

Metabolic Syndrome is an Independent Risk Factor for the Development of Type 2 Diabetes in Women with a Previous History of Gestational Diabetes Mellitus

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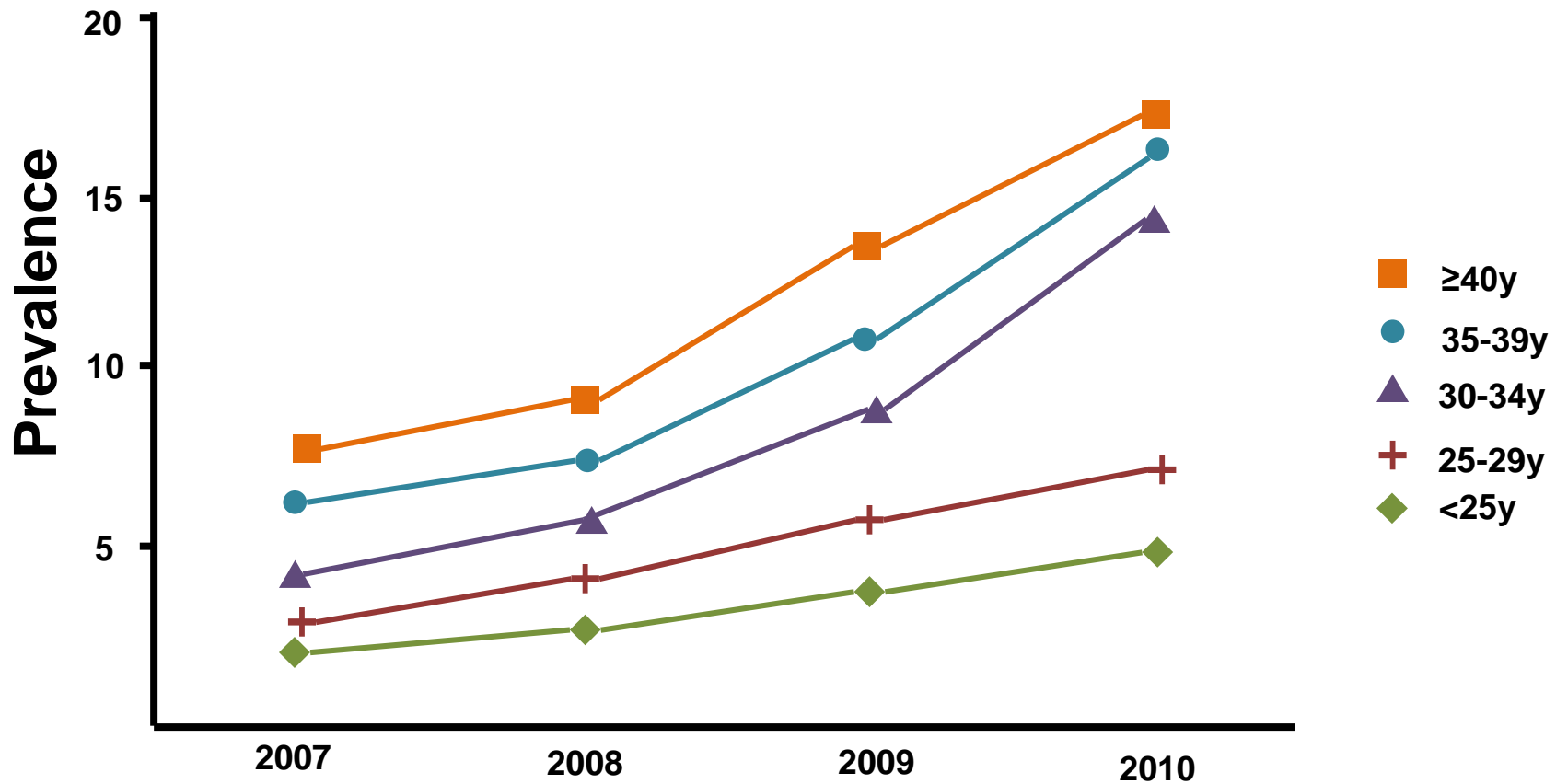
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Conflict of interest disclosure

None

Gestational diabetes mellitus (GDM) in Korea



Pathophysiology of GDM

Normal pregnancy

Physiologic
increase of
insulin resistance

Increased insulin
secretion

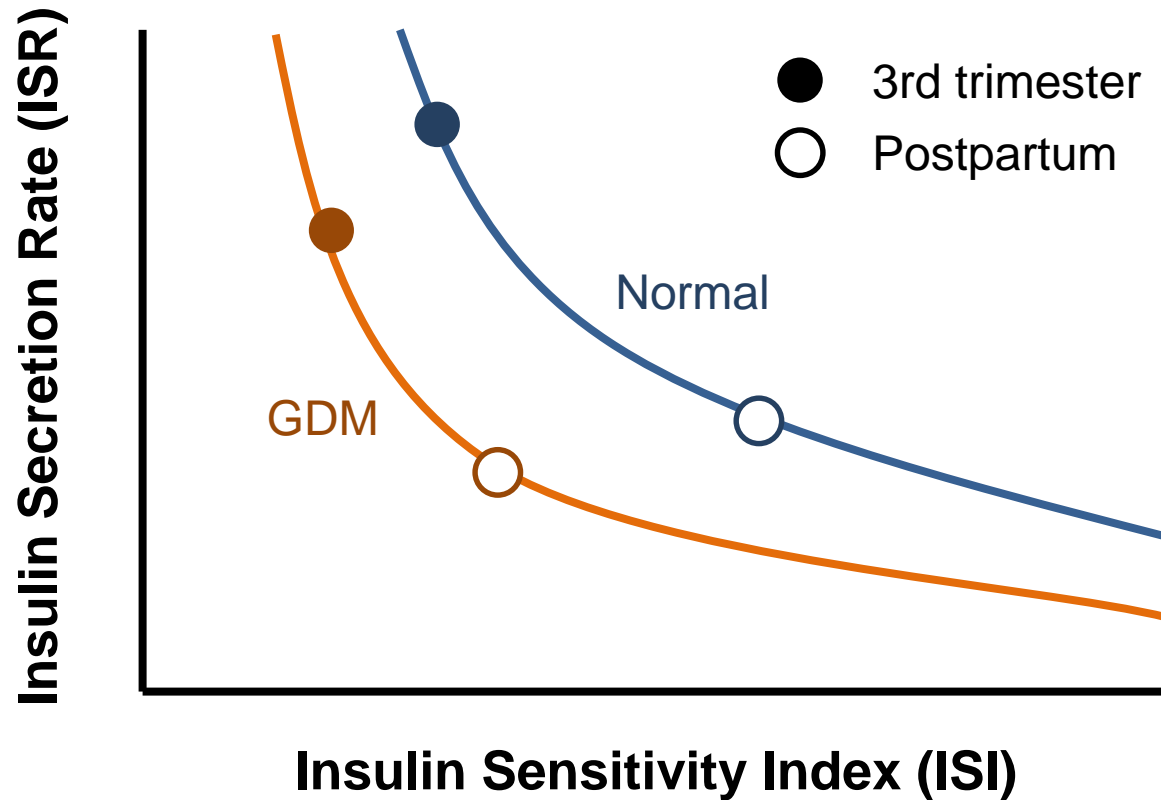


GDM

Excess insulin
resistance

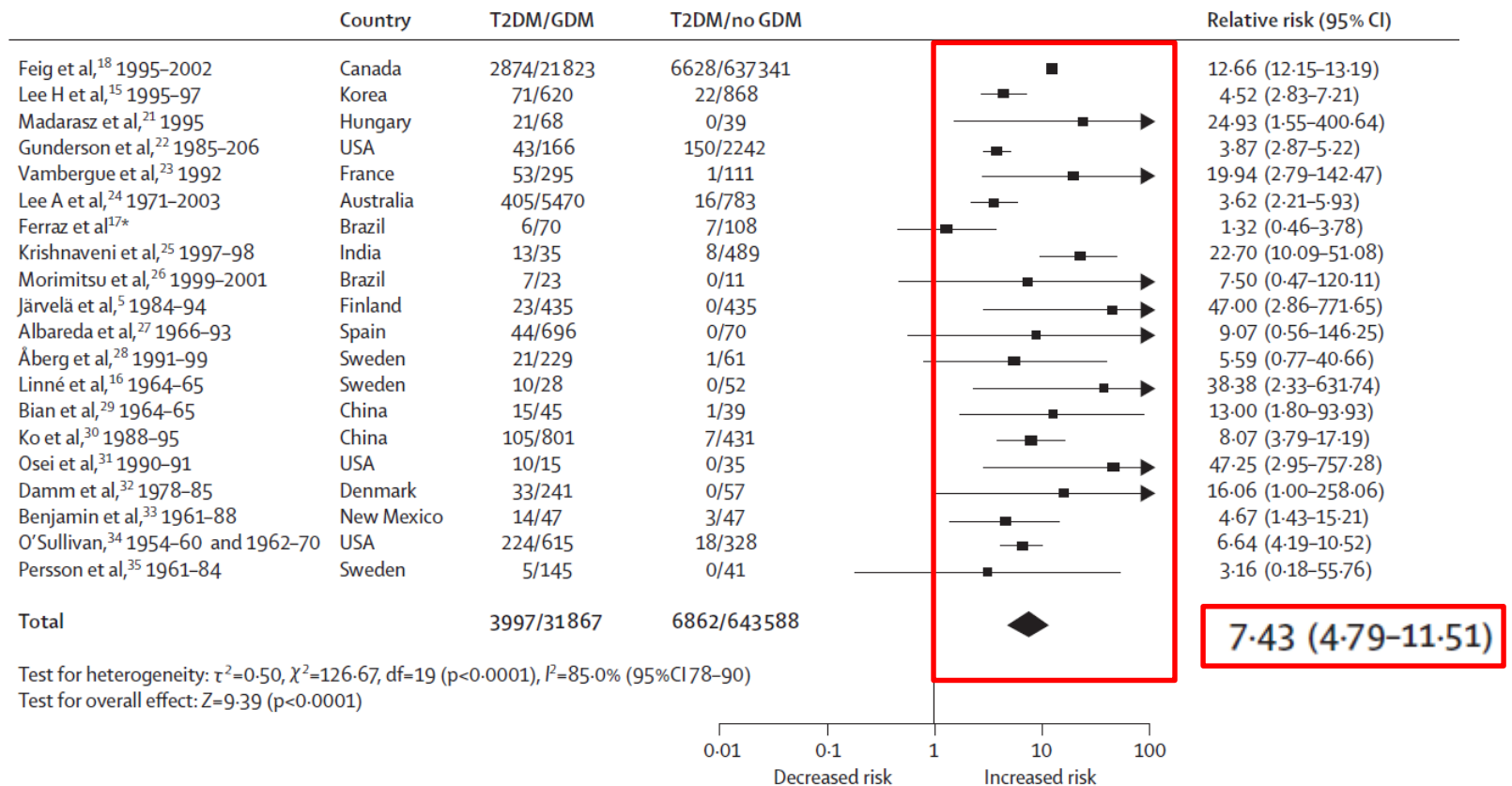
Impaired insulin
secretion

GDM after delivery: still impaired glucose metabolism

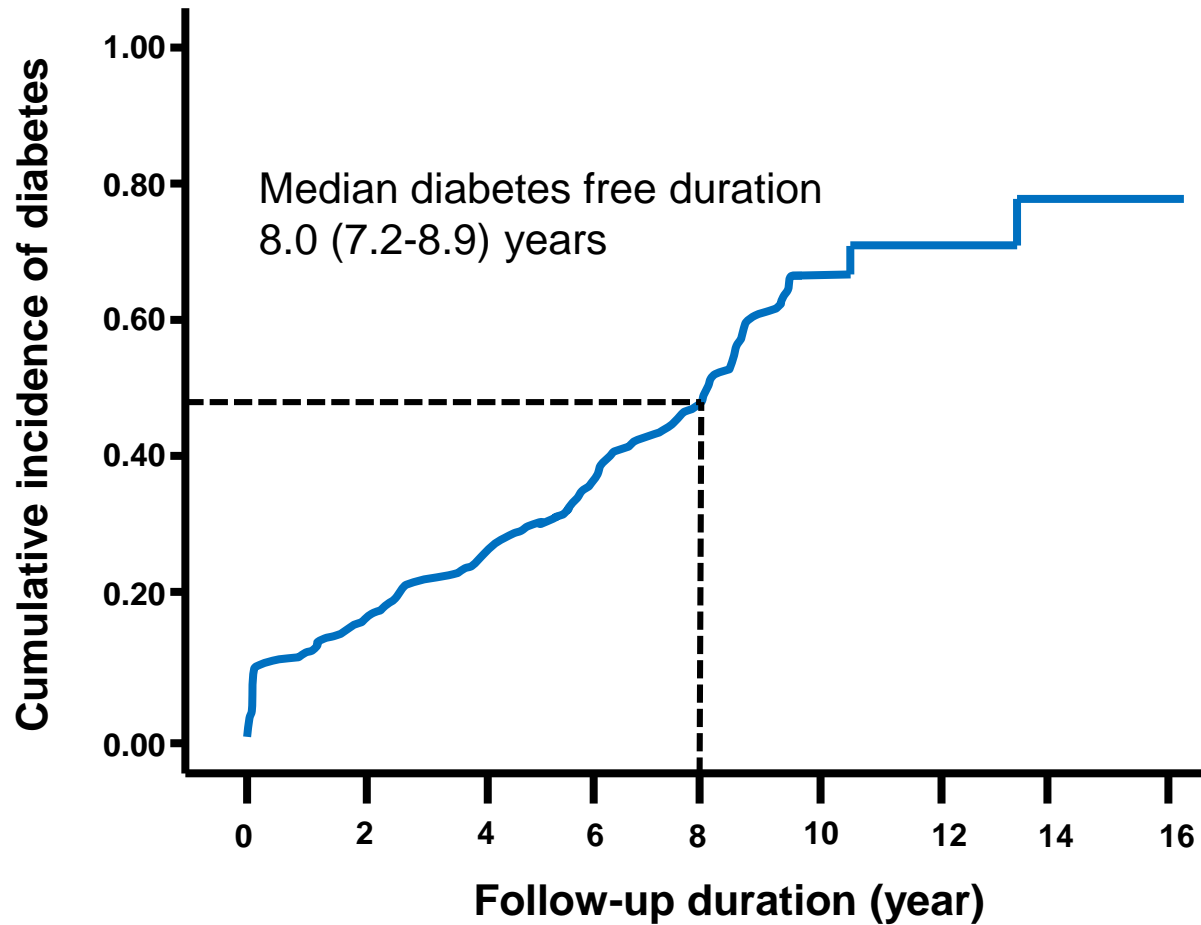


GDM and the risk of T2DM

- History of GDM is a major risk factor for T2DM



GDM and the risk of T2DM



Impaired pancreatic beta cell function and the development of T2DM after GDM

Table 2. Clinical Characteristics and Measures of Diagnostic 100-Gram OGTT During Pregnancy According to the Glucose Tolerance State at 2 Months Post Partum and at More Than 1 Year (Excluding Early T2DM Converters)^a

	Follow-up at 2 Months Post Partum			Follow-up at More Than 1 Year (Excluding Early T2DM Converters)			Early vs Late Converters, P_3
	NGT/IGT	T2DM (Early Converters)	P_1	NGT/IGT	T2DM (Late Converters)	P_2	
AUC of insulin	1431 (1024–1934)	896 (558–1257)	<.001	1340 (953–1861)	1221 (767–1629)	.036	<.001
1-h $\Delta I/\Delta G$, pmol/mmol ^b	69 (46–107)	35 (16–56)	<.001	67 (42–107)	50 (34–74)	.011	<.001
Matsuda Index ^b	3.42 (2.51–4.65)	3.48 (2.65–5.63)	.120	3.70 (2.59–5.18)	3.46 (2.63–4.98)	.250	.204
IS/IR disposition index	166 ± 60	98 ± 53	<.001	169 ± 58	131 ± 57	<.001	<.001

Impaired pancreatic beta cell function and the development of T2DM after GDM

Table 4. Independent Risk Factors for T2DM Early or Late Post Partum According to Multivariate Logistic Regression Analysis^a

	Model 1		Model 2		Model 3	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
T2DM at 2 mo post partum (early converters)						
Prepregnancy BMI	1.08 (1.01–1.16)	.028	1.08 (1.00–1.17)	.051	1.09 (1.00–1.18)	.045
Gestational week at diagnosis	0.95 (0.90–1.01)	.092	0.93 (0.86–1.00)	.047	0.93 (0.86–1.00)	.048
Insulin treatment	1.71 (0.81–3.60)	.159	1.97 (0.83–4.70)	.126	2.06 (0.87–4.87)	.101
Fasting glucose	0.98 (0.96–1.01)	.142	0.98 (0.96–1.01)	.308	0.99 (0.96–1.01)	.317
AUC of glucose	1.01 (1.00–1.01)	.006	1.01 (1.00–1.01)	.060	1.01 (1.00–1.01)	.076
Log fasting insulin	0.04 (0.00–0.38)	.006	0.05 (0.00–0.89)	.041	0.04 (0.00–0.71)	.028
Log AUC of insulin	1.40 (0.16–12.47)	.765	1.00 (0.07–13.91)	1.000	1.34 (0.10–18.57)	.825
IS/IR disposition index	0.10 (0.02–0.49)	.005	0.15 (0.02–0.99)	.049	0.13 (0.02–0.87)	.036
rs10811661 (CDKN2A/2B)			1.18 (0.76–1.84)	.462		
rs1111875 (HHEX)					1.44 (0.93–2.23)	.106
T2DM at more than 1 y of follow-up (late converters)						
Prepregnancy BMI	1.11 (1.02–1.20)	.013	1.08 (0.98–1.19)	.114		
Insulin treatment	0.92 (0.40–2.14)	.849	0.76 (0.30–1.92)	.558		
Fasting glucose	1.01 (0.98–1.04)	.622	1.01 (0.97–1.04)	.665		
AUC of glucose	1.01 (1.00–1.01)	.013	1.01 (1.00–1.01)	.082		
Log AUC of insulin	0.48 (0.14–1.71)	.260	0.73 (0.17–3.26)	.685		
IS/IR disposition index	0.61 (0.22–1.66)	.329	0.25 (0.06–0.99)	.049		
rs7754840 (CDKAL1)			1.39 (0.89–2.18)	.147		

Risk factors for the development of T2DM in women with a history of GDM

- Age
- Prepregnancy body weight
- Family history of DM
- Breast feeding (protective)
- Multiparity
- The level of hyperglycemia during pregnancy
 - Fasting glucose during pregnancy
 - Insulin treatment during pregnancy
- Beta cell function (disposition index) Kwak et al., JCEM, 2013;98:E744-52
- Postpartum BMI change

Moon et al. JCEM 2015; 100:3548-3555,

Metabolic syndrome (MetS) as a precursor of T2DM in general population

		Age adjusted RR
The Framingham Offspring Cohort	Men	6.92 (4.47-10.81)
	Women	6.90 (4.35-10.94)

Wilson et al. Circulation 2005

	Unadjusted OR	Age, sex, ethnicity, FHx adjusted OR	+ IGT, fasting insulin adjusted OR
The San Antonio Heart Study	6.30 (4.60-8.63)	5.54 (4.01-7.66)	3.30 (2.27-4.80)

Lorenzo et al. Diabetes Care 2003

Bidirectional relationship between GDM and Metabolic syndrome (MetS)

- History of GDM increased the risk of MetS by 3.96-fold in a meta-analysis

Xu et al. Plos One 2014; 31:9(1):e87863

- MetS at early pregnancy (before gestational age of 15 weeks) increased the risk of developing GDM by 3.17-fold

Chatzi et al. Diabetes & Metabolism 2009; 35(6):490-4

- However, the impact of MetS on the development of T2DM has not been thoroughly evaluated in women with a history of GDM

Aim of this study

- To investigate the impact of MetS on the development of T2DM in women with a history GDM
 - Does MetS have additional risk of T2DM in women with a history of GDM who are already at high risk of T2DM?

Methods

- Study design
 - Multi-center, prospective cohort study of the women with a previous history of GDM
- Study subjects
 - Women with GDM or single positive result of 100g OGTT
 - Recruit from Aug 1995 to May 1997 at four centers in Korea
- Postpartum evaluations
 - Initial: postpartum 6~8 weeks
 - 1 year and annually up to 8 years (median 4.0 year)

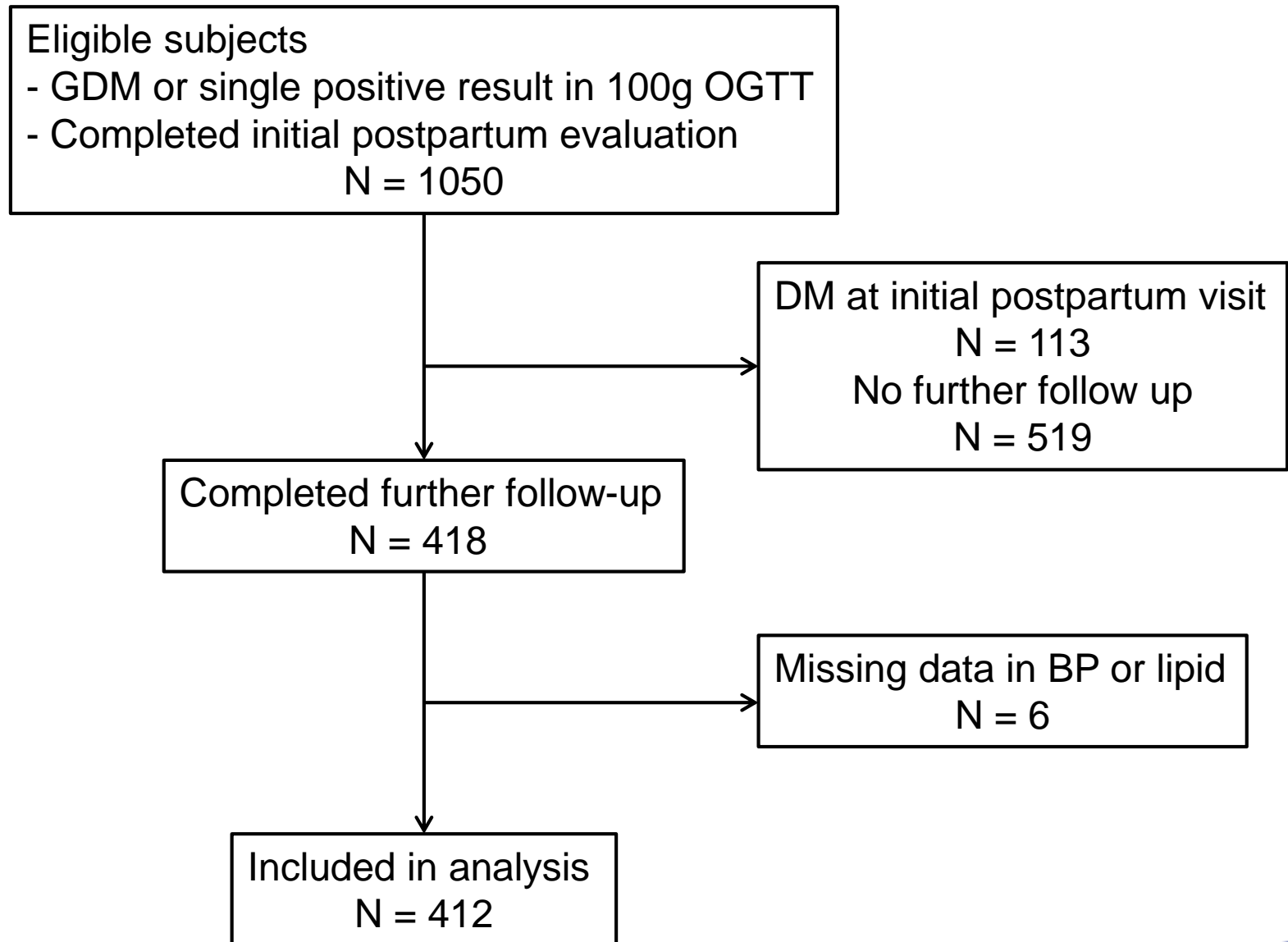
Methods

- Diagnosis of GDM: two or more positive results in 100g OGTT
 - The Third International Workshop-Conference on Gestational Diabetes Mellitus
 - 1) Fasting plasma glucose ≥ 105 mg/dl
 - 2) 1 hour glucose ≥ 190 mg/dl
 - 3) 2 hour glucose ≥ 165 mg/dl
 - 4) 3 hour glucose ≥ 145 mg/dl

- Diagnosis of T2DM: 75g OGTT at each postpartum evaluation
 - Fasting plasma glucose ≥ 126 mg/dl or 2 hour plasma glucose ≥ 200 mg/dl

Methods

- Diagnosis of MetS: at first postpartum evaluation (postpartum 6 weeks)
 - The revised National Cholesterol Education Program (NCEP) definition using the Asian criterion of waist circumference
 - 1) Waist circumference ≥ 80 cm
 - 2) Systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg
 - 3) Triglyceride level ≥ 150 mg/dl
 - 4) HDL cholesterol level < 50 mg/dl
 - 5) Fasting plasma glucose ≥ 100 mg/dl



Baseline characteristics of subjects according to the presence of MetS

	MetS (-) n=346	MetS (+) n=66	P value
Age at delivery (year)	30.8 ±4.2	30.4 ±4.0	0.445
Height (cm)	158.3 ±4.7	157.7 ±4.4	0.361
Prepregnancy weight (kg)	54.5 ±7.0	63.1 ±9.9	<0.001
Prepregnancy BMI (kg/m ²)	21.7 ±2.7	25.3 ±3.7	<0.001
Family history of diabetes	170 (49.1%)	26 (39.4%)	0.147
Physically active at initial postpartum	129 (37.3%)	28 (42.4%)	0.431
Physically active at last postpartum	187 (45.0%)	34 (51.5%)	0.706
Insulin treatment during pregnancy	61 (17.6%)	27 (40.9%)	<0.001
Multiparity	254 (73.4%)	50 (75.8%)	0.691
Fasting glucose during pregnancy (mg/dl)	88.7 ±12.8	97.6 ±20.8	0.001
Breast feeding	169 (48.8%)	29 (43.9%)	0.465

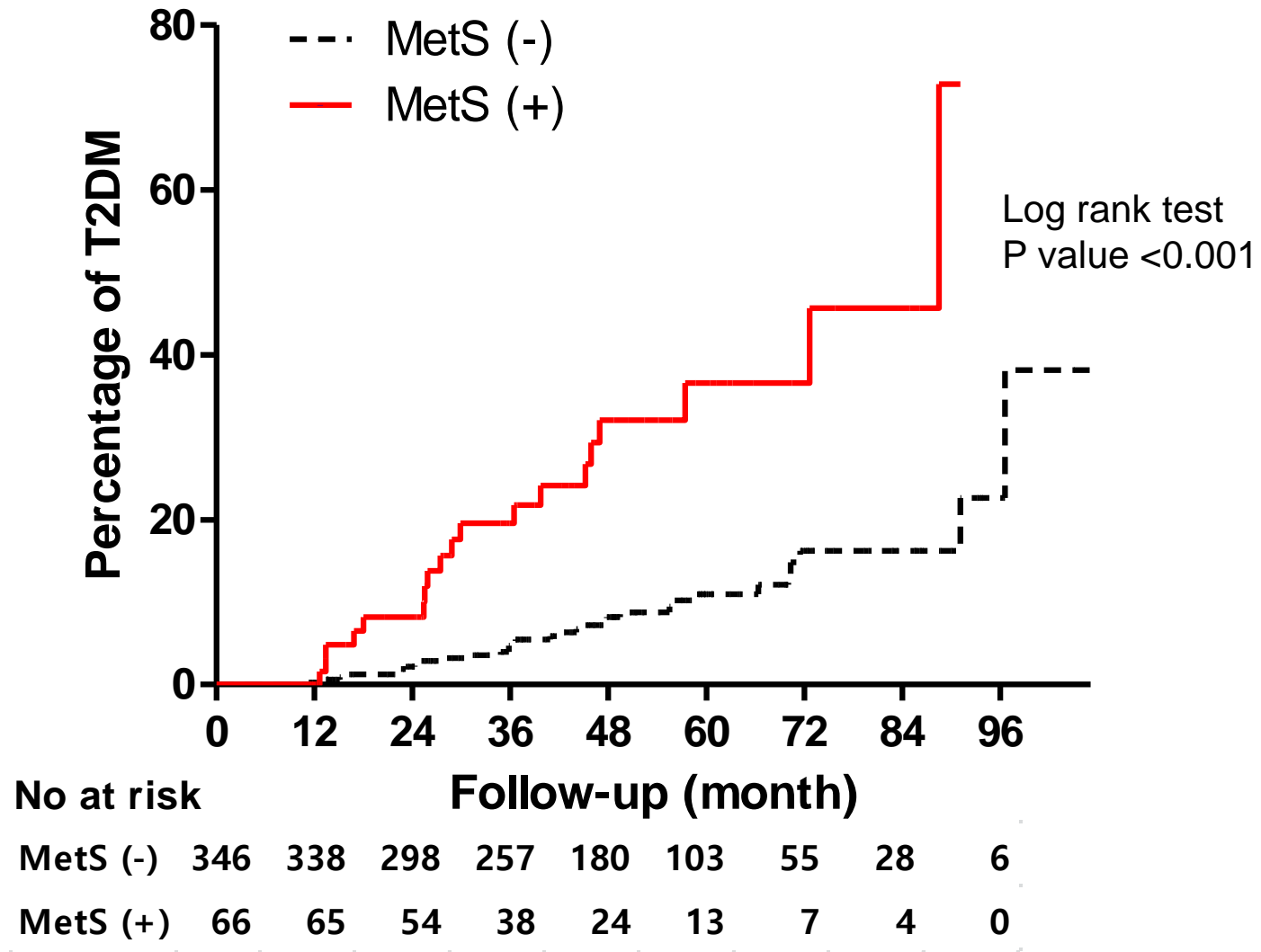
Mean ±SD or number (%)

Initial postpartum evaluation of subjects

	MetS (-) n=346	MetS (+) n=66	P value
Waist circumference (cm)	73.7 ±6.9	82.7 ±6.5	<0.001
Postpartum BMI (kg/m ²)	22.7 ±2.7	26.4 ±3.4	<0.001
Systolic blood pressure (mmHg)	109.4 ±11.0	118.8 ±13.0	<0.001
Diastolic blood pressure (mmHg)	68.4 ±8.4	74.8 ±9.6	<0.001
Total cholesterol (mg/dl)	196.3 ±35.1	206.3 ±33.6	0.034
Triglyceride (mg/dl)	107.6 ±59.3	194.8 ±88.9	<0.001
HDL cholesterol (mg/dl)	55.1 ±14.4	44.9 ±10.3	<0.001
LDL cholesterol (mg/dl)	119.7 ±30.3	122.4 ±30.7	0.505
Fasting plasma glucose (mg/dl)	90.7 ±9.0	102.5 ±9.8	<0.001
2hr plasma glucose (mg/dl)	123.1 ±27.7	139.1 ±29.3	<0.001
Fasting insulin (μIU/ml)	9.1 ±4.0	11.9 ±6.0	0.001
Metabolic parameters			
Matsuda index	4.47 (-3.63-5.84)	3.06 (2.16-4.07)	<0.001
Insulinogenic index	0.40 (0.24-0.64)	0.49 (0.26-0.77)	0.102
Disposition index	1.76 (1.16-2.89)	1.60 (0.80-2.34)	0.018

Mean ±SD or Median (IQR)

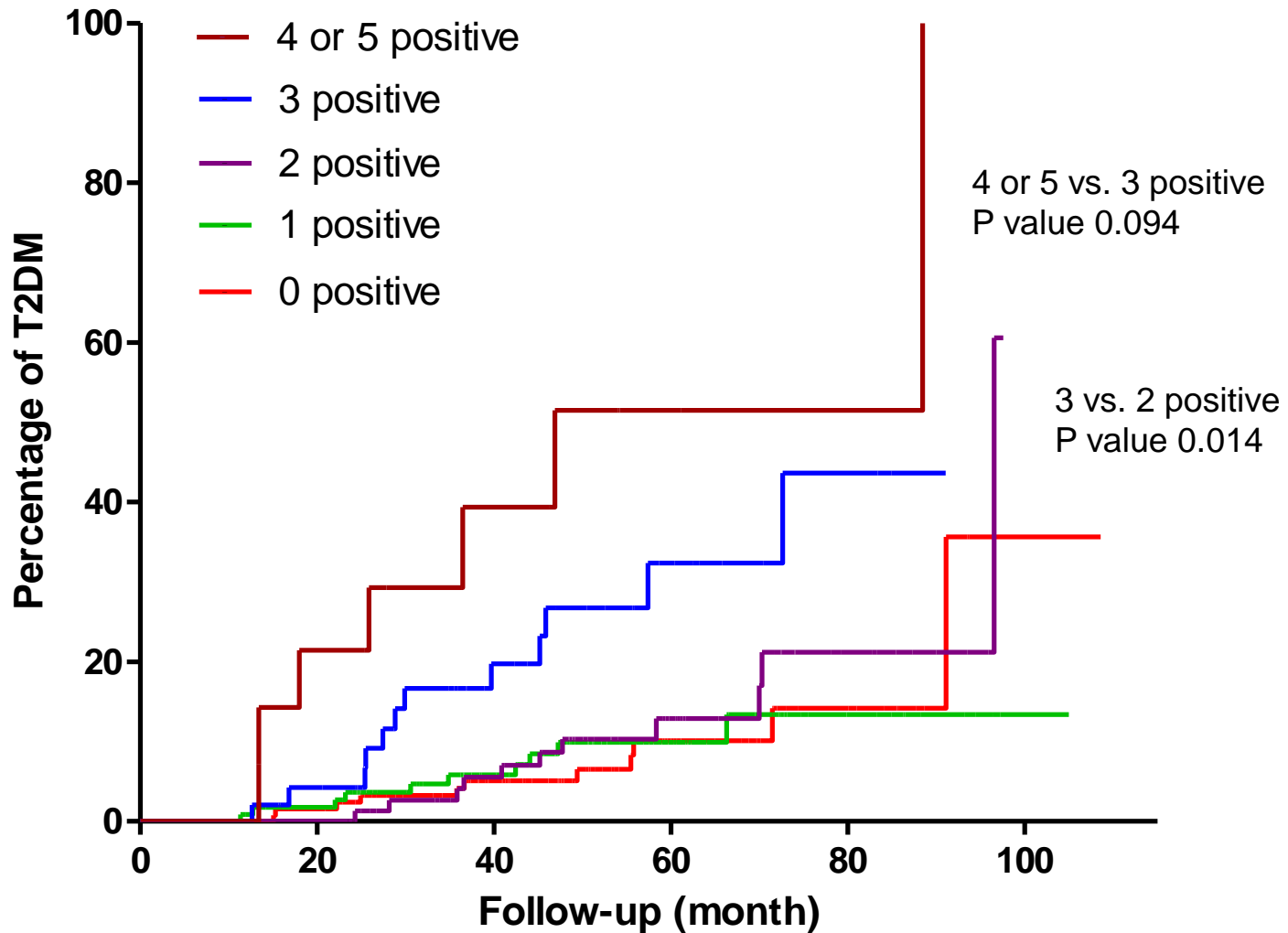
Cumulative incidence of T2DM



Multivariate analysis of risk factors for the development of T2DM

	Model 1		Model 2	
	HR (95% CI)	P value	HR (95% CI)	P value
MetS	4.35 (2.15-8.78)	<0.001	2.97 (1.39-6.33)	0.005
Age at delivery	0.98 (0.91-1.05)	0.601	0.99 (0.92-1.06)	0.686
Postpartum BMI	1.00 (0.91-1.10)	0.987	1.01 (0.92-1.11)	0.839
Family history of DM	1.41 (0.80-2.48)	0.236	1.45 (0.81-2.60)	0.215
Physically active at last postpartum	0.47 (0.26-0.84)	0.011	0.36 (0.19-0.68)	0.001
Breast feeding			0.50 (0.27-0.94)	0.031
Multiparity			0.87 (0.44-1.71)	0.684
Fasting plasma glucose during pregnancy			1.03 (1.02-1.04)	<0.001

Cumulative incidence of T2DM by positive numbers of MetS components



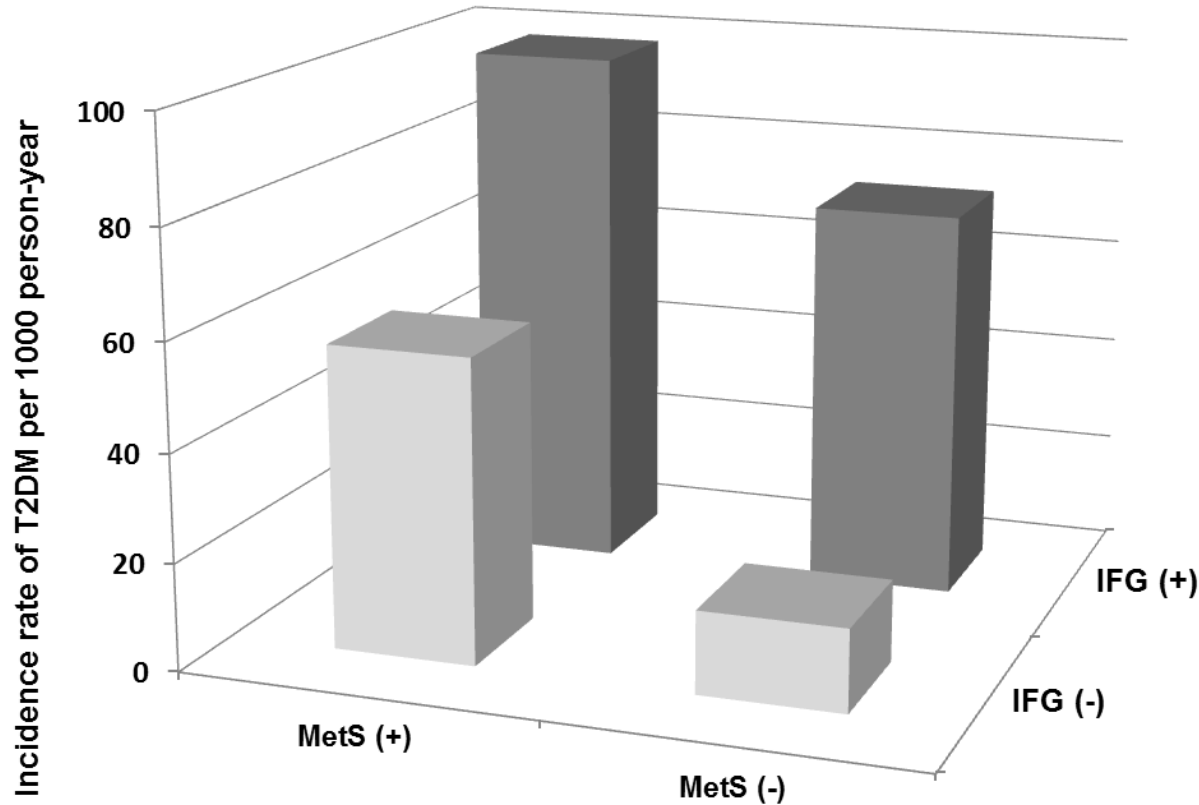
Hazard ratios of positive MetS components number and each component of MetS

	Model 1	Model 2
	HR (95% CI)	HR (95% CI)
Number of positive MetS criteria	1.68 (1.29-2.19)	1.40 (1.06-1.85)
Waist circumference ≥ 80 cm	0.58 (0.24-1.37)	0.58 (0.24-1.42)
Blood pressure $\geq 130/85$ mmHg	3.01 (1.48-6.10)	1.76 (0.78-3.96)
Triglyceride ≥ 150 mg/dL	3.19 (1.76-5.79)	3.35 (1.83-6.14)
HDL cholesterol < 50 mg/dL	0.89 (0.51-1.56)	0.67 (0.36-1.22)
FPG ≥ 100 mg/dL	4.61 (2.63-8.07)	2.86 (1.52-5.36)

Model 1: adjusted for age, BMI, family history of DM, physical activity

Model 2: model 1 + breast feeding, multiparity, fasting glucose during pregnancy

Risk for the development of T2DM according to the presence of MetS and IFG



	Adjusted HR (95% CI)	P value
No IFG and MetS	1.00 (ref)	
IFG only	3.70 (1.21-11.34)	0.022
MetS only	3.04 (1.42-6.51)	0.004
Both IFG and MetS	4.22 (1.78-9.97)	0.001

Conclusion

- MetS is an independent risk factor for the development of T2DM in women with a previous history of GDM
- The risk of T2DM was gradually increased by the number of positive MetS components.
 - Triglyceride and FPG had the strongest association
- IFG and MetS increased the risk of T2DM individually and in combination

- Stratified risk management to prevent the development of T2DM in women with a history of GDM is required

Can the physical activity prevent the development of T2DM in women with GDM?

- Regular exercise
 - The type of exercise (jogging, swimming, golf, tennis etc.)
 - Total hours per week = Frequency per week x Duration of exercise per each time
- Regular exercise divided into 3 groups
 - Least: no regular exercise
 - Low: lower half of total hours per week
 - High: upper half of total hours per week

	N	%
Least	235	56.2
Low	73	17.5
High	110	26.3

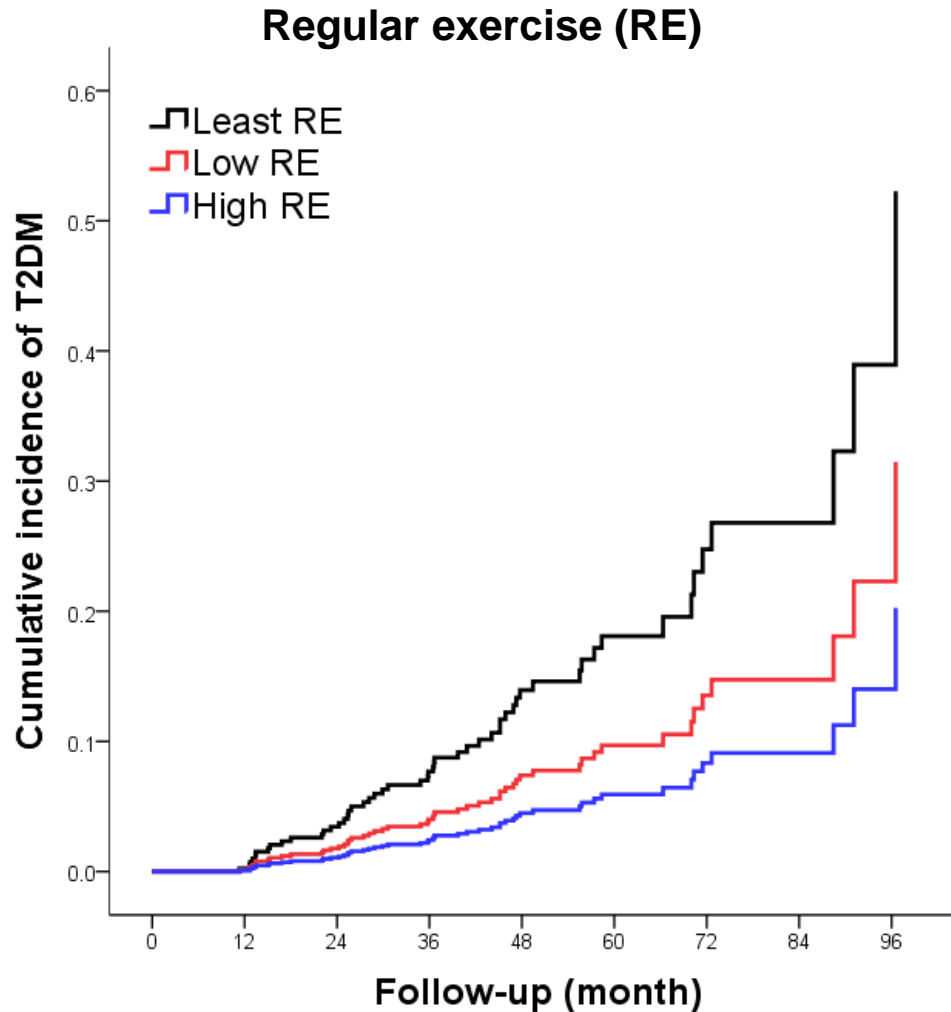
Can the physical activity prevent the development of T2DM in women with GDM?

	Model 1		Model 2	
	Hazard ratio	P value	Hazard ratio	P value
Least exercise	1.00 (ref)		1.00 (ref)	
Low exercise	0.47 (0.21-1.06)	0.070	0.54 (0.24-1.25)	0.151
High exercise	0.33 (0.16-0.70)	0.004	0.32 (0.15-0.69)	0.004

Model 1: adjusted for age, postpartum BMI

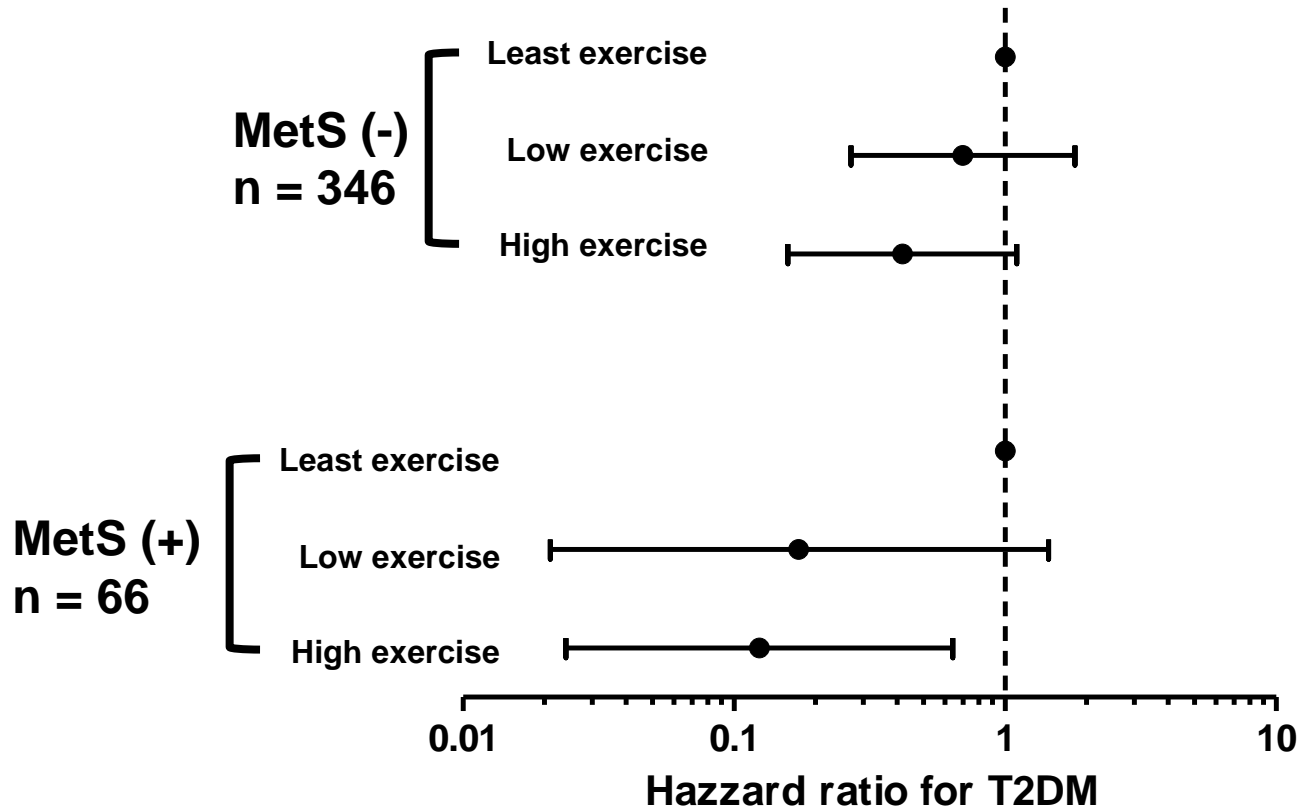
Model 2: Model 1 + family history of T2DM, multiparity, breastfeeding, fasting blood glucose during pregnancy

Cumulative incidence of T2DM




Cox proportional hazards models adjusted for age, postpartum BMI, family history of T2DM, breast feeding, multiparity, fasting glucose during pregnancy

Impact of physical activity on women with/without MetS



*Cox proportional hazards models adjusted for age, postpartum BMI, family history of T2DM, breast feeding, multiparity, fasting glucose during pregnancy

Conclusion

- High frequency of regular exercise independently reduced the risk of T2DM in women with previous history of GDM
 - In subgroup analysis, the impact of regular exercise was higher in women with MetS
 - The lifestyle management should be emphasized for women with a history of GDM and MetS at early postpartum period who have the highest risk for the development of T2DM.
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Thank you for your attention