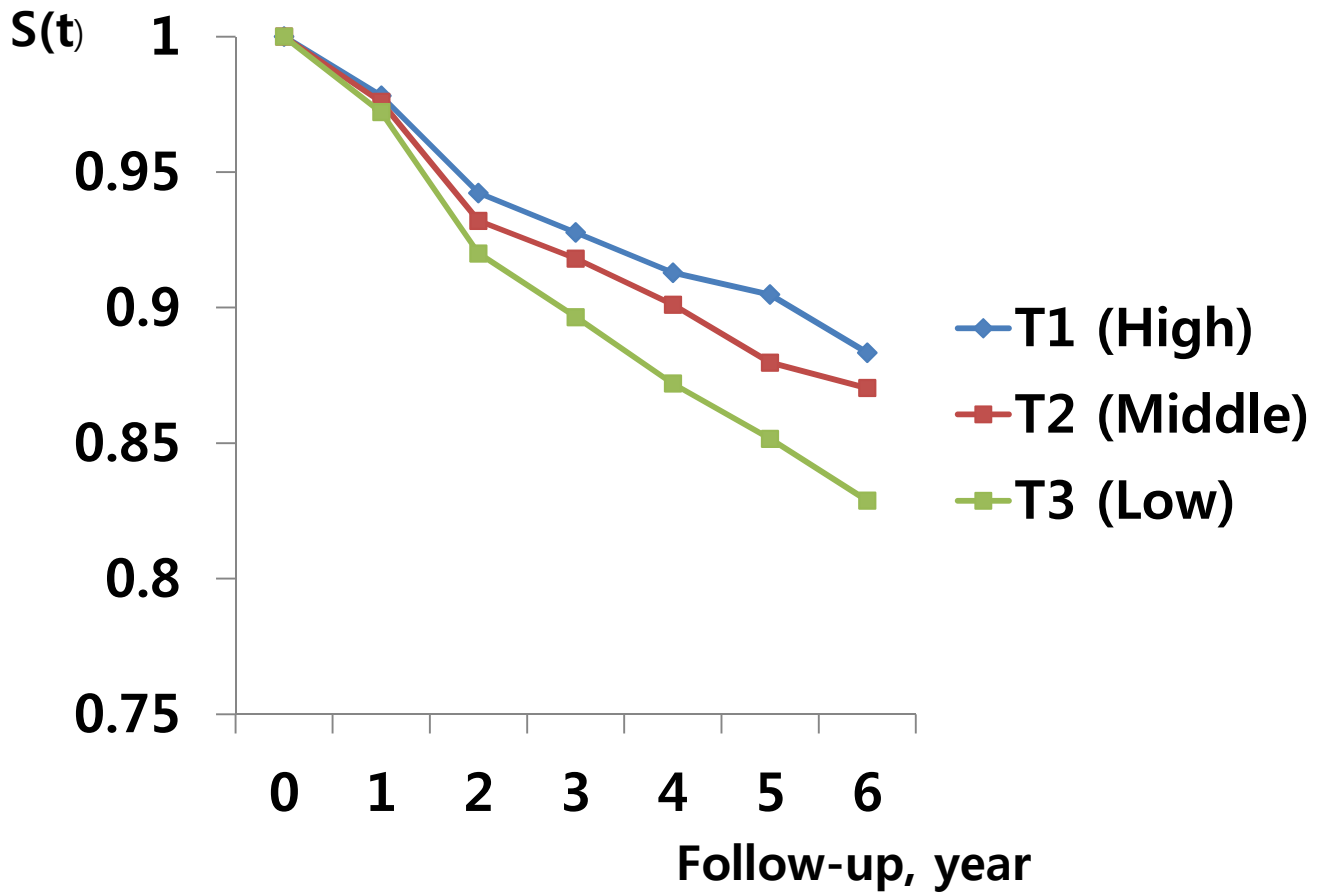
Incidence rate per 100 PY of type 2 diabetes among men



Serum adiponectin

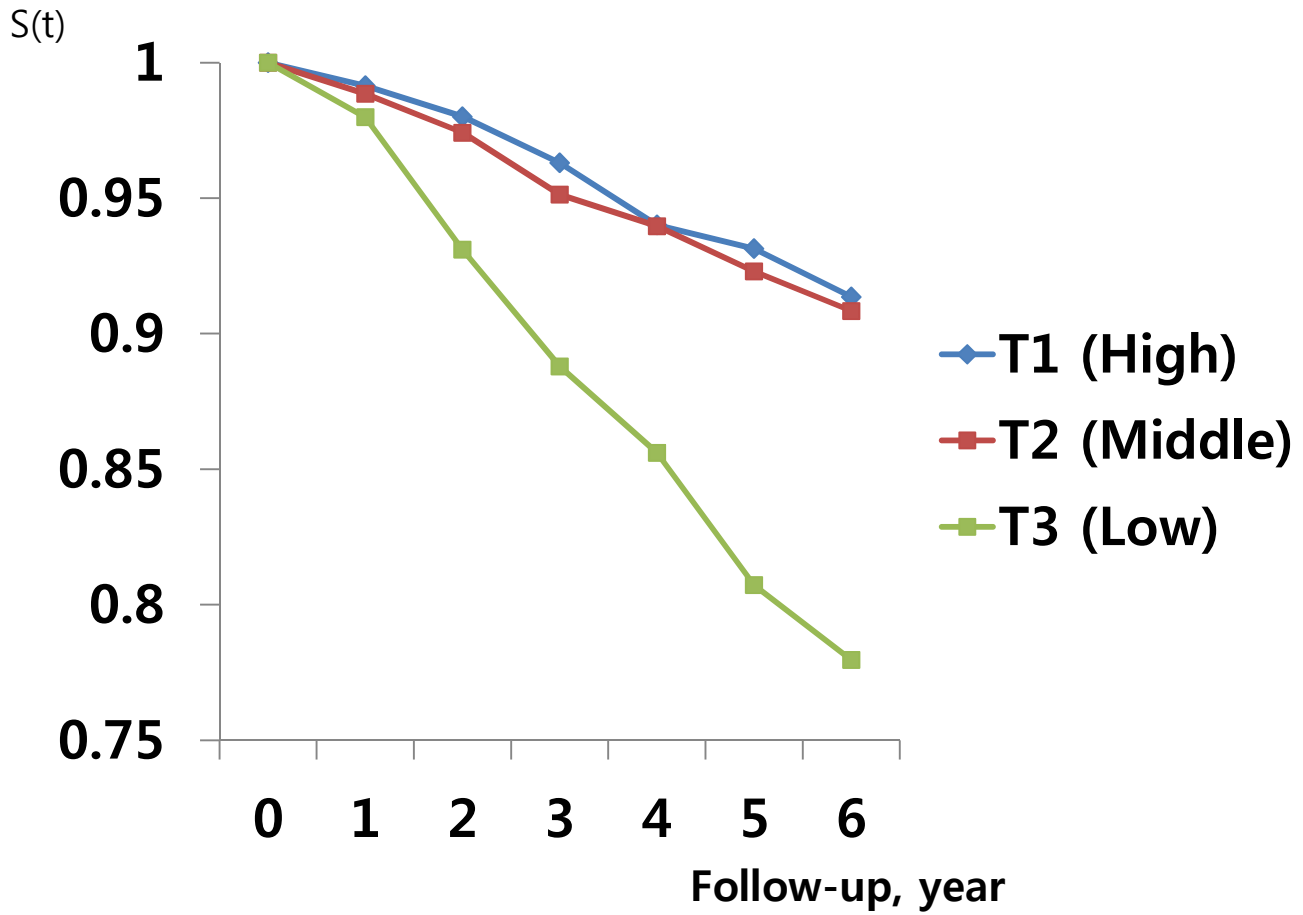
- **Men**
  - **T1 (High) ≥6.24 μg/mL**
  - **T2 (Middle) 3.91 – 6.23 μg/mL**
  - **T3 (Low) < 3.91 μg/mL**
- **Women**
  - **T1 (High) ≥9.42 μg/mL**
  - **T2 (Middle) 5.99 – 9.41 μg/mL**
  - **T3 (Low) < 5.99 μg/mL**

Adiponectin and type 2 DM among men with pre-diabetes



The Kaplan-Meier survival curve

Adiponectin and type 2 DM among women with pre-diabetes



The Kaplan-Meier survival curve

HR (95% CI) for low adiponectin levels on type 2 diabetes

		Conversion status at 6 yrs follow-up	
	Adiponectin	Diabetes	Non diabetes
Pre diabetes	Low	a	b
	High	c	d

$$RR = \frac{\frac{a}{a+b}}{\frac{c}{c+d}}$$

Men, 1.27 (1.00-1.63)

Women, 2.08 (1.25-3.46)

Adjusting for age, smoking, BMI, WC, HTN, TC, FDM and fasting glucose

Summary

- **BMI (x), waist circumference (x), HTN (x), Cholesterol (x), 가족력 (x)…**
- **pre-diabetes, 동일한 수준의 공복혈당에서…**
- **Adiponectin may be used as a predictor of diabetes in pre-diabetic individuals.**

Korean Data III

- **Korean Cancer Prevention Study**
  - **An optimum fasting glucose level**

Diabetes Care Symposium
ORIGINAL ARTICLE

Fasting Glucose Level and the Risk of Incident Atherosclerotic Cardiovascular Diseases

Chanshin Park, MD[1]
Eliseo Guallar, MD[2,3]
John A. Linton, MD[1,4]
Duk-Chul Lee, MD[4]
Yangsoo Jang, MD[5]
Dong-Koog Son, PHD[6]
Eun Jeong Han, MS[6]
Soo-Jin Baek, MS[6]
Young Duk Yun, MD[6]
Sun Ha Jee, PHD[7,8]
Jonathan M. Samet, MD[9]

OBJECTIVE—Although diabetes increases the risk of cardiovascular disease and mortality, the dose-response relationship between fasting glucose levels below those diagnostic of diabetes with cardiovascular events has not been well-characterized.

RESEARCH DESIGN AND METHODS—A prospective cohort study of more than one million Koreans was conducted with a mean follow-up of 16 years. A total of 1,197,384 Korean adults with no specific medical conditions diagnosed were classified by baseline fasting serum glucose level. Associations of fasting glucose level with cardiovascular disease incidence and mortality, stroke incidence and mortality, and all-cause mortality were analyzed using multivariate proportional hazards regression.

relevance of IFG as a predictor of CVD is still unclear (8–11). In addition, the shape of the dose-response relationship between CVD risk and fasting glucose level has not been well-characterized across the full range of fasting blood glucose values.

It is unclear whether there is an optimum fasting glucose level associated with the lowest level of CVD risk (12,13), or whether risk increases at very low fasting glucose levels (14). Several studies have shown J-shape or U-shape relationships between fasting glucose levels and mortality (3,5,14,15).

The Korean Cancer Prevention Study (16,17) (KCPS) is a cohort study of >1.3 million Korean adults designed to evalu-

Park C al., Diabetes Care 2013

An optimum fasting glucose level

- **The shape of the dose-response relationship between CVD risk and fasting glucose level has not been well-characterized across the full range of fasting blood glucose values.**

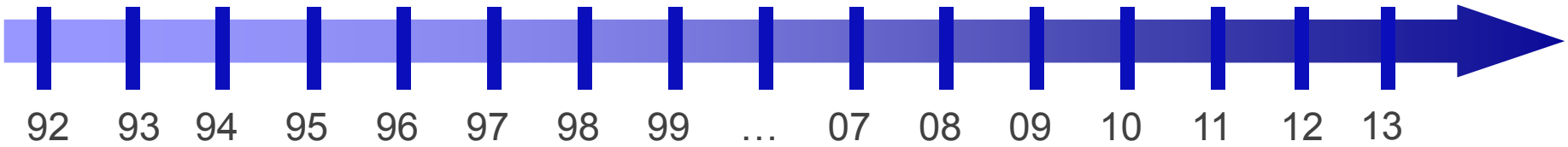
- **It is unclear whether there is an optimum fasting glucose level associated with the lowest level of CVD risk, or whether risk increases at very low fasting glucose levels.**

Park C al., Diabetes Care 2013

Korean Cancer Prevention Study (KCPS)

Design of the KCPS

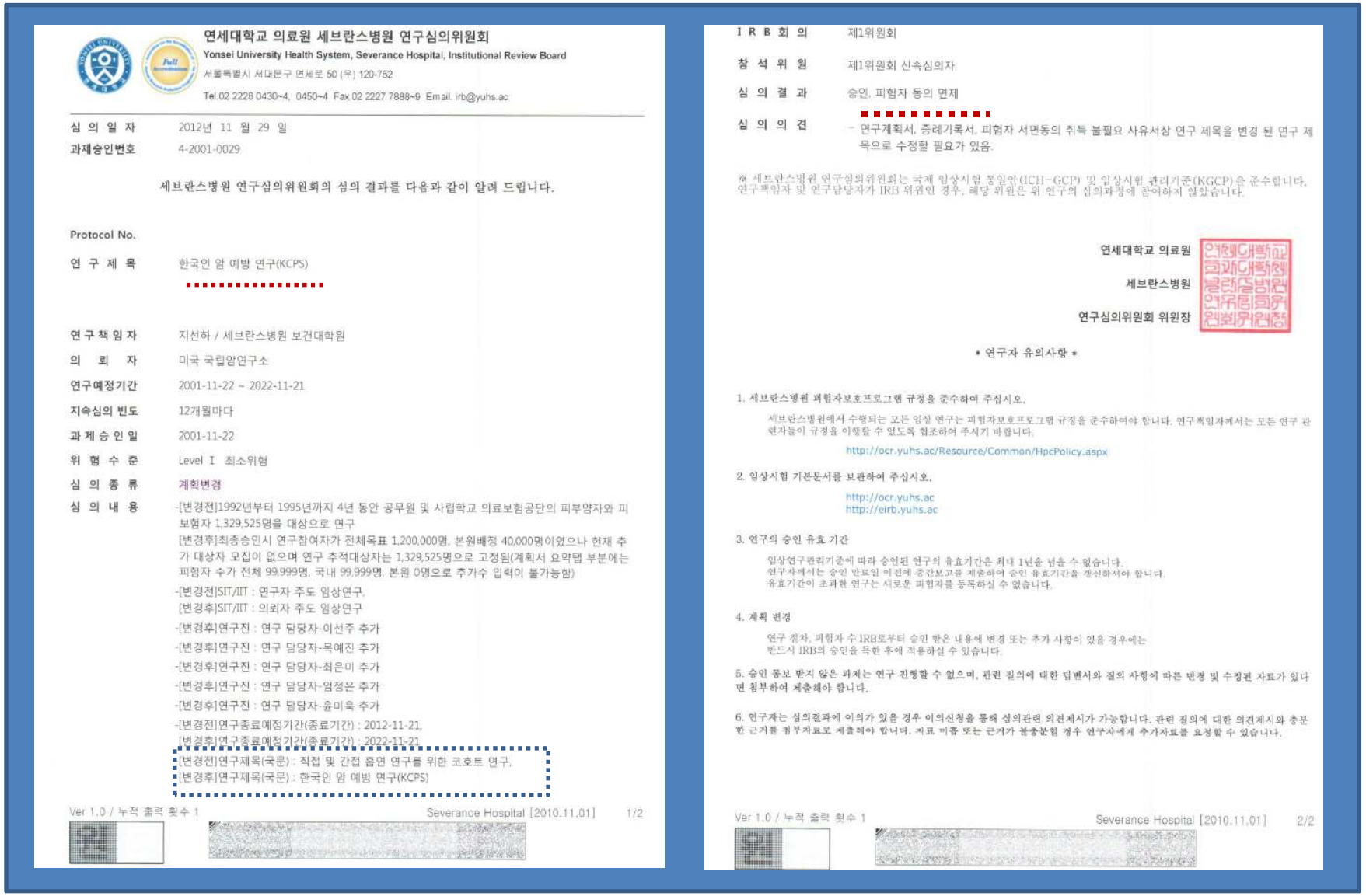
- 19-year prospective cohort study
- Participants enrolled through the National Health Insurance Service (NHIS)
- Insured and dependents (N=1,329,525), ages 30 and older
- Answered questionnaires in 1992-1995 and subsequent years
- Follow-up by record linkage to NHIS



Baseline

Incidence/Mortality	
All-causes	**168,325**
All cancers	**144,370**
All cardiovascular diseases	**147,907**

KCPS IRB



연세대학교 의료원 세브란스병원 연구심의위원회
Yonsei University Health System, Severance Hospital, Institutional Review Board
서울특별시 서대문구 연세로 50 (우) 120-752
Tel.02 2228 0430~4, 0450~4 Fax.02 2227 7888~9 Email. irb@yuhs.ac

심 의 일 자 2012년 11 월 29 일
과제승인번호 4-2001-0029

세브란스병원 연구심의위원회의 심의 결과를 다음과 같이 알려 드립니다.

Protocol No.
연 구 제 목 한국인 암 예방 연구(KCPS)

연 구 책 임 자 지선하 / 세브란스병원 보건대학원
의 뢰 자 미국 국립암연구소
연구예정기간 2001-11-22 ~ 2022-11-21
지속심의 빈도 12개월마다
과 제 승 인 일 2001-11-22
위 험 수 준 Level I 최소위험
심 의 종 류 계획변경
심 의 내 용 -[변경전]1992년부터 1995년까지 4년 동안 공무원 및 사립학교 의료보험공단의 피부양자와 피보험자 1,329,525명을 대상으로 연구
[변경후]최종승인시 연구참여자가 전체목표 1,200,000명, 본원배정 40,000명이었으나 현재 추가 대상자 모집이 없으며 연구 추적대상자는 1,329,525명으로 고정됨(계획서 요약탭 부분에는 피험자 수가 전체 99,999명, 국내 99,999명, 본원 0명으로 추가수 입력이 불가능함)
-[변경전]SIT/IIT : 연구자 주도 임상연구,
[변경후]SIT/IIT : 의뢰자 주도 임상연구
-[변경후]연구진 : 연구 담당자-이선주 추가
-[변경후]연구진 : 연구 담당자-목예진 추가
-[변경후]연구진 : 연구 담당자-최은미 추가
-[변경후]연구진 : 연구 담당자-임정은 추가
-[변경후]연구진 : 연구 담당자-윤미숙 추가
-[변경전]연구종료예정기간(종료기간) : 2012-11-21,
[변경후]연구종료예정기간(종료기간) : 2022-11-21
[변경전]연구제목(국문) : 직접 및 간접 흡연 연구를 위한 코호트 연구,
[변경후]연구제목(국문) : 한국인 암 예방 연구(KCPS)

I R B 회 의 제1위원회
참 석 위 원 제1위원회 신속심의자
심 의 결 과 승인, 피험자 동의 면제
심 의 의 견 - 연구계획서, 증례기록서, 피험자 서면동의 취득 불필요 사유서상 연구 제목을 변경 된 연구 제목으로 수정할 필요가 있음.

※ 세브란스병원 연구심의위원회는 국제 임상시험 통일안(ICH-GCP) 및 임상시험 관리기준(KGCP)을 준수합니다. 연구책임자 및 연구담당자가 IRB 위원인 경우, 해당 위원은 위 연구의 심의과정에 참여하지 않았습니다.

연세대학교 의료원
세브란스병원
연구심의위원회 위원장

* 연구자 유의사항 *

1. 세브란스병원 피험자보호프로그램 규정을 준수하여 주십시오.
세브란스병원에서 수행되는 모든 임상 연구는 피험자보호프로그램 규정을 준수하여야 합니다. 연구책임자께서는 모든 연구 관련자들이 규정을 이행할 수 있도록 협조하여 주시기 바랍니다.
http://ocr.yuhs.ac/Resource/Common/HpcPolicy.aspx

2. 임상시험 기본문서를 보관하여 주십시오.
http://ocr.yuhs.ac
http://eirb.yuhs.ac

3. 연구의 승인 유효 기간
임상연구관리기준에 따라 승인된 연구의 유효기간은 최대 1년을 넘을 수 없습니다.
연구자께서는 승인 만료일 이전에 중간보고를 제출하여 승인 유효기간을 갱신하셔야 합니다.
유효기간이 초과한 연구는 새로운 피험자를 등록하실 수 없습니다.

4. 계획 변경
연구 절차, 피험자 수 IRB로부터 승인 받은 내용에 변경 또는 추가 사항이 있을 경우에는 반드시 IRB의 승인을 득한 후에 적용하실 수 있습니다.

5. 승인 통보 받지 않은 과제는 연구 진행할 수 없으며, 관련 질의에 대한 답변서와 질의 사항에 따른 변경 및 수정된 자료가 있다면 첨부하여 제출해야 합니다.

6. 연구자는 심의결과에 이의가 있을 경우 이의신청을 통해 심의관련 의견제시가 가능합니다. 관련 질의에 대한 의견제시와 충분한 근거를 첨부자료로 제출해야 합니다. 지표 미흡 또는 근거가 불충분할 경우 연구자에게 추가자료를 요청할 수 있습니다.

OBJECTIVE

- **While diabetes increases the risk of cardiovascular disease and mortality, the dose-response relationship between fasting glucose levels below those diagnostic of diabetes with cardiovascular events has not been well characterized.**

Park C al., Diabetes Care 2013

RESEARCH DESIGN AND METHODS

- **Associations of fasting glucose level with cardiovascular disease and stroke**
  - **Incidence**
  - **Mortality**
- **16 years follow-up**
- **Cox's proportional hazards regression.**
- **Restricted quadratic spline models with knots at fasting glucose levels of 70, 85, 100, 110, 126, and 140 mg/dL.**

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Results

- The relationships between fasting glucose levels and cardiovascular disease risks generally followed J-shape curves, with lowest risk in the glucose range of 85–99 mg/dL.
- As fasting glucose levels increased to ≥100 mg/dL, risks for CVD, IHD, MI, and thrombotic stroke progressively increased, but risk for hemorrhagic stroke did not.

Park C al., Diabetes Care 2013

Results

- **Fasting glucose levels<70 mg/dL were associated with increased risk of all stroke**
  - **(HR 1.06, 95% CI 1.01–1.11) in men**
  - **(HR 1.11, 95% CI 1.05–1.17) in women**

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Table 1—*Fasting serum glucose levels at enrollment and risk of cardiovascular diseases in male participants of the Korean Cancer Prevention Study 1993–2010*

Fasting serum glucose, mg/dL	Atherosclerotic cardiovascular disease (*N* = 100,808) HR (95% CI)	Ischemic heart disease (*N* = 40,026) HR (95% CI)	Myocardial infarction (*N* = 12,528) HR (95% CI)	All stroke (*N* = 45,582) HR (95% CI)	Thrombotic stroke (*N* = 28,922) HR (95% CI)	Hemorrhagic stroke (*N* = 12,282) HR (95% CI)
<70	1.04 (1.01–1.08)	1.00 (0.96–1.06)	1.02 (0.94–1.11)	1.06 (1.01–1.11)	1.06 (1.00–1.12)	1.02 (0.94–1.11)
70–84	1.00 (0.99–1.02)	1.00 (0.97–1.02)	1.00 (0.96–1.05)	1.00 (0.98–1.03)	1.00 (0.98–1.04)	1.00 (0.95–1.04)
85–99	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
100–109	1.04 (1.02–1.06)	1.04 (1.01–1.08)	1.02 (0.97–1.08)	1.04 (1.00–1.07)	1.08 (1.04–1.12)	0.98 (0.93–1.04)
110–125	1.12 (1.09–1.15)	1.14 (1.10–1.19)	1.17 (1.09–1.25)	1.15 (1.11–1.18)	1.21 (1.16–1.26)	1.08 (1.02–1.16)
126–139	1.27 (1.22–1.33)	1.27 (1.18–1.37)	1.50 (1.34–1.69)	1.38 (1.30–1.47)	1.51 (1.41–1.63)	1.15 (1.01–1.30)
≥140	1.75 (1.70–1.80)	1.79 (1.71–1.87)	2.13 (1.97–2.29)	1.87 (1.80–1.94)	2.20 (2.10–2.31)	1.24 (1.13–1.35)

To convert glucose from mg/dL to mmol/L, multiply by 0.0555. Adjusted for age, smoking status, alcohol drinking, exercise, BMI, and systolic blood pressure. BMI was calculated as weight in kilograms divided by the square of height in meters.

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Table 2—*Fasting serum glucose levels at enrollment and risk of cardiovascular diseases in female participants of the Korean Cancer Prevention Study 1993–2010*

Fasting serum glucose, mg/dL	Atherosclerotic cardiovascular disease (*N* = 59,353) HR (95% CI)	Ischemic heart disease (*N* = 18,122) HR (95% CI)	Myocardial infarction (*N* = 4,131) HR (95% CI)	All stroke (*N* = 28,779) HR (95% CI)	Thrombotic stroke (*N* = 17,674) HR (95% CI)	Hemorrhagic stroke (*N* = 7,125) HR (95% CI)
<70	1.06 (1.02–1.10)	0.95 (0.88–1.02)	0.97 (0.83–1.14)	1.11 (1.05–1.17)	1.05 (0.98–1.13)	1.16 (1.04–1.29)
70–84	1.02 (1.00–1.04)	0.97 (0.94–1.01)	1.00 (0.92–1.08)	1.04 (1.01–1.07)	1.03 (0.99–1.06)	1.04 (0.99–1.10)
85–99	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
100–109	1.03 (1.00–1.05)	1.00 (0.95–1.05)	1.08 (0.98–1.20)	1.05 (1.02–1.10)	1.09 (1.04–1.14)	0.96 (0.89–1.04)
110–125	1.14 (1.10–1.18)	1.15 (1.08–1.23)	1.37 (1.21–1.54)	1.17 (1.11–1.22)	1.23 (1.16–1.30)	0.99 (0.89–1.09)
126–139	1.31 (1.23–1.39)	1.36 (1.23–1.51)	1.91 (1.59–2.29)	1.45 (1.34–1.57)	1.62 (1.48–1.78)	1.12 (0.93–1.33)
≥140	1.80 (1.73–1.88)	2.12 (1.98–2.26)	3.18 (2.84–3.57)	1.87 (1.77–1.97)	2.29 (2.15–2.44)	1.14 (1.00–1.30)

To convert glucose from mg/dL to mmol/L, multiply by 0.0555. Adjusted for age, smoking status, alcohol drinking, exercise, BMI, and systolic blood pressure. BMI was calculated as weight in kilograms divided by the square of height in meters.

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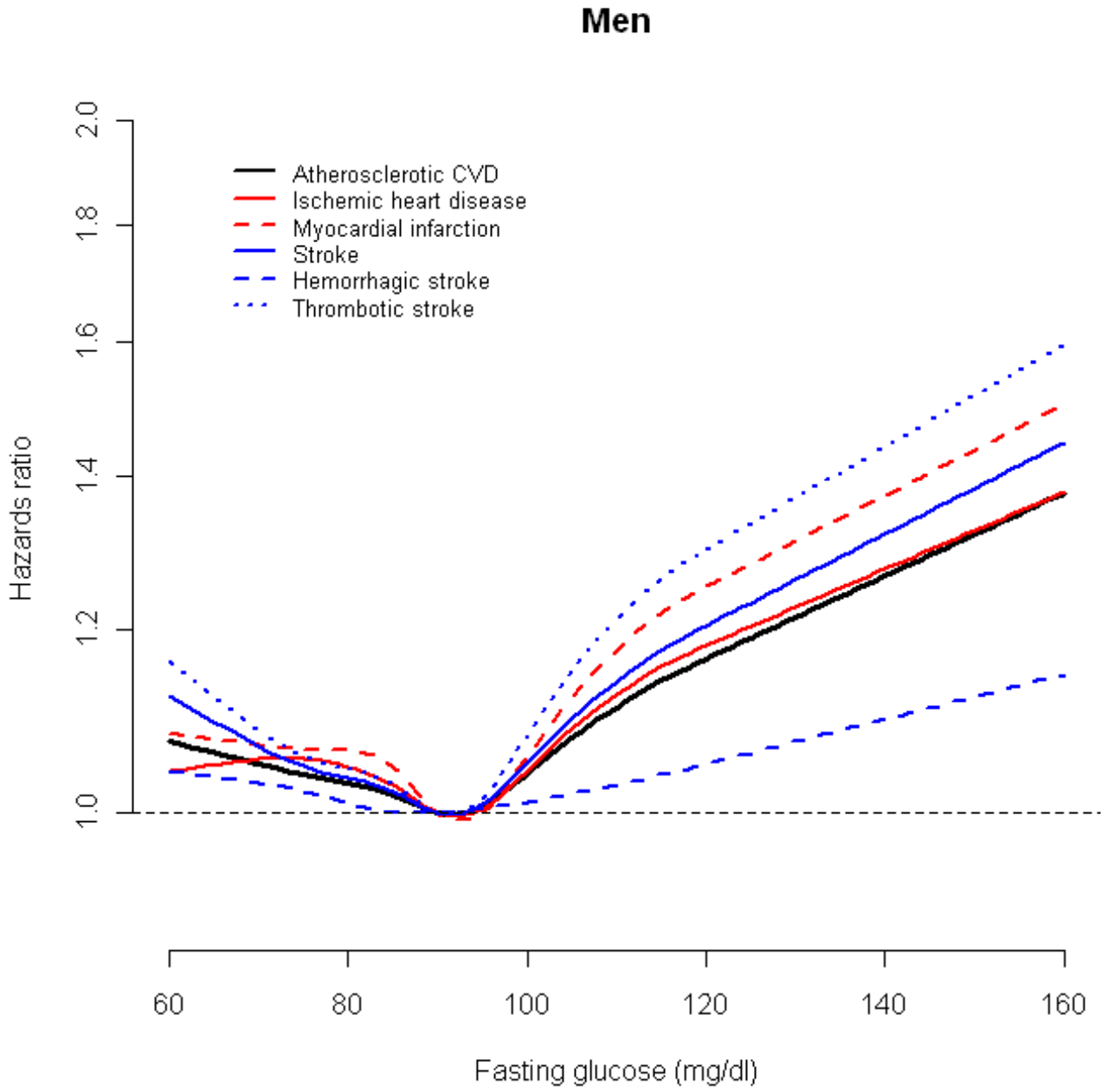

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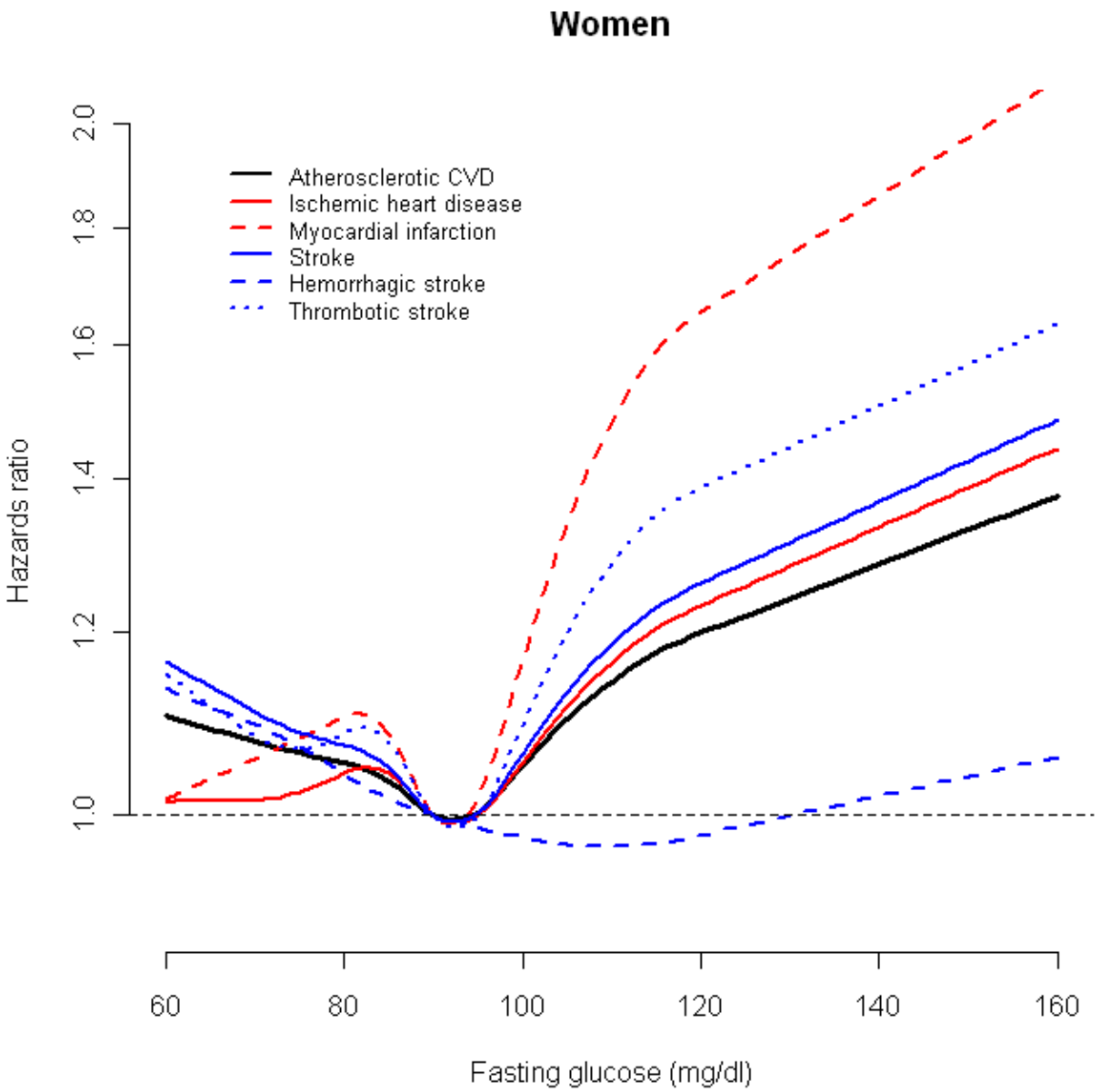

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Mechanism

- **Through abnormal cardiac activity and thrombosis, particularly with atherosclerosis (Wei et al., 2000)**

- **Hypoglycemia or rapid changes in plasma glucose may lead to elevations of counter-regulatory hormones, such as epinephrine and norepinephrine, and these increases induce vasoconstriction and platelet aggregation (Tanne et al, 2004)**

CONCLUSION

- **Both low glucose level (<70 mg/dL) and impaired fasting glucose should be considered as predictors of risk for stroke and coronary heart disease.**
- **The fasting glucose level associated with the lowest cardiovascular risk may fall in a narrow range (85-99 mg/dL).**

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Thank you for your attention

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Welcome reception (Ocean view, ICC JEJU 5F, 2013. 5. 9)