제2형 당뇨병 조기발견을 위한 전략

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CONTENTS

- Basic epidemiology of T2DM* and Prediabetes
- Diabetes Screening Guidelines
- Natural Course of Diabetes Development
- Risk Factors of Diabetes: Genetic and Environmental
- Strategies for Early Diagnosis of T2DM

*T2DM: Type 2 Diabetes

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*T2DM: Type 2 Diabetes

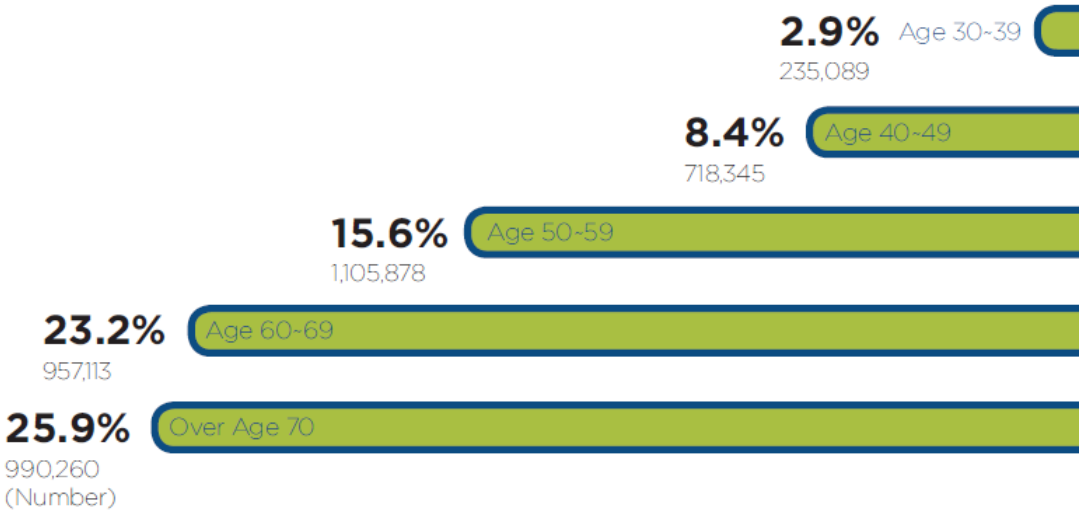
PREVALENCE OF DIABETES 2011 (≥ 30 YRS OLD)

› The prevalence of diabetes in adults 30 years and older is 12.4%.
› As of 2011, an estimated 4.0 million people (about 1 every 8 adults) had diabetes.

Total
12.4%
4,006,686

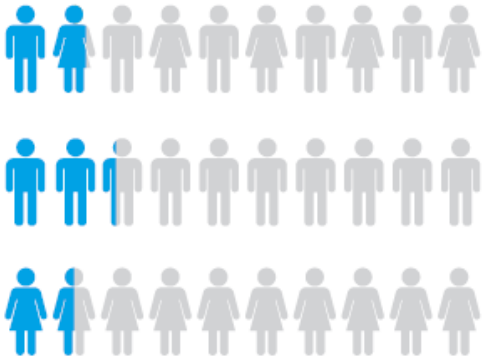
Men
14.5%
2,246,205

Women
10.4%
1,760,481



From Diabetes Fact Sheet 2013, 대한당뇨병학회

IMPAIRED FASTING GLUCOSE

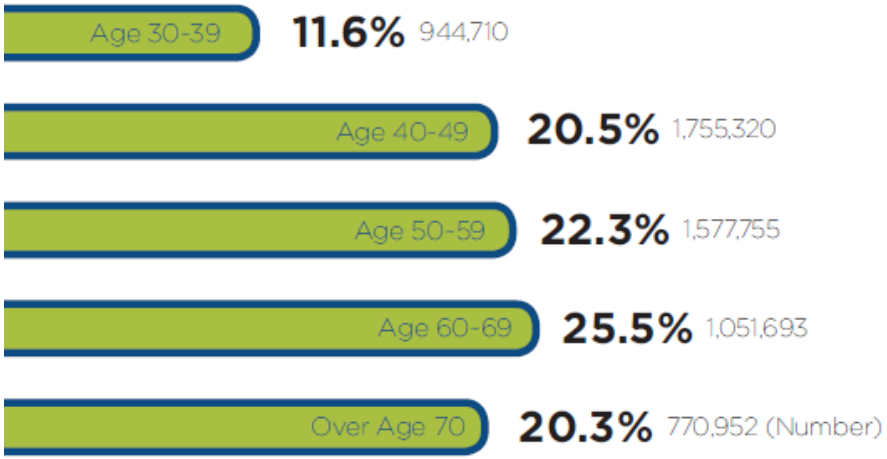


Total
19.3%
6,100,430

Men
23.8%
3,667,699

Women
14.9%
2,432,730

› Approximately 20% of adults 30 years and older(6.1 million people) have impaired fasting glucose.
› Therefore, about 1 in 3 adults was diabetes or had potential risk for diabetes.



From Diabetes Fact Sheet 2013, 대한당뇨병학회

AWARENESS OF DIABETES

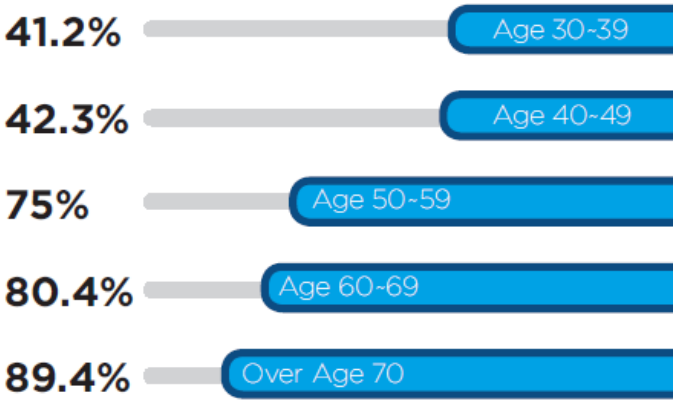
3 out of 10

diabetic patients are not aware of their condition.
(diabetes awareness rate: 72%).

In a younger population of age < 50,

6 out of 10

are unaware of their diabetes.



From Diabetes Fact Sheet 2013, 대한당뇨병학회

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*T2DM: Type 2 Diabetes

Diabetes Screening (ADA)

Table 2.2—Criteria for testing for diabetes or prediabetes in asymptomatic adults

1. Testing should be considered in all adults who are overweight (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) and have additional risk factors:
   - physical inactivity
   - first-degree relative with diabetes
   - high-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - women who delivered a baby weighing >9 lb or were diagnosed with GDM
   - hypertension (≥140/90 mmHg or on therapy for hypertension)
   - HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
   - women with polycystic ovary syndrome
   - A1C ≥5.7%, IGT, or IFG on previous testing
   - other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
   - history of CVD
2. For all patients, particularly those who are overweight or obese, testing should begin at age 45 years.
3. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results (e.g., those with prediabetes should be tested yearly) and risk status.

ADA Position Statement , Diabetes Care 2015

Diabetes Screening (대한당뇨병학회)

- 40세 이상에서 선별 검사를 시행
- 아래 위험인자가 있는 경우 30세 이상

표 1. 제2형 당뇨병의 위험인자

- 과체중 (체질량지수 23 kg/m^2 이상)
- 직계 가족 (부모, 형제자매)에 당뇨병이 있는 경우
- 공복혈당장애나 내당능장애의 과거력
- 임신성 당뇨병이나 4 kg 이상의 거대아 출산력
- 고혈압 (140/90 mm Hg 이상, 또는 약제 복용)
- HDL 콜레스테롤 35 mg/dL 미만 혹은 중성지방 250 mg/dL 이상
- 인슐린저항성 (다낭난소증후군, 흑색가지세포증 등)
- 심혈관질환 (뇌졸중, 관상동맥질환 등)

대한당뇨병학회, 당뇨병 진료지침 2013

Diabetes Screening (USPSTF)

Annals of Internal Medicine REVIEW

Screening for Type 2 Diabetes Mellitus: A Systematic Review for the U.S. Preventive Services Task Force

Shelley Selph, MD, MPH; Tracy Dana, MLS; Ian Blazina, MPH; Christina Bougatsos, MPH; Hetal Patel, MD; and Roger Chou, MD

- Screening for diabetes did not improve mortality rates after 10years follow-up in 2 trials
- But it was found to decrease mortality rate in a lifestyle intervention study with 23 years of follow up
- More evidence is needed to determine the effectiveness of treatments for screen detected diabetes
- Treatment of IFG or IGT was associated with delayed progression to diabetes

Selph S., et al., Annals of Internal Medicine 2015

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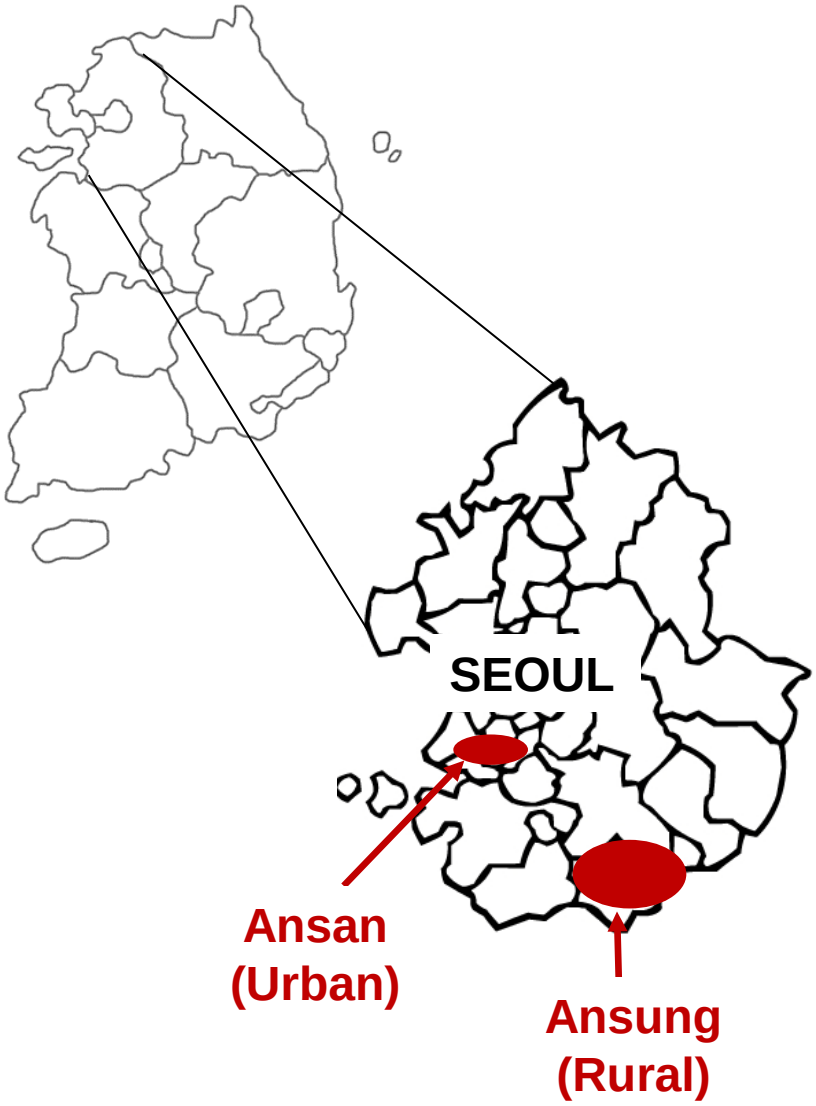
*T2DM: Type 2 Diabetes

Korea Human Genomic Study

-Research Design and Methods

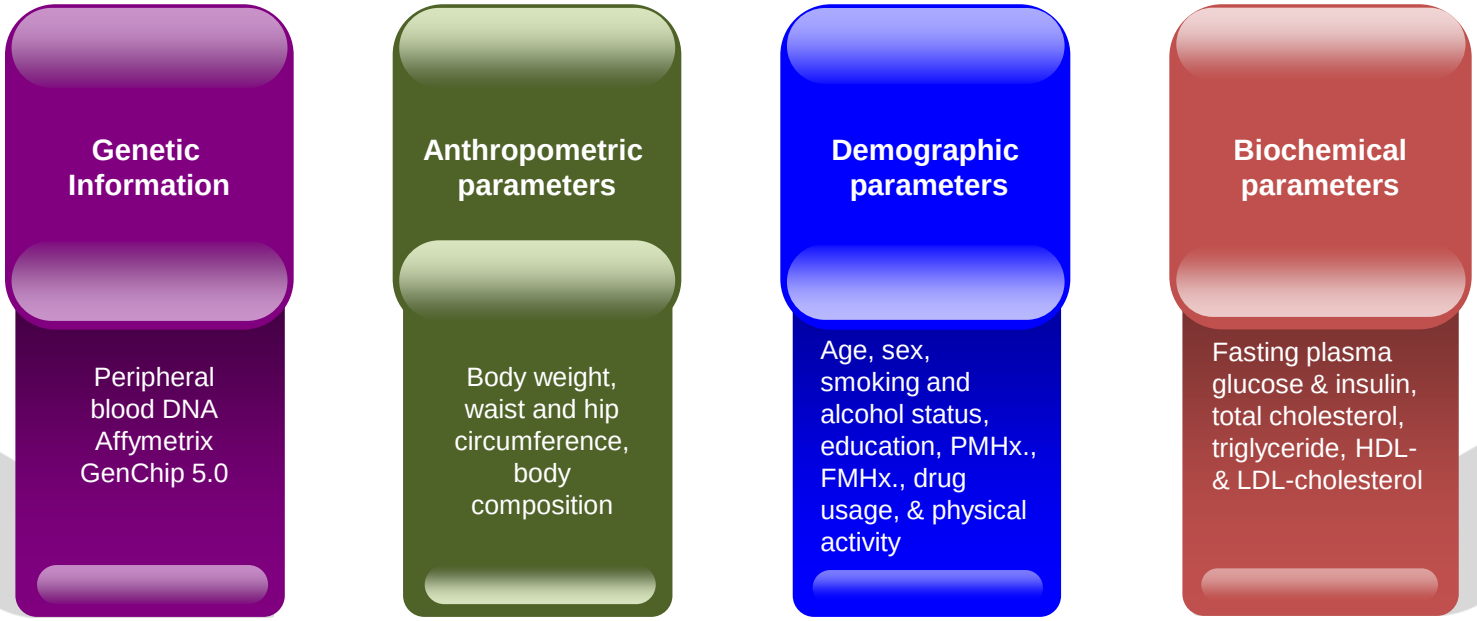
- Ansung cohort (Rural)
  - Population: 135,000
  - Farming area
  - Age: 40-69 yr
  - Subject: 5,024
- Ansan cohort (Urban)
  - Population: 550,000
  - Industrial area
  - Age: 40-69 yr
  - Subject: 5,014

* Eligibility criteria
  - 40-69 years,
  - residence within the borders of the survey area for at least 6 months
  - mental and physical ability to participate.



Ohn JH and Kwak SH, et al., Lancet Diabetes and Endocrinology, Accepted

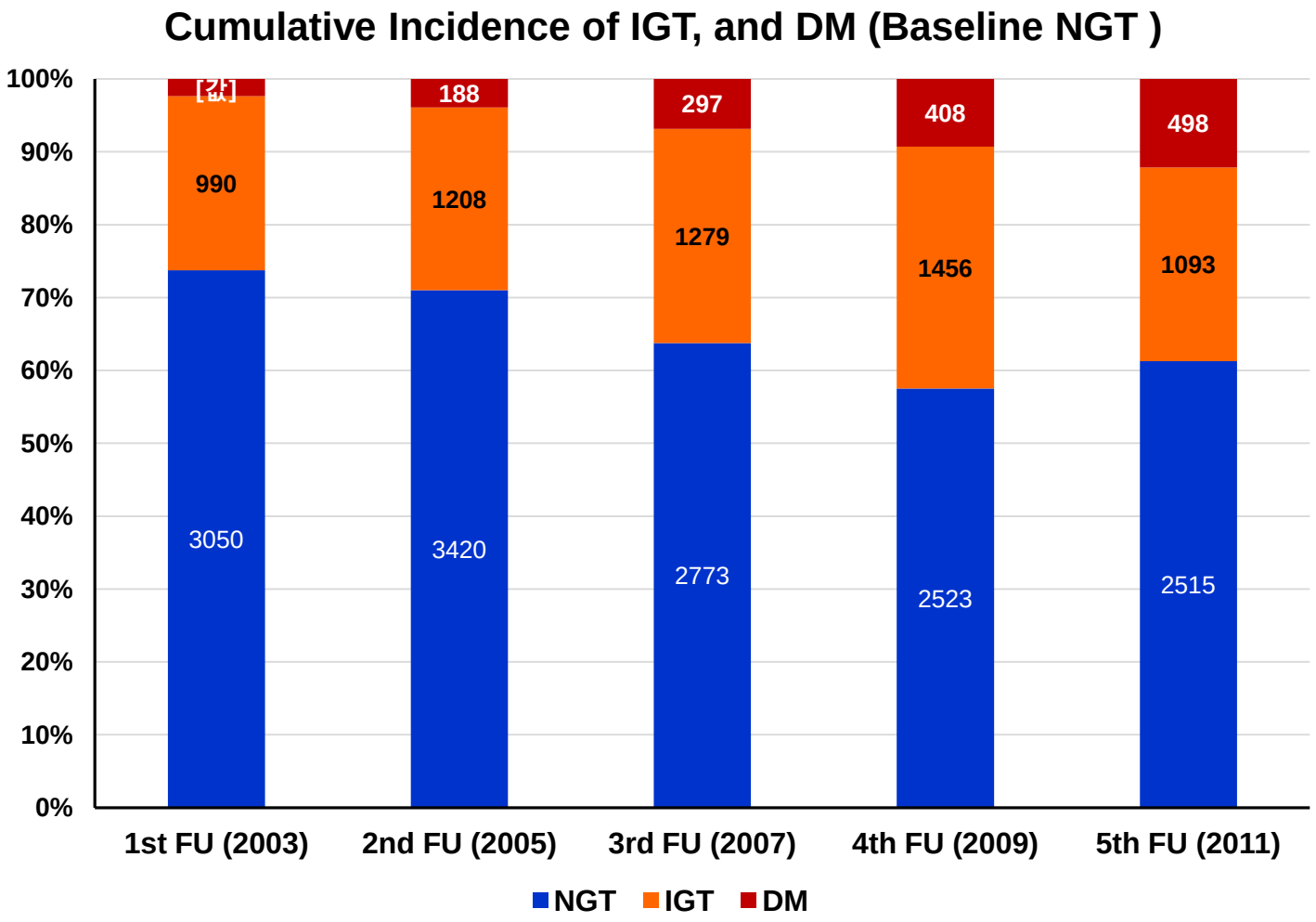
Biannual FU with Detailed Clinical and Biochemical Information



The follow-up is still ongoing

Ohn JH and Kwak SH, et al., Lancet Diabetes and Endocrinology, Accepted

10 Year FU of Baseline NGT



Ohn JH and Kwak SH, et al., Lancet Diabetes and Endocrinology, Accepted

Measurement of beta cell function and insulin resistance

- 10,038 participant
- 75 g OGTT with 0, 60, 120 min Glucose and Insulin
- **Biennial follow-up (2001-2010)**
- **Insulin secretion index**
  - Insulinogenic Index (60 min) = $\frac{(Insulin_{60} - Insulin_0, \mu U/ml)}{(Glucose_{60} - Glucose_0, mmol/l)}$
  - HOMA-B = $20 \times (Insulin_0, \mu U/ml) \times (Glucose_0 - 3.5, mmol/l)$
- **Insulin sensitivity index**
  - Matsuda Index = $\frac{10{,}000}{\sqrt{(Glucose_0, mg/dl) \times (Insulin_0, \mu U/ml) \times (mean\ Glucose, mg/dl) \times (mean\ Insulin, \mu U/ml)}}$
  - HOMA-IR = $\frac{(Glucose_0, mmol/,) \times (Insulin_0, \mu U/ml)}{22.5}$
- **Disposition index**
  - (Insulinogenic Index)x(Matsuda Index)

Ohn JH and Kwak SH, et al., Lancet Diabetes and Endocrinology, Accepted

Baseline characteristics of study participants by the glycemic status at the end of 10-year follow-up

	Non-progressor (n=2,515)	Progressor to prediabetes (n=1,093)	Progressor to diabetes (n=498)	p value
Age (yr)	50·6±8·3	51·4±8·2	52·8±8·9	**<0·001**
Male (%)	1134(45·1)	526(48·1)	285(57·2)	**<0·001**
BMI (kg/m^2)	24·0±2·9	25·0±3·0	24·9±3·2	**<0·001**
Waist circumference (cm)	80·9±8·4	83·3±8·2	84·5±8·7	**<0·001**
Systolic BP (mmHg)	114±16	118±17	119±18	**<0·001**
Diastolic BP (mmHg)	73±11	76±12	77±11	**<0·001**
FPG (mmol/L)	4·5±0·4	4·7±0·4	4·8±0·4	**<0·001**
2-h glucose (mmol/L)	5·7±1·1	6·1±1·1	6·3±1·1	**<0·001**
HbA1c (%)	5·2±0·3	5·4±0·3	5·5±0·4	**<0·001**
Fasting insulin (pmol/L)*	37·8(36·9-38·7)	40·1(38·6-41·5)	39·0(36·9-41·2)	**0·015**
IGI_{60}*	7·9(7·4-8·3)	6·6(6·1-7·1)	5·1(4·5-5·7)	**<0·001**
HOMA-β*	131(128-135)	122(117-127)	110(103-117)	**<0·001**
Composite ISI*	10·0(9·8-10·2)	8·6(8·3-8·9)	8·2(7·8-8·7)	**<0·001**
HOMA-IR*	1·27(1·24-1·30)	1·38(1·33-1·43)	1·37(1·29-1·45)	**<0·001**
DI*	72·9(69·1-76·9)	52·9(49·3-56·6)	39·7(36·1-43·7)	**<0·001**
Total cholesterol (mmol/L)*	4·79(4·76-4·83)	4·89(4·84-4·94)	4·96(4·88-5·04)	**<0·001**
HDL cholesterol (mmol/L)*	1·20(1·19-1·21)	1·14(1·13-1·16)	1·11(1·09-1·13)	**<0·001**
Triglycerides (mmol/L)*	1·34(1·32-1·37)	1·58(1·54-1·63)	1·77(1·70-1·85)	**<0·001**
Hypertension (%)	169(6·7%)	129(11·8%)	80(16·1%)	**<0·001**
Family history of diabetes (%)	223(8·9%)	139(12·7%)	64(12·9%)	**<0·001**

P values are adjusted for age and sex. Data are means±SD, geometric means(95% CI), or n(percentage).
*Log transformed before statistical analysis.
BMI, body mass index; BP, blood pressure; FPG, fasting plasma glucose; IGI60, insulinogenic index at 60 minute; HOMA-β, Homeostasis Model Assessment of β-cell function; ISI, insulin sensitivity index; HOMA-IR, Homeostasis Model Assessment of insulin resistance; DI, disposition index.

Impairment in β-cell function has more profound impact on incident diabetes compared to decreased insulin sensitivity

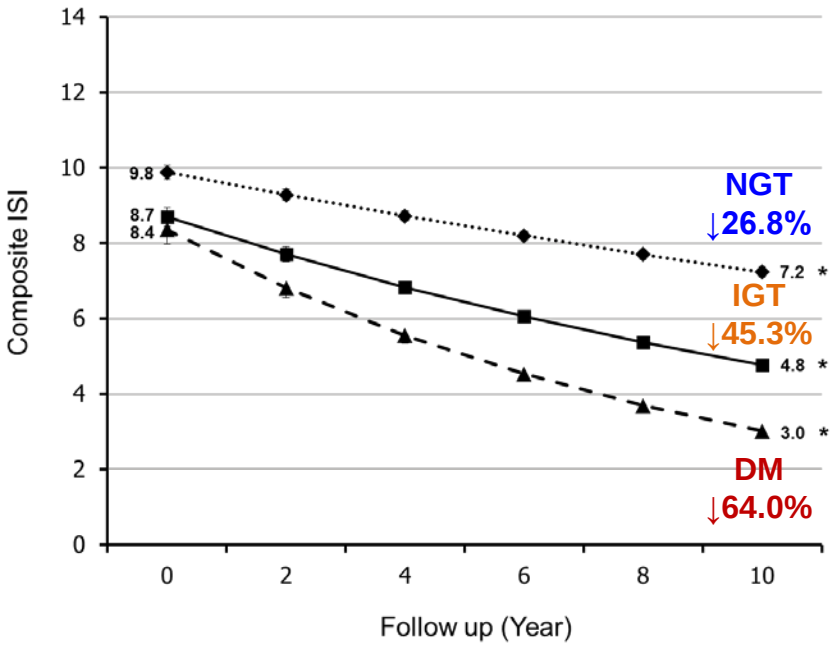
	High-IGI_{60}, High-ISI	High-IGI_{60}, Low-ISI		Low-IGI_{60}, High-ISI		Low-IGI_{60}, Low-ISI	
	Reference	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Number of subjects	658	717		1,574		425	
Incident diabetes (%)	23(**3·5**%)	84(**11·7**%)		213(**13·5**%)		106(**24·9**%)	
Model A	1·00	3·4(2·2-5·4)	<0·001	4·1(2·7-6·3)	<0·001	8·0(5·1-12·6)	<0·001
Model B	1·00	3·5(2·2-5·5)	<0·001	4·0(2·6-6·1)	<0·001	8·2(5·2-12·8)	<0·001
Model C	1·00	3·3(2·1-5·3)	<0·001	3·8(2·5-5·9)	<0·001	7·9(5·0-12·5)	<0·001
Model D	1·00	**2·6**(1·6-4·1)	<0·001	**3·8**(2·4-5·8)	<0·001	**6·2**(3·9-9·8)	<0·001
PAF(95% CI), %[a]	-	**12·1** (7·5-14·9)		**36·7** (29·5-41·4)		**20·9** (18·5-22·3)	

The cutoffs for dichotomizing IGI_{60} and composite ISI into high vs. low groups are **10.5** and **6.9**, respectively.
Model A: unadjusted.
Model B: age, sex, and center adjusted.
Model C: Model B + smoking, sporting activity, alcohol intake, and family history of diabetes adjusted.
Model D: Model C + systolic BP, waist circumference, ALT, total cholesterol, HDL cholesterol, and triglyceride adjusted.
[a]Population-attributable fraction(PAF, %) was calculated using multivariable-adjusted HR (Model D).

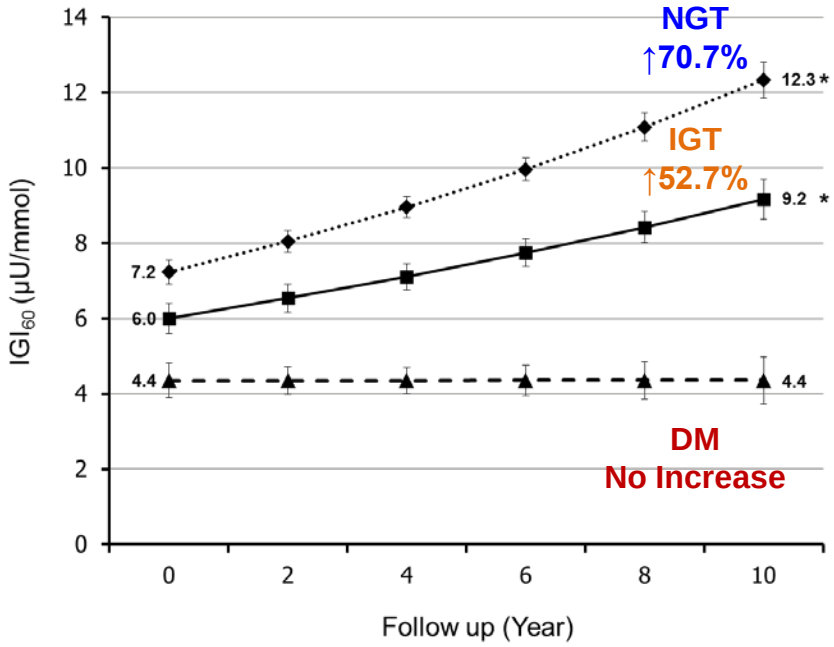
Ohn JH and Kwak SH, et al., Lancet Diabetes and Endocrinology, Accepted

Trajectory of Insulin Sensitivity and Insulin Secretion During 10 Years Of Follow-up.

Change in Insulin Sensitivity
Composite ISI (Matsuda Idex)



Change in Insulin Secretion
Insulingenic Index (60min)

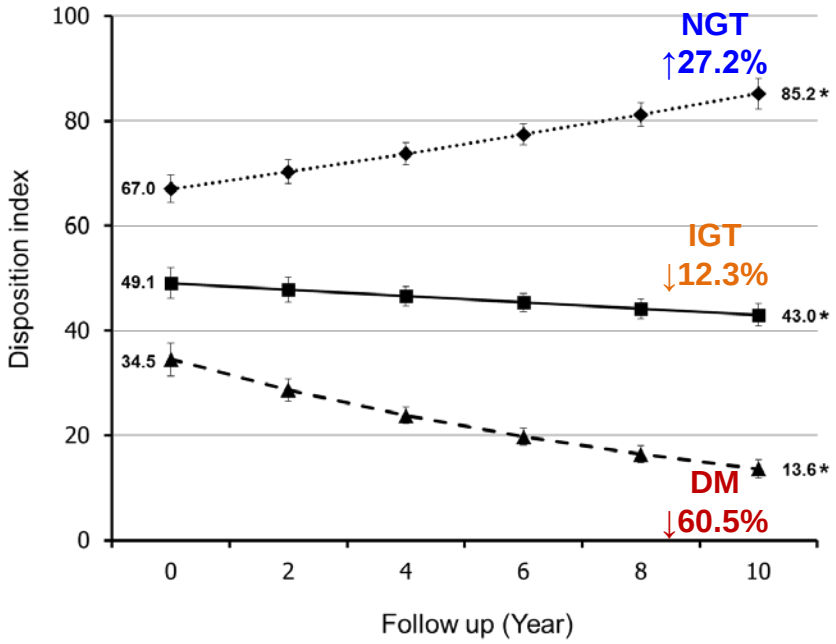


*p<0.01 for 10 vs. 0 years.

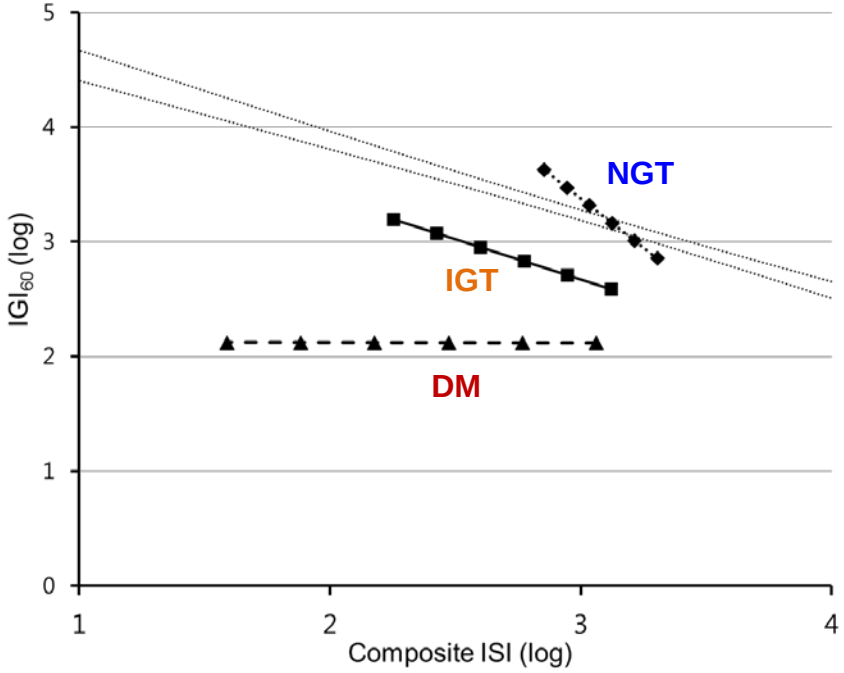
Ohn JH and Kwak SH, et al., Lancet Diabetes and Endocrinology, Accepted

Overall Trajectory of Disposition Index, Insulin Sensitivity and Insulin Secretory Function

Change in Disposition Index



Change in Insulin Sensitivity and Insulin Secretion



*p<0.01 for 10 vs. 0 years.

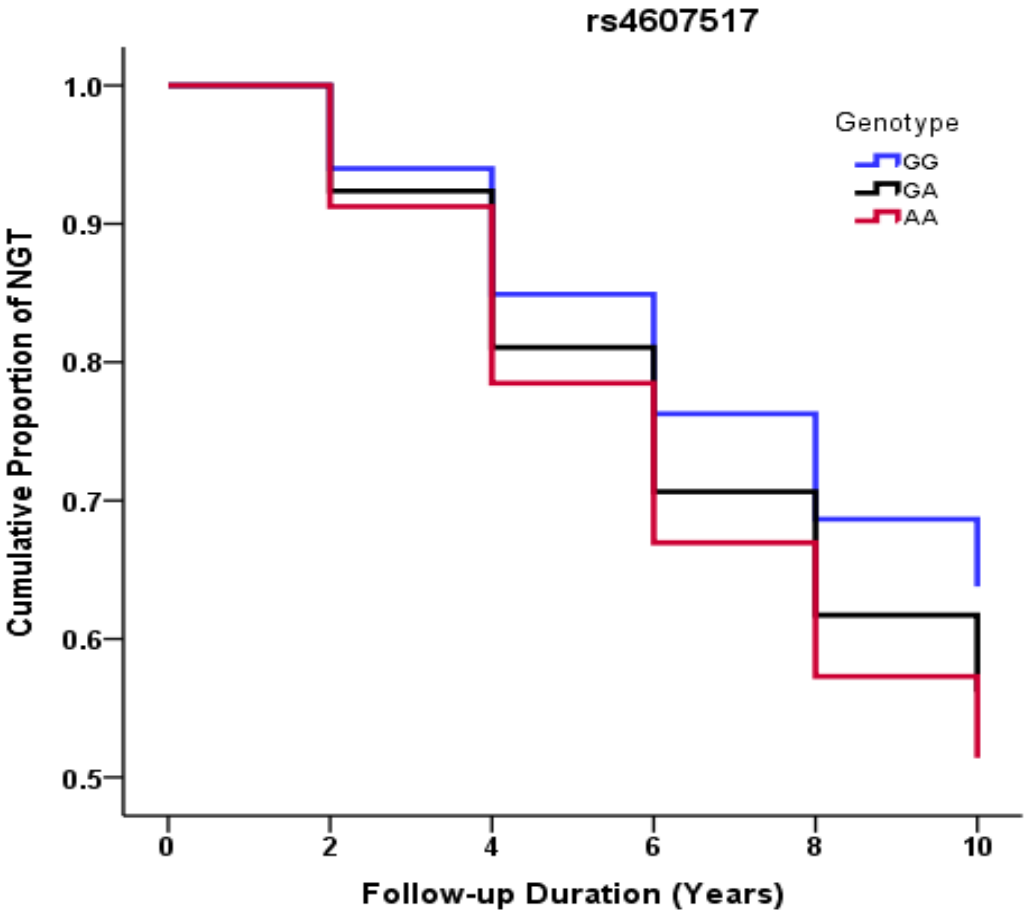
Ohn JH and Kwak SH, et al., Lancet Diabetes and Endocrinology, Accepted

Genetic Variants Associated With Progression To Diabetes

SNP	Chr	Position	Nearest Gene	Risk allele	RAF in non-progressor (n=2,046)	Non-progressor vs. progressor to either prediabetes or diabetes				Non-progressor vs. progressor to diabetes			
						RAF in prediabetes or diabetes (n=1,349)	HR	95% CI	p value	RAF in diabetes (n=431)	HR	95% CI	p value
rs17106184	1	50,682,573	*FAF1*	G	0·88	0·89	1·06	(0·94 to 1·19)	0·33	0·91	1·33	(1·06 to 1·67)	**0·014**
rs10923931	1	120,319,482	*NOTCH2*	T	0·03	0·03	1·10	(0·88 to 1·39)	0·40	0·03	1·21	(0·83 to 1·77)	0·33
rs2075423	1	212,221,342	*PROX1*	G	0·81	0·82	1·04	(0·94 to 1·15)	0·46	0·82	1·01	(0·85 to 1·21)	0·88
rs780094	2	27,594,741	*GCKR*	C	0·47	0·47	1·00	(0·93 to 1·08)	0·92	0·49	1·07	(0·93 to 1·22)	0·33
rs10203174	2	43,543,534	*THADA*	C	0·99	0·99	2·14	(0·96 to 4·77)	0·063	0·99	3·72	(0·52 to 26·49)	0·19
rs243088	2	60,422,249	*BCL11A*	T	0·64	0·65	1·05	(0·96 to 1·13)	0·29	0·65	1·03	(0·89 to 1·19)	0·66
rs6723108	2	135,196,450	*TMEM163*	T	0·98	0·98	0·86	(0·67 to 1·11)	0·24	0·98	0·79	(0·51 to 1·21)	0·28
rs7560163	2	151,346,182	*RND3*	C	0·90	0·90	0·93	(0·81 to 1·05)	0·23	0·88	0·73	(0·59 to 0·90)	**0·0027**
rs7593730	2	160,879,700	*RBMS1*	C	0·82	0·83	1·04	(0·94 to 1·16)	0·41	0·85	1·19	(0·99 to 1·44)	0·064
rs3923113	2	165,210,095	*GRB14*	A	0·88	0·88	1·09	(0·96 to 1·24)	0·20	0·88	1·03	(0·83 to 1·28)	0·81
rs2943640	2	226,801,829	*IRS1*	C	0·95	0·95	0·99	(0·84 to 1·18)	0·93	0·95	1·07	(0·78 to 1·46)	0·68
rs1801282	3	12,368,125	*PPARG*	C	0·94	0·95	1·16	(0·96 to 1·39)	0·12	0·95	1·08	(0·79 to 1·49)	0·62
rs7612463	3	23,311,454	*UBE2E2*	C	0·80	0·81	1·11	(1·00 to 1·22)	**0·043**	0·82	1·16	(0·98 to 1·38)	0·093
rs831571	3	64,023,337	*PSMD6*	C	0·62	0·63	1·02	(0·94 to 1·10)	0·67	0·64	1·07	(0·93 to 1·23)	0·37
rs6795735	3	64,680,405	*ADAMTS9*	C	0·20	0·21	1·03	(0·94 to 1·14)	0·49	0·21	1·02	(0·86 to 1·21)	0·82
rs4402960	3	186,994,381	*IGF2BP2*	T	0·28	0·29	1·04	(0·96 to 1·13)	0·31	0·29	1·06	(0·91 to 1·22)	0·46
rs16861329	3	188,149,155	*ST6GAL1*	C	0·85	0·84	0·88	(0·78 to 0·98)	**0·025**	0·85	0·96	(0·78 to 1·18)	0·70
rs6815464	4	1,299,901	*MAEA*	C	0·60	0·60	1·01	(0·93 to 1·09)	0·79	0·62	1·10	(0·96 to 1·26)	0·18
rs4458523	4	6,340,887	*WFS1*	G	0·98	0·97	0·97	(0·77 to 1·24)	0·83	0·97	0·96	(0·63 to 1·46)	0·84
rs6813195	4	153,739,925	*TMEM154*	C	0·51	0·54	1·10	(1·02 to 1·19)	**0·011**	0·55	1·12	(0·98 to 1·28)	0·091
rs702634	5	53,307,177	*ARL15*	A	0·89	0·90	1·08	(0·96 to 1·23)	0·21	0·90	1·17	(0·93 to 1·47)	0·17
rs459193	5	55,842,508	*ANKRD55*	G	0·51	0·53	1·04	(0·97 to 1·12)	0·29	0·53	1·04	(0·91 to 1·19)	0·57
rs9502570	6	7,235,436	*SSR1/RREB1*	T	0·59	0·59	1·05	(0·97 to 1·14)	0·26	0·59	1·04	(0·91 to 1·20)	0·56
rs7756992	6	20,787,688	*CDKAL1*	G	0·53	0·54	1·05	(0·97 to 1·13)	0·25	0·52	0·97	(0·84 to 1·11)	0·62
rs9470794	6	38,214,822	*ZFAND3*	C	0·25	0·24	0·97	(0·88 to 1·06)	0·47	0·23	0·93	(0·79 to 1·09)	0·36
rs1535500	6	39,392,028	*KCNK16*	T	0·41	0·42	1·01	(0·94 to 1·09)	0·77	0·41	0·98	(0·85 to 1·12)	0·74
rs17168486	7	14,864,807	*DGKB*	T	0·38	0·39	1·08	(0·99 to 1·16)	0·071	0·36	0·89	(0·77 to 1·03)	0·11
rs849135	7	28,162,938	*JAZF1*	G	0·99	0·99	0·95	(0·50 to 1·84)	0·89	0·99	0·91	(0·29 to 2·84)	0·87
rs4607517	7	44,223,721	*GCK*	A	0·16	0·21	1·27	(1·16 to 1·38)	**$1·70\times10^{-7}$**	0·21	1·20	(1·02 to 1·40)	**0·025**
rs6467136	7	126,952,194	*GCC1*	G	0·76	0·75	0·97	(0·89 to 1·07)	0·56	0·75	0·97	(0·83 to 1·14)	0·72
rs13233731	7	130,088,229	*KLF14*	G	0·70	0·69	0·99	(0·92 to 1·08)	0·89	0·69	1·00	(0·87 to 1·16)	1·00
rs516946	8	41,638,405	*ANK1*	C	0·86	0·88	1·13	(1·01 to 1·27)	**0·038**	0·89	1·19	(0·97 to 1·47)	0·10
rs7845219	8	96,006,678	*TP53INP1*	T	0·28	0·28	1·04	(0·96 to 1·13)	0·32	0·29	1·11	(0·96 to 1·29)	0·16

Ohn JH and Kwak SH, et al., Lancet Diabetes and Endocrinology, Accepted

Genetic Variant in Glucokinase



Ohn JH and Kwak SH, et al., Lancet Diabetes and Endocrinology, Accepted

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*T2DM: Type 2 Diabetes

Optimal Cutoff for BMI

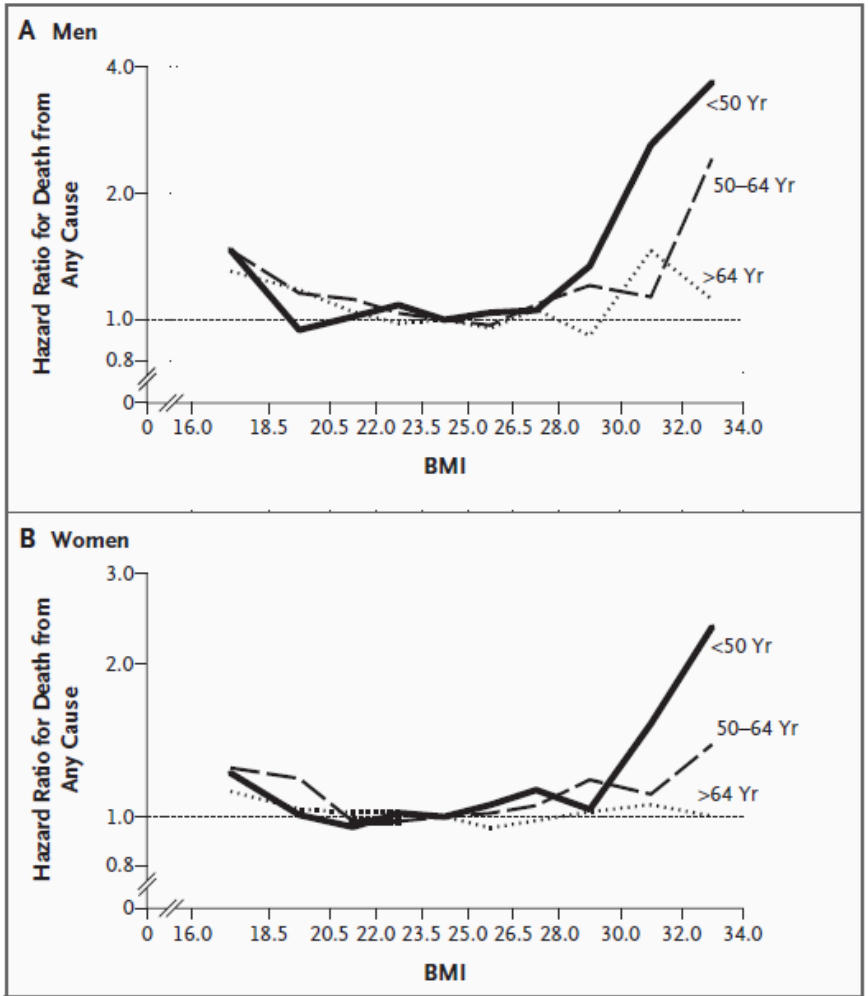


Figure 3. Hazard Ratios for Death from Any Cause among Men and Women with No History of Smoking, According to Age Group and BMI.

Data are from the KCPS, 1993–2004.[12,13] The reference category was a BMI of 23.0 to 24.9. All hazard ratios were adjusted for age. Panel A and Panel B have different scales for hazard ratios.

OBESITY
- ✓ Based on Mortality
- ✓ BMI ≥ 25 kg/m^2

OVERWEIGHT
- ✓ Based on Morbidity
- ✓ BMI ≥ 23 kg/m^2

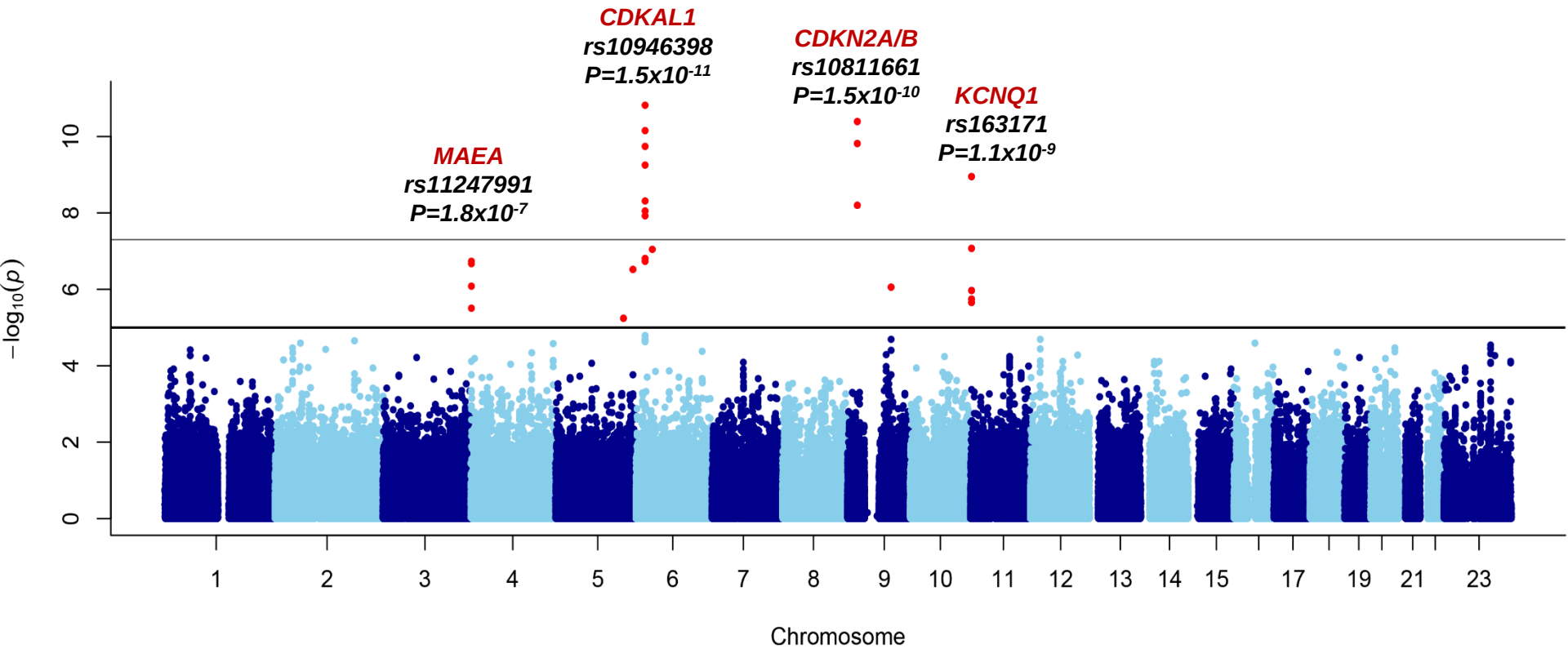
WEIGHT CIRCUMFERENCE
- ✓ Male ≥ 90 cm
- ✓ Female ≥ 85 cm

Jee SH , NEJM 2006
Kim MK, Endocrinology and Metabolism 2015

Evidence of Genetic Etiology in DM

1. Familial clustering:
   - "Diabetes runs in my family"
   - Life time risk of diabetes: one parent with T2DM – 35%
     both parents with T2DM – 70%
2. Sibling recurrence risk ratio (λ_s): 2-3
3. Twin study:
   - Heritability (h^2) in monozygotic twins: 35-70%
   - Heritability (h^2) in dizygotic twins: 20-30%
4. Ethnic difference in prevalence of diabetes
5. Monogenic diabetes as specific type (MODY)

Genome-Wide Association Study in Korean T2DM vs Control Subjects



Subjects are from Ansung cohort and Seoul National University Hospital.
N = **3,596** (Cases/Controls = 2,601/995).
Logistic regression analysis adjusting for age, sex, and BMI.
Normal controls: Age > 60, NGT, No FHx of DM, No PHx of DM.

Unpublished Data

PAX4 (Paired Box 4)

Chr	rsID	Position	Non-Ref Allele		Non-Ref AF in T2DM	Non-Ref AF in Controls	No. Subjects (Case/Control)	OR	se	*P*
7	rs2233580	127,253,550	T	**Stage 1**	0.122	0.057	917 (619/298)	2.54	0.23	**2.91×10^{-5}**
				Stage 2*	0.094	0.051	3,039 (2,021/1,018)	1.46	0.09	**2.26×10^{-6}**
				Meta-Analysis**			3,956 (2,640/1,316)	**1.81**	0.10	**5.48×10^{-9}**
7	rs3824004	127,253,551	T	**Stage 1**	0.045	0.037	917 (619/298)	1.06	0.31	**0.858**
				Stage 2*	0.054	0.029	3,036 (2,018/1,018)	1.81	0.15	**5.75×10^{-5}**
				Meta-Analysis**			3,956 (2,640/1,316)	**1.63**	0.14	**4.26×10^{-4}**

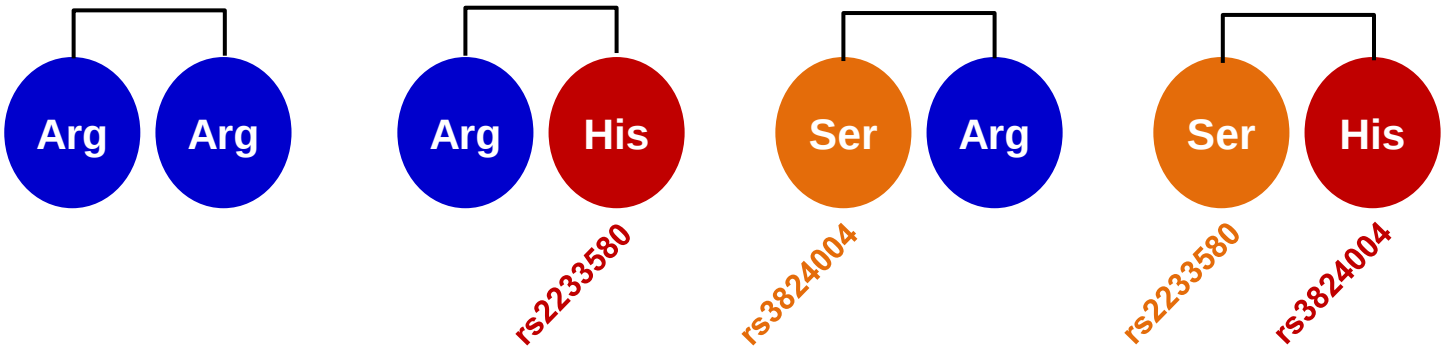
P values are from logistic regression adjusting for age and sex. ** Meta-analysis was done using METAL with inverse-variance weighted fixed effect model.

PAX4 Haplotype Association

CHR	SNP1	SNP2	HAPLOTYPE	AA	Group	Frequency	OR	P	Overall P
7	rs2233580	rs3824004	ACG	Arginine	Positive Charge	0.874	0.57	2.53E-09	1.81E-08
7	rs2233580	rs3824004	ATG	Histidine	Positive Charge	0.080	1.66	1.11E-05	
7	rs2233580	rs3824004	ACT	Serine	Polar Uncharged	0.044	1.80	0.000199	
7	rs2233580	rs3824004	ATT	Asparagine	Polar Uncharged	0	-	-	

LD measure for two SNPs: R-sq 0.002, D'=0.619

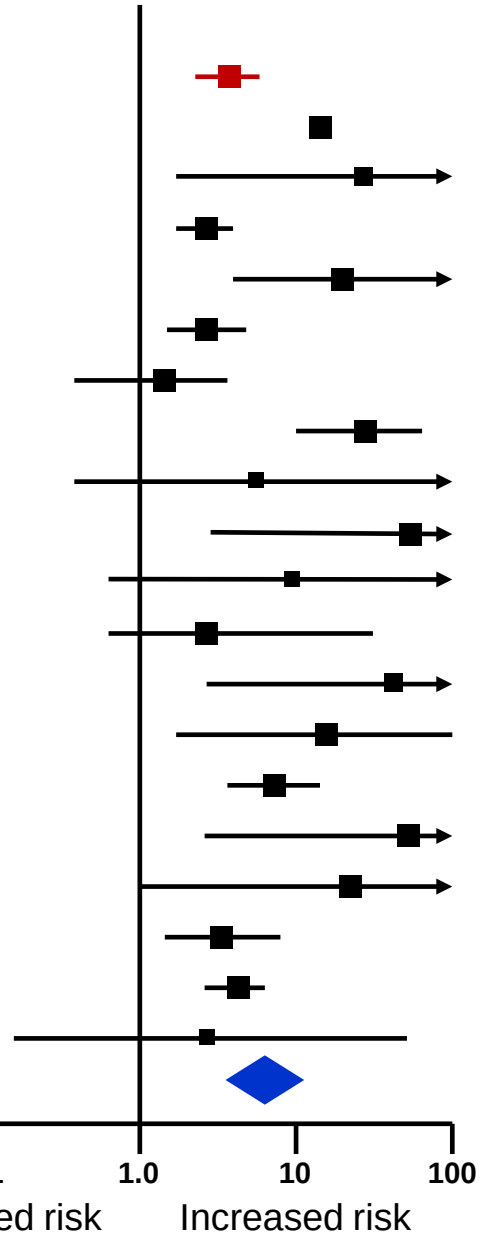
Possible Amino Acid Changes



Dosage	0	1	1	2

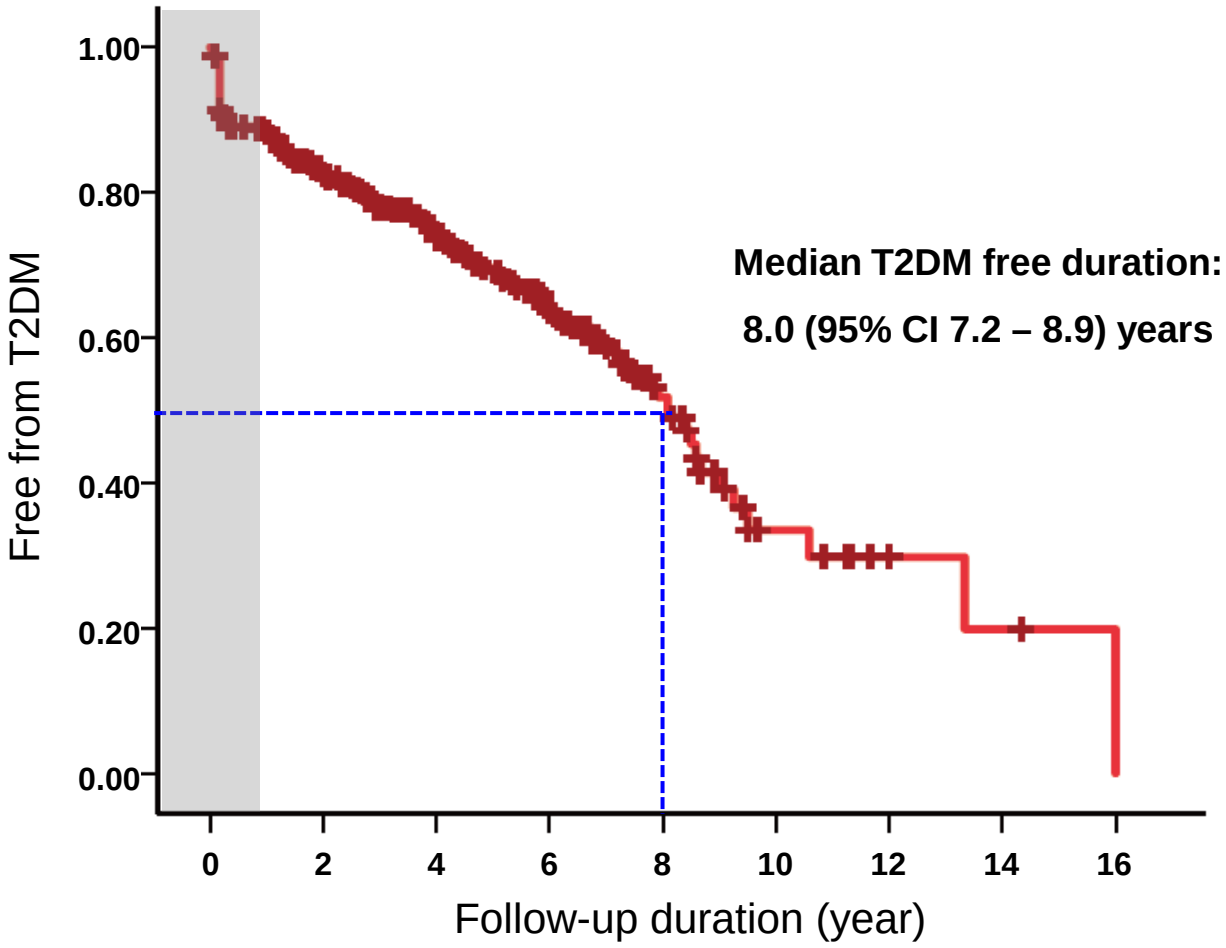
Risk of T2DM after GDM

Study	Year	Country	T2DM/GDM	T2DM/no GDM	RR	(95%CI)
Lee H et al	**1995-1997**	**Korea**	**71/620**	**22/868**	**4.52**	**(2.83-7.21)**
Feig et al	1995-2002	Canada	2,874/21,823	6,628/637,341	12.66	(12.15-13.19)
Madarasz et al	1995	Hungary	21/68	0/39	24.93	(1.55-400.64)
Gunderson et al	1985-2006	USA	43/166	150/2,242	3.87	(2.87-5.22)
Vambergue et al	1992	France	53/295	1/111	19.94	(2.79-142.47)
Lee A et al	1971-2003	Australia	405/5,470	16/783	3.62	(2.21-5.93)
Ferraz et al	2007	Brazil	6/70	7/108	1.32	(0.46-3.78)
Krishnaveni et al	1997-1998	India	13/35	8/489	22.70	(10.09-51.08)
Morimitsu et al	1999-2001	Brazil	7/23	0/11	7.50	(0.47-120.11)
Jarvela et al	1984-1994	Finland	23/435	0/435	47.00	(2.86-771.65)
Albareda et al	1966-1993	Spain	44/696	0/70	9.07	(0.56-146.25)
Aberg et al	1991-1999	Sweden	21/229	1/61	5.59	(0.77-40.66)
Linne et al	1964-1965	Sweden	10/28	0/52	38.38	(2.33-631.74)
Bian et al	1964-1965	China	15/45	1/39	13.00	(1.80-93.93)
Ko et al	1988-1995	China	105/801	7/431	8.07	(3.79-17.19)
Osei et al	1990-1991	USA	10/15	0/35	47.25	(2.95-757.28)
Damm et al	1978-1985	Denmark	33/241	0/57	16.06	(1.00-258.06)
Benjamin et al	1961-1988	USA	14/47	3/47	4.67	(1.43-15.21)
O'Sullivan et al	1962-1970	USA	224/615	18/328	6.64	(4.19-10.52)
Persson et al	1961-1984	Sweden	5/145	0/41	3.16	(0.18-55.76)
Total			**3,997/31,867**	**6,862/643,588**	**7.43**	**(4.79-11.51)**



Bellamy et al. Lancet 2009

Incidence of T2DM after GDM in Koreans



Kwak SH et al. , JCEM 2013

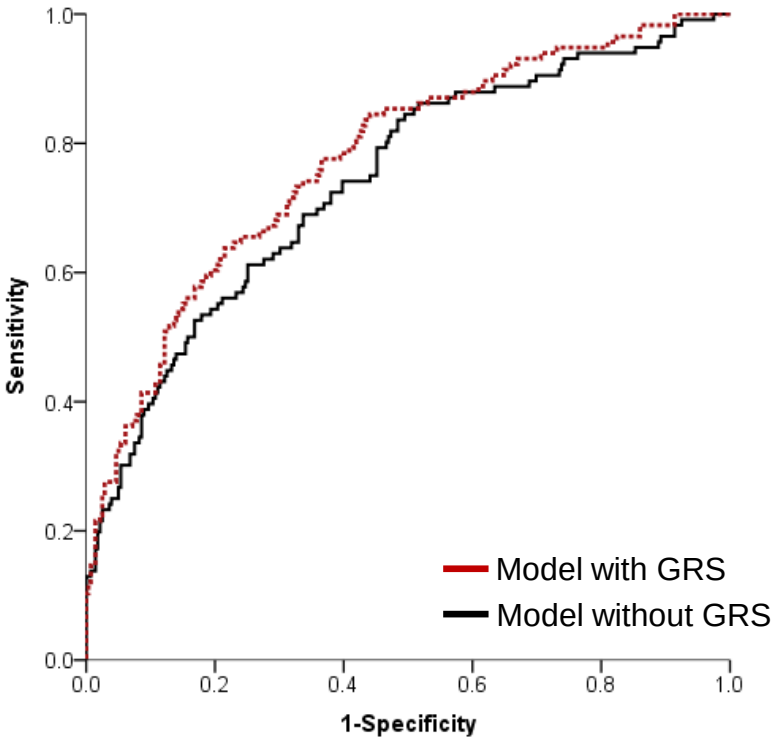
Early vs. Late Converters: Genetic Risk Factors

CHR	Nearby Gene	SNP	Risk Allele	Risk Allele Frequency			OR		*P*	
				Early Converters (N=64)	Late Converters (N=75)	Non-diabetic Controls (N=632)	**Early Converters**	**Late Converters**	**Early Converters**	**Late Converters**
3	*PPARG*	rs1801282	C	0.97	0.95	0.95	1.74	1.14	0.286	0.742
3	*PPARG*	rs3856806	C	0.84	0.85	0.82	1.09	1.24	0.731	0.366
3	***IGF2BP2***	rs4402960	T	0.36	0.42	0.30	1.34	1.71	0.136	**0.00253**
6	***CDKAL1***	rs7754840	C	0.57	0.65	0.46	1.54	2.18	**0.02165**	**0.000012**
6	***CDKAL1***	rs7756992	G	0.60	0.66	0.53	1.37	1.73	0.098	**0.00256**
8	***SLC30A8***	rs13266634	C	0.64	0.70	0.59	1.26	1.62	0.226	**0.00947**
9	*CDKN2A/2B*	rs564398	T	0.89	0.89	0.87	1.20	1.13	0.542	0.645
9	*CDKN2A/2B*	rs1333040	C	0.34	0.31	0.32	1.14	0.98	0.516	0.904
9	*CDKN2A/2B*	rs10757278	G	0.52	0.48	0.45	1.29	1.12	0.177	0.527
9	***CDKN2A/2B***	rs10811661	T	0.69	0.65	0.51	2.10	1.75	**0.00015**	**0.00177**
10	***HHEX***	rs1111875	C	0.44	0.37	0.30	1.77	1.35	**0.00211**	0.097
10	***HHEX***	rs5015480	C	0.28	0.24	0.19	1.71	1.38	**0.00944**	0.112
10	***HHEX***	rs7923837	G	0.33	0.27	0.21	1.88	1.40	**0.00145**	0.091
10	*TCF7L2*	rs7903146	T	0.04	0.06	0.02	1.60	2.52	0.332	**0.014**
10	*TCF7L2*	rs12255372	T	0.01	0.01	0.00	4.95	4.22	0.149	0.202
11	*KCNQ1*	rs2074196	G	0.63	0.61	0.58	1.22	1.14	0.308	0.458
11	*KCNQ1*	rs2237892	C	0.68	0.65	0.61	1.37	1.20	0.123	0.329
11	*KCNQ1*	rs2237895	A	0.72	0.35	0.70	1.10	1.27	0.643	0.189
11	*KCNJ11*	rs5215	G	0.41	0.65	0.38	1.13	1.11	0.523	0.565
11	*KCNJ11*	rs5219	A	0.42	0.64	0.38	1.18	1.10	0.399	0.587
16	*FTO*	rs8050136	C	0.88	0.91	0.88	1.05	1.36	0.863	0.299

T2DM Prediction Model Using GRS

- Model adjusted for Age, Prepregnancy BMI, Family History of DM, Mean Arterial Pressure, Fasting Glucose, Fasting Insulin

	Without wGRS	With wGRS
Age (years)		
OR (95% CI)	1.01 (0.95 - 1.07)	1.01 (0.95 - 1.07)
P	0.876	0.765
Family history of diabetes		
OR (95% CI)	1.49 (0.92 - 2.43)	1.53 (0.93 - 2.52)
P	0.107	0.094
Prepregnancy BMI		
OR (95% CI)	1.10 (1.02 - 1.19)	1.10 (1.02 - 1.19)
P	0.015	0.014
Mean arterial pressure		
OR (95% CI)	1.01 (0.98 - 1.04)	1.01 (0.98 - 1.04)
P	0.518	0.502
Fasting glucose		
OR (95% CI)	2.47 (1.79 - 3.40)	2.33 (1.69 - 3.20)
P	3.6×10^{-8}	2.4×10^{-7}
Log fating insulin*		
OR (95% CI)	0.62 (0.19 - 2.02)	0.64 (0.18 - 2.21)
P	0.423	0.476
Weighted GRS		
OR (95% CI)	-	**1.66 (1.30 - 2.13)**
P	-	**6.3×10^{-5}**
Discriminatory capability		
C statistic (95% CI)	**0.74** (0.69 - 0.80)	**0.78** (0.72 - 0.83)
P for difference	0.015	
Calibration accuracy		
χ^2	3.72	7.34
P	0.88	0.5
Reclassification improvement		
Continuous NRI (95% CI)	-	**0.430 (0.218 - 0.642)**
P	-	**7.0×10^{-5}**



Kwak SH, Diabetologia 2015

CONTENTS

*T2DM: Type 2 Diabetes

Strategies for Early Diagnosis of T2DM

1. Measurement of Beta Cell Dysfunction
2. Genetic Information (Family History)
3. Environmental Factors
   - Age
   - Obesity (BMI, Waist Circumference)
   - Diet, Physical Inactivity, Smoking, Alcohol
4. Simple Score Screening Tools
5. HbA1c

SIMPLE SCORE SCREENING TOOL

Question	Answer (Score)		Enter your Score (Enter 0 if you don't know)
1. Your age group?	< 35 y (0 point) 35–44 y (2 points) ≥ 45 y (3 points)		
2. Have either of your parents or siblings been diagnosed with diabetes?	No (0 point) Yes (1 point)		
3. Are you currently taking medication for hypertension or do you have hypertension (i.e.g, blood pressures greater than 140/90 mmHg)?	No (0 point) Yes (1 point)		
4. What is your waist circumference (taken below the ribs, usually at the level of the navel) ?	Men < 84 cm (33 inch) (0 point) 84–89.9 cm (33–34.9 inch) (2 points) ≥ 90 cm (35 inch) (3 points)	Women < 77 cm (30 inch) (0 point) 77–83.9 cm (30–32.9 inch) (2 points) ≥ 84 cm (33 inch) (3 points)	
5. Do you currently smoke cigarettes on a daily basis?	Never or Ex-smoker (0 point) Current smoker (1 point)		
6. How much alcohol do you drink on a daily basis? (regardless of types of alcohols)	Never or less than 1 drink / day (0 point) 1–4.9 drinks /day (1 point) ≥ 5 drinks /day (2 points)		
TOTAL SCORE (add points from questions 1–6)			
If the TOTAL SCORE is ≥5, you are at high risk for diabetes, so see your doctor for a blood test.			

Your total score from questionnaire	Probability of having diabetes now
≤ 4	2%
5~7	6%
8~9	12%
≥ 10	19%

Lee Y, Diabete Care 2012

Hemoglobin A_{1c} as a Diagnostic Tool for Diabetes Screening and New-Onset Diabetes Prediction

A 6-year community-based prospective study

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Nam H. Cho, md, phd[3]

indicated by the estimated 40% of people who have undiagnosed diabetes (1).

The hemoglobin A_{1c} (A1C) level is

Table 2—*Sensitivity, specificity, and positive and negative predictive value of increasing A1C cutoff levels for detecting undiagnosed diabetes and for predicting the incidence of type 2 diabetes at the 6-year follow-up*

	Baseline undiagnosed diabetes				Incident diabetes after 6 years of follow-up			
	Predictive value				Predictive value			
A1C cutoff (%)	Sensitivity	Specificity	Positive	Negative	Sensitivity	Specificity	Positive	Negative
5.0 (−1.00 SDs above normal mean)	0.972	0.115	0.074	0.982	0.962	0.121	0.162	0.947
5.1 (−0.75 SDs above normal mean)	0.956	0.185	0.079	0.98	0.935	0.198	0.171	0.945
5.2 (−0.50 SDs above normal mean)	0.945	0.279	0.087	0.986	0.886	0.302	0.184	0.937
5.3 (−0.25 SDs above normal mean)	0.915	0.390	0.098	0.984	0.827	0.419	0.201	0.932
5.4 (0.00 SDs above normal mean)	0.887	0.506	0.115	0.984	0.768	0.547	0.231	0.930
5.5 (0.25 SDs above normal mean)	0.866	0.616	0.141	0.984	0.682	0.665	0.265	0.922
5.6 (0.50 SDs above normal mean)	0.822	0.717	0.174	0.982	**0.594**	**0.769**	**0.313**	**0.914**
5.7 (0.75 SDs above normal mean)	0.770	0.797	0.216	0.979	0.508	0.847	0.370	0.907
5.8 (1.00 SDs above normal mean)	0.720	0.862	0.274	0.977	0.420	0.908	0.448	0.898
5.9 (1.25 SDs above normal mean)	**0.676**	**0.907**	**0.344**	**0.975**	0.333	0.947	0.527	0.889
6.0 (1.50 SDs above normal mean)	0.619	0.935	0.411	0.971	0.263	0.967	0.586	0.881
6.2 (2.00 SDs above normal mean)	0.523	0.968	0.544	0.965	0.152	0.987	0.677	0.868
6.6 (3.00 SDs above normal mean)	0.372	0.992	0.771	0.956	0.051	0.999	0.885	0.856

Hemoglobin A_{1c} as a Diagnostic Tool for Diabetes Screening and New-Onset Diabetes Prediction

A 6-year community-based prospective study

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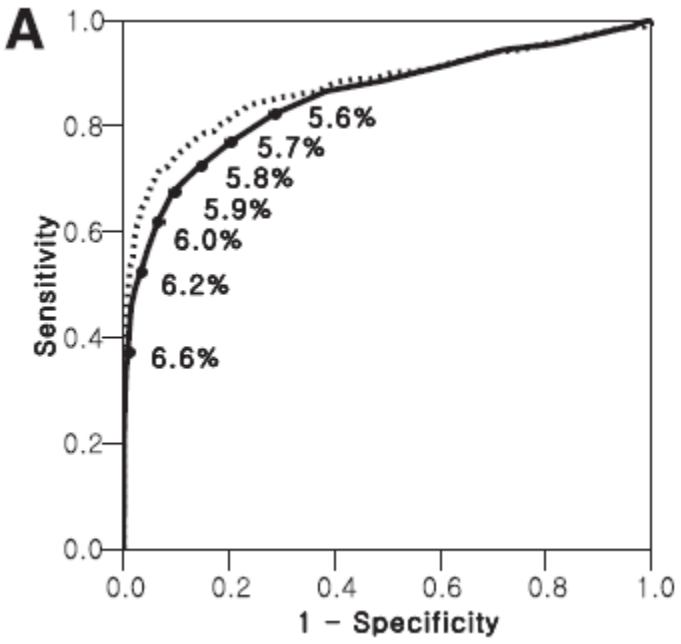
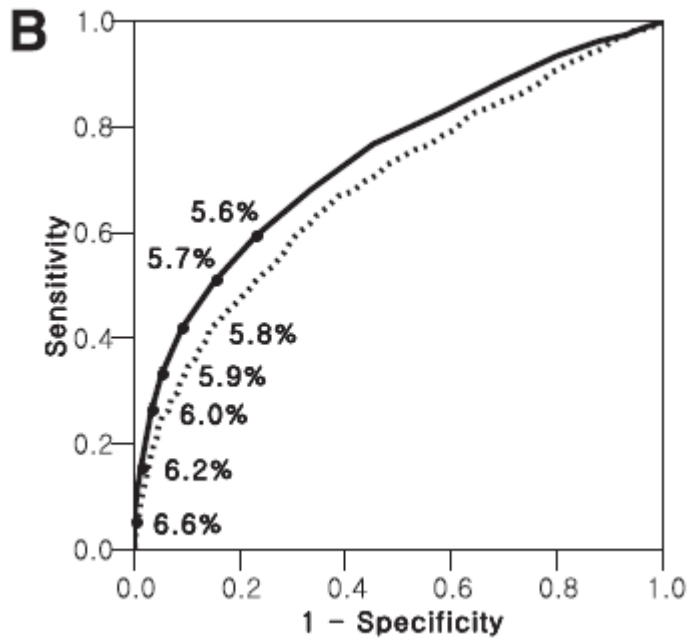
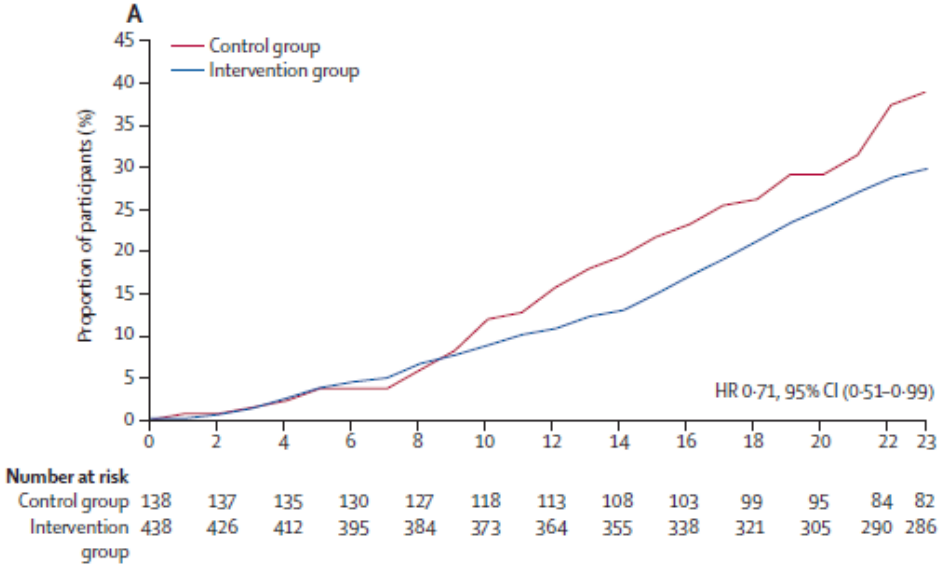
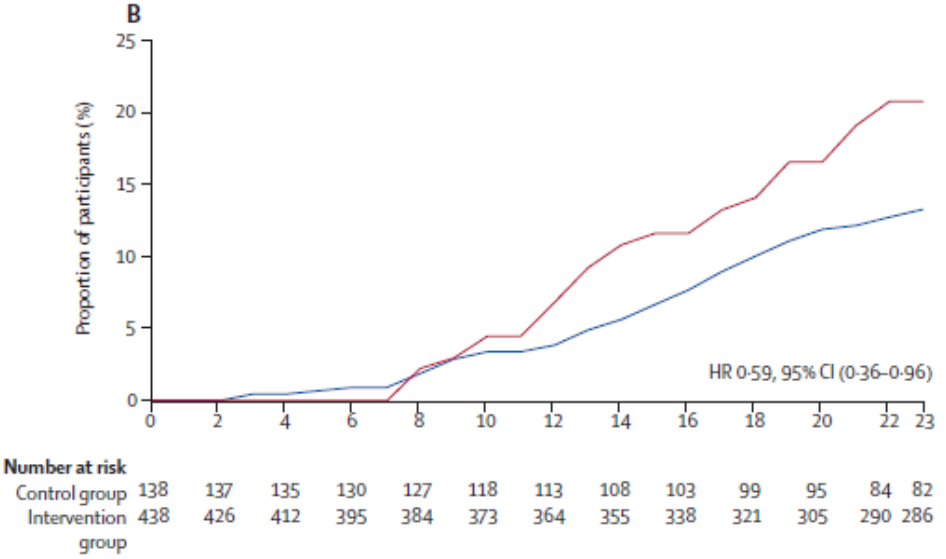
The hemoglobin A_{1c} (A1C) level is





OUTCOME OF DIABETES SCREENING?





Lee G, et al., Lancet Diabetes and Endocrinology, 2014

SUMMARY

- 우리나라 당뇨병 유병율은 30세 이상 성인에서 12.4%에 이르며 공복혈당 장애의 유병율은 19.3%임. 당뇨병 환자 수는 2050년 경에는 약 591만명으로 현재 보다 약 1.9배 정도 증가할 것으로 추정됨

- 국내외 당뇨병 관련 선별 권고안이 있으나 목적 및 실정에 맞게 변형이 필요함

- 한국인의 전향적 코호트 연구에 의하면 나이가 증가함에 따라 인슐린 감수성이 감소하며 이를 보상하기 위한 베타세포 기능의 대상성 증가가 나타나지 않는 것이 당뇨병 발병의 중요한 병태 생리 기전임. 베타세포 관련 기능은 유전적 소인에 의하여 일부 결정됨.

- 당뇨병 발병의 위험 요소로 유전적 소인, 임신성 당뇨병의 과거력, 인슐린 분비능력의 저하, 비만 등을 고려해야 함

- 당뇨병 선별을 위하여 고위험 요소를 파악하는 것이 중요하고 특히 간편선별 도구를 이용하는 것이 좋은 방법이 될 수 있음. 유전적 소인에 대한 연구는 아직 더 많은 연구가 필요하며 선별시 당화혈색소 등의 검사를 사용하는 것이 도움이 됨.