DANISH CENTRE FOR STRATEGIC RESEARCH IN TYPE 2 DIABETES

Pathophysiologic phenotypes of patients clinically diagnosed as type 2 diabetes

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Conflict of interest:

Will receive research support from Novo Nordisk

WHO classification of diabetes mellitus

- Type 1 diabetes
- Type 2 diabetes
- Other specific types
  - Genetic defects
  - Disease of the exocrine pancreas
  - Drug-induced
- Gestational diabetes mellitus

Classification in clinical practice

- Non-obese and young ketosis prone patients are classified as type 1 diabetes
- Obese and elderly patients are classified as type 2 diabetes

Type 2 diabetes heterogeneity

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However patients with clinically diagnosed type 2 diabetes does not constitute a homogeneous entity

AIM

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Our aim has been to identify pathophysiological phenotypes hidden behind the clinical type 2 diabetes diagnose

Phenotypes we investigate

- Gad positives (LADA)
- Secondary diabetes (pancreatitis)
- Steroid associated diabetes
- Rare subtypes of diabetes
- Genuine Type 2 diabetes

Phenotype definitions

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- Gad positives defined as GAD > =20 IU/ml
- Secondary diabetes defined as a history of pancreatitis, pancreas resection or increased amylase >65 U/l
- Steroid induced diabetes defined by treatment with oral corticosteroids in supraphysiologic concentrations before and during onset of diabetes
- Rare subtypes: Register based

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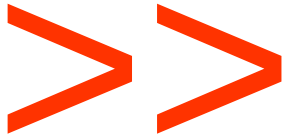

The DD2 cohort

- Patients clinically diagnosed with type 2 diabetes
- From general practitioners and outpatient clinics
- Newly diagnosed, unselected and consecutive patients
- 1048 patients
- 454 females (43.3%)
- 594 males (56.7%)
- Median age 61 years (53- 67)

Prevalence of the phenotypes

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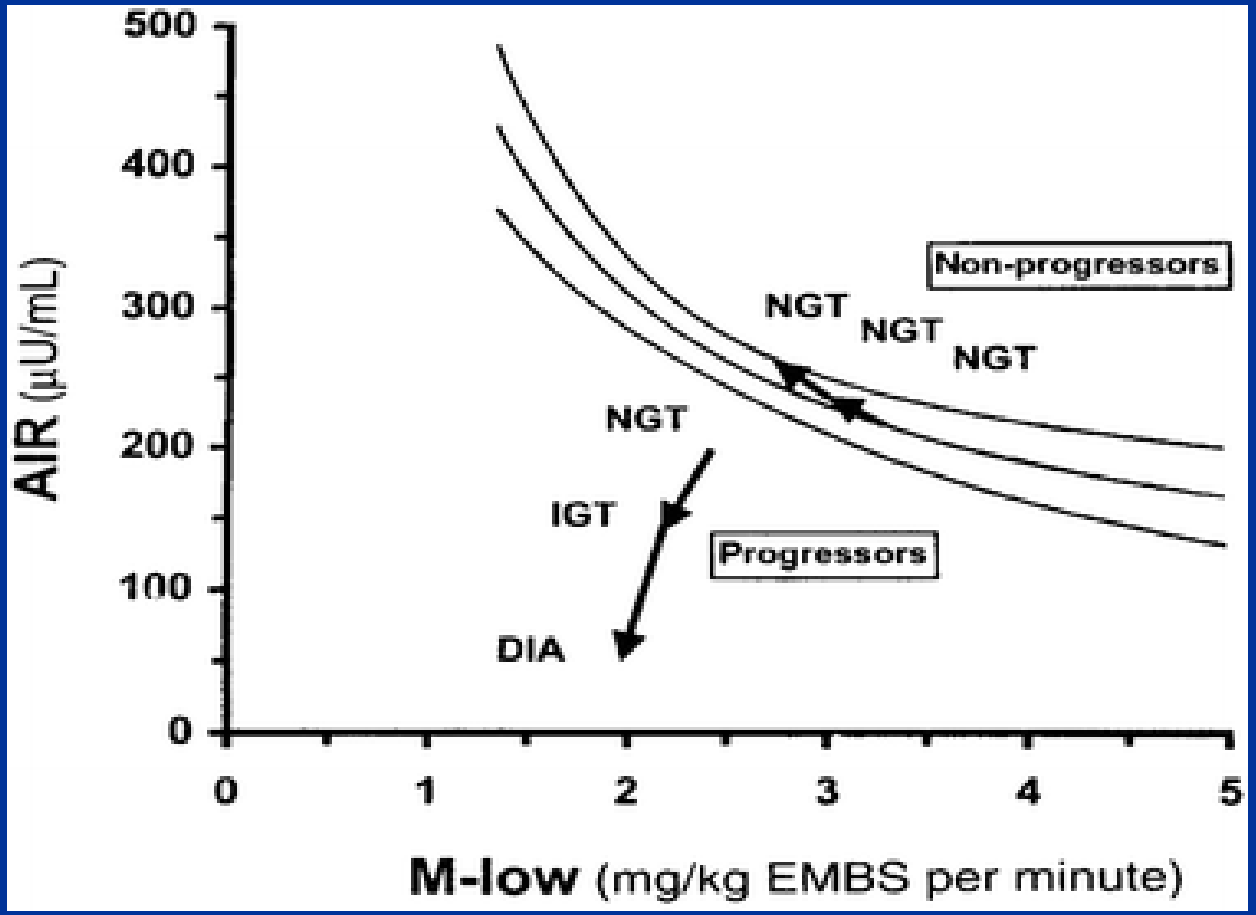
Rare subtypes of diabetes	6 (0.6%)
Gad positives	31 (3.0%)
Secondary diabetes (pancreatitis)	41 (3.9%)
Steroid associated diabetes	61 (5.8%)
Genuine T2D	918 (86,7%)

Can genuine T2D be subdivided in pathophysiological subphenotypes?

Pathophysiology of T2D

Hyperglycemia develops when beta cells are unable to compensate for the degree of insulin resistance

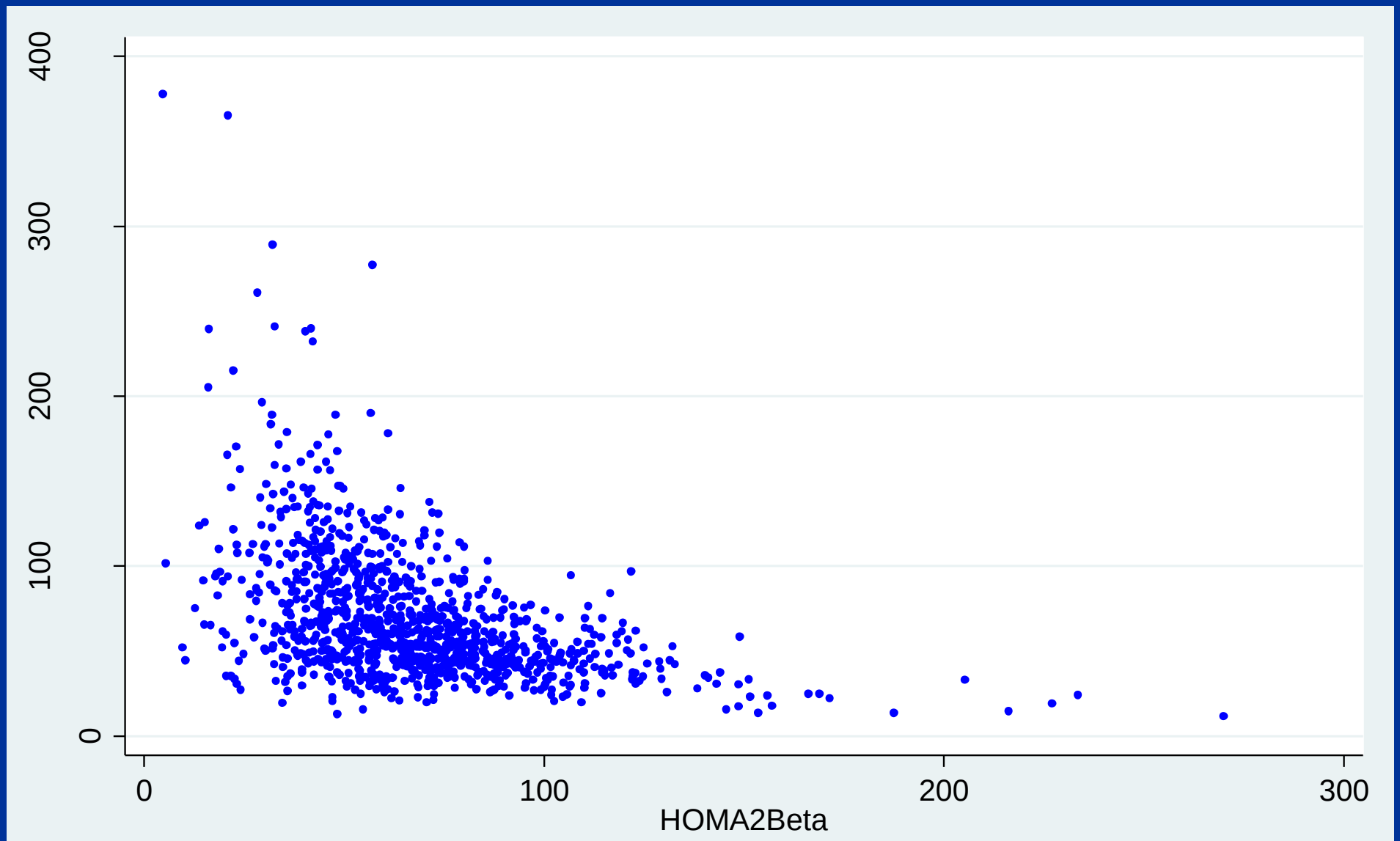
Relationship between insulin sensitivity and beta cell function



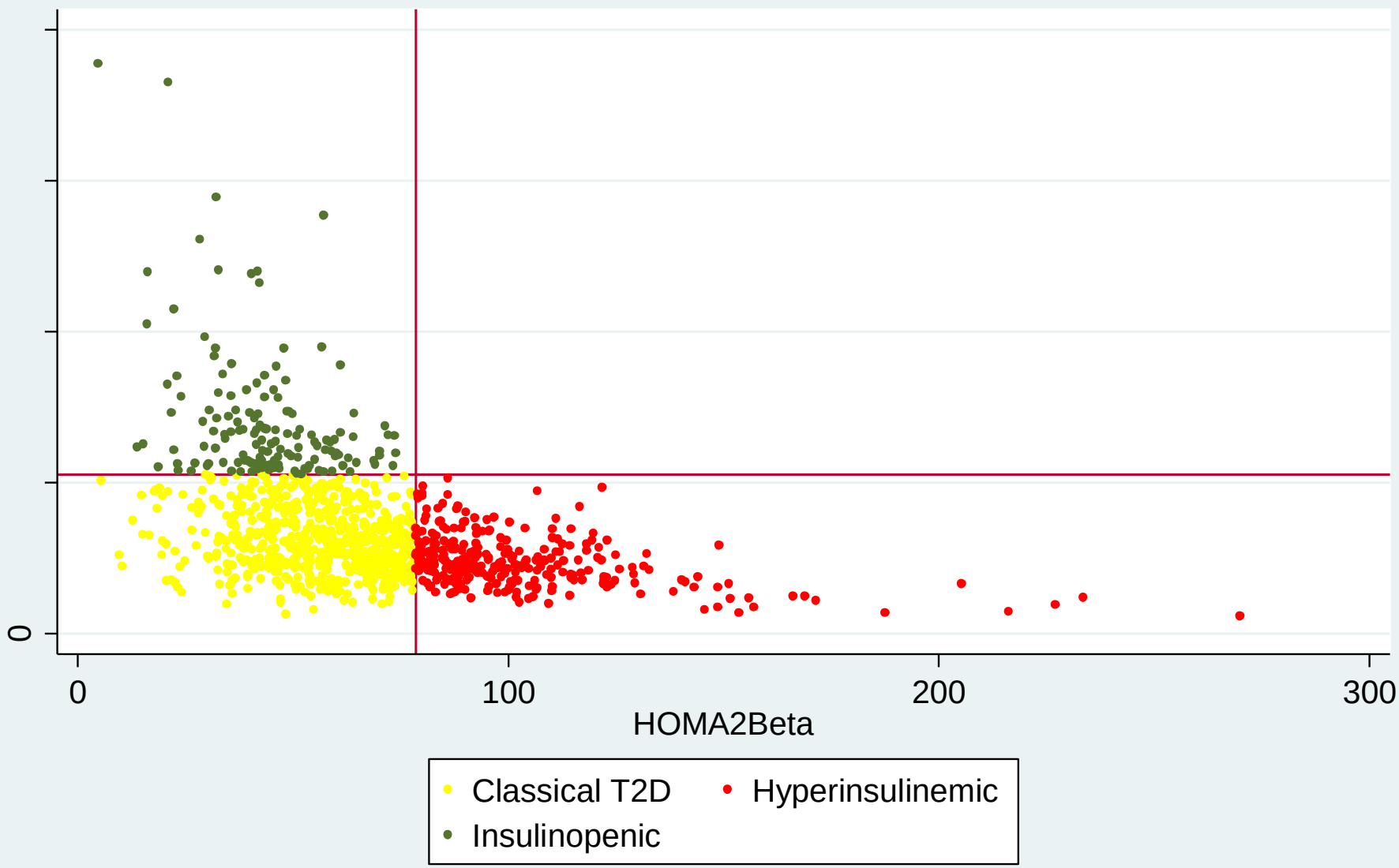
Phenotypes by HOMA modeling

- “Type 2 diabetes” patients not belonging to specific diabetes subtypes are characterized by the HOMA2 model (fasting C-peptide and FPG)
- Insulin sensitivity are defined by HOMA2-S
- Beta cell function is defined by HOMA2beta
- The median of the background population are used to define high and low IS and high and low beta cell function

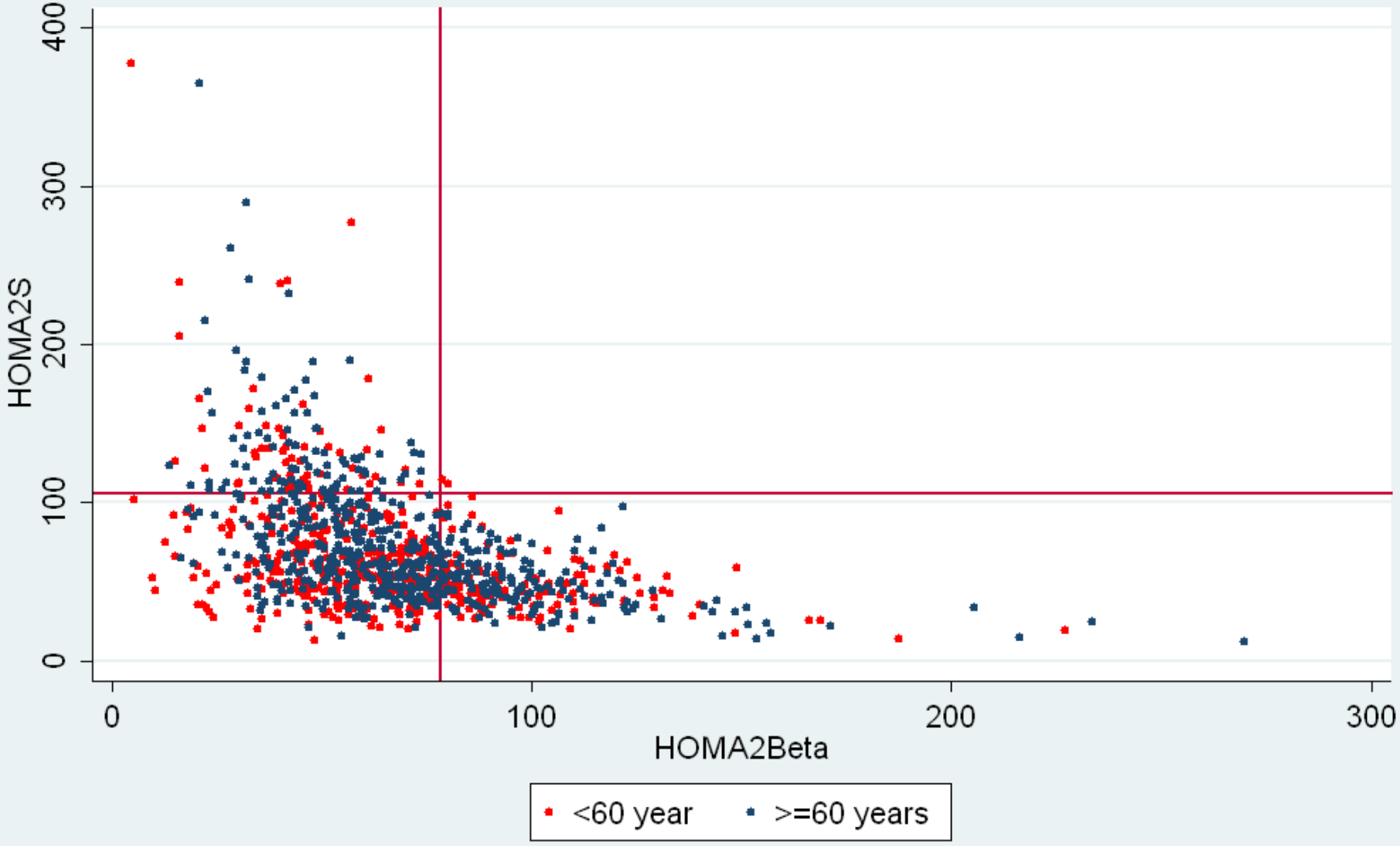
HOMA modeling



HOMA modeling



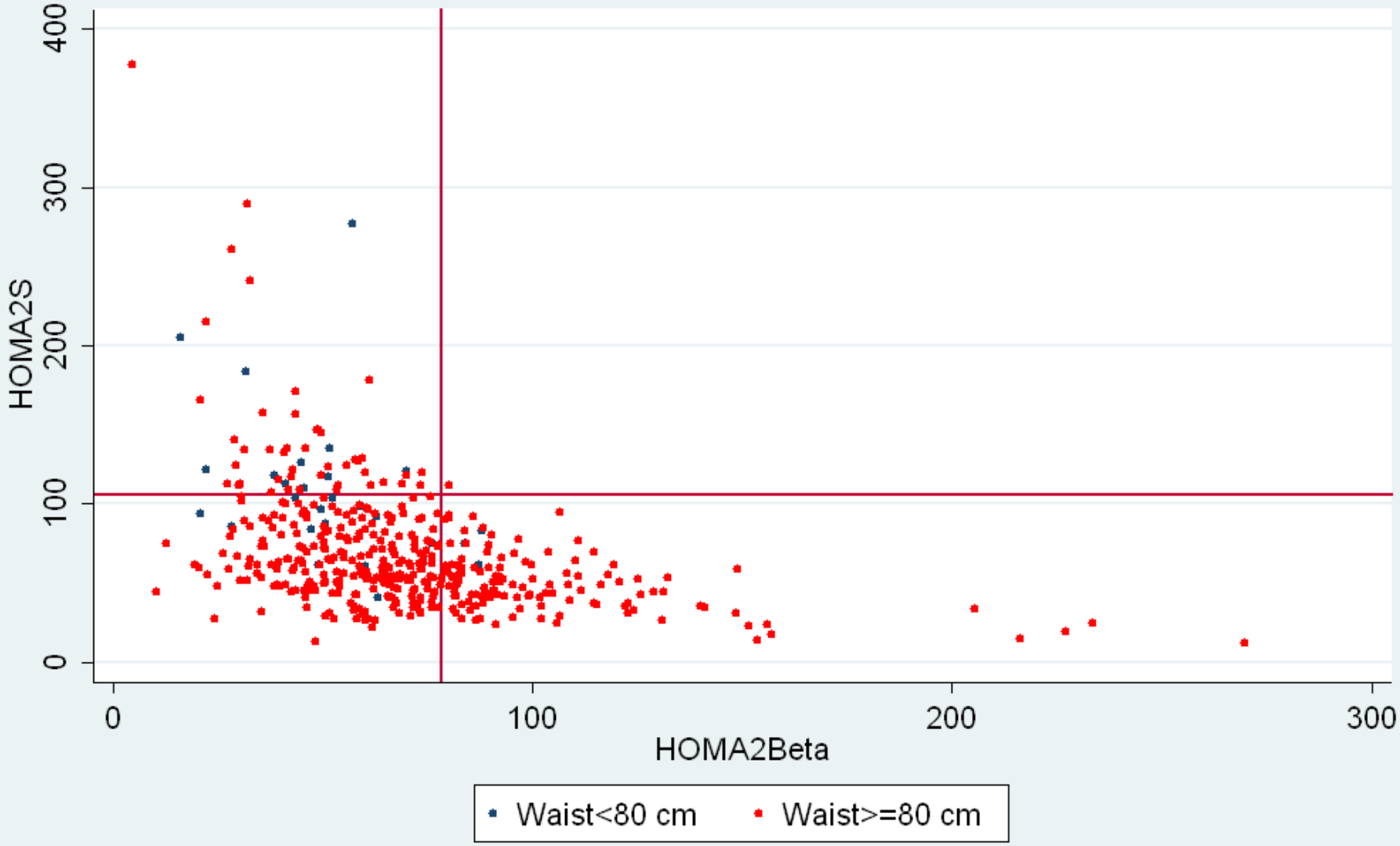
HOMA and age


HOMA2S
400
300
200
100
0
0
100
200
300
HOMA2Beta
<60 year
>=60 years

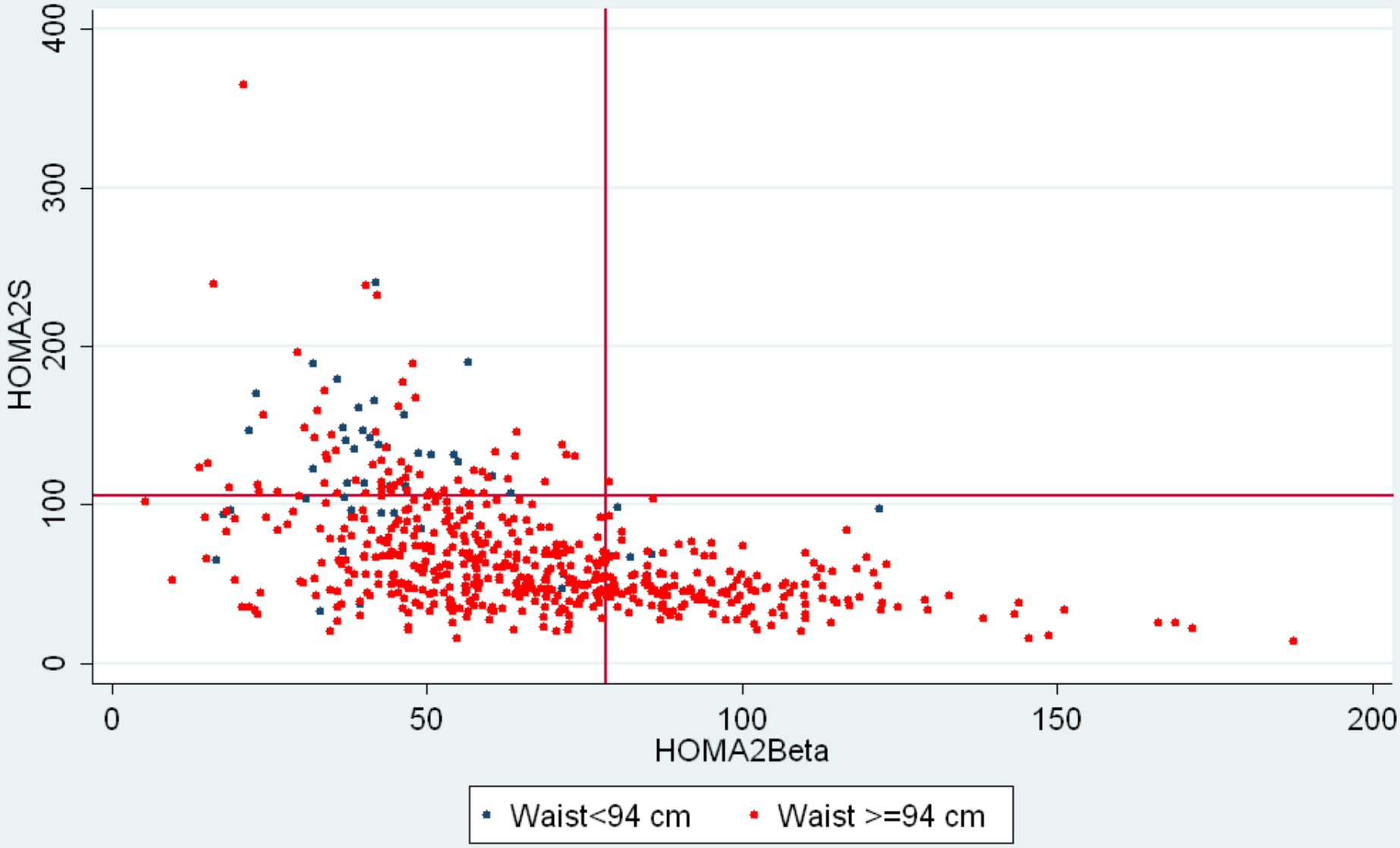
Age and gender

	Classical T2D	Hyperinsulinemic	Insulinopenic
Women	304 (56.9%)	136 (54.2%)	81 (65.9%)
Men	230 (43.1%)	115 (45.8%)	42 (34.1%)
Age (median, quartiles)	60 (53-66)	61 (54-69)	63 (55-67)

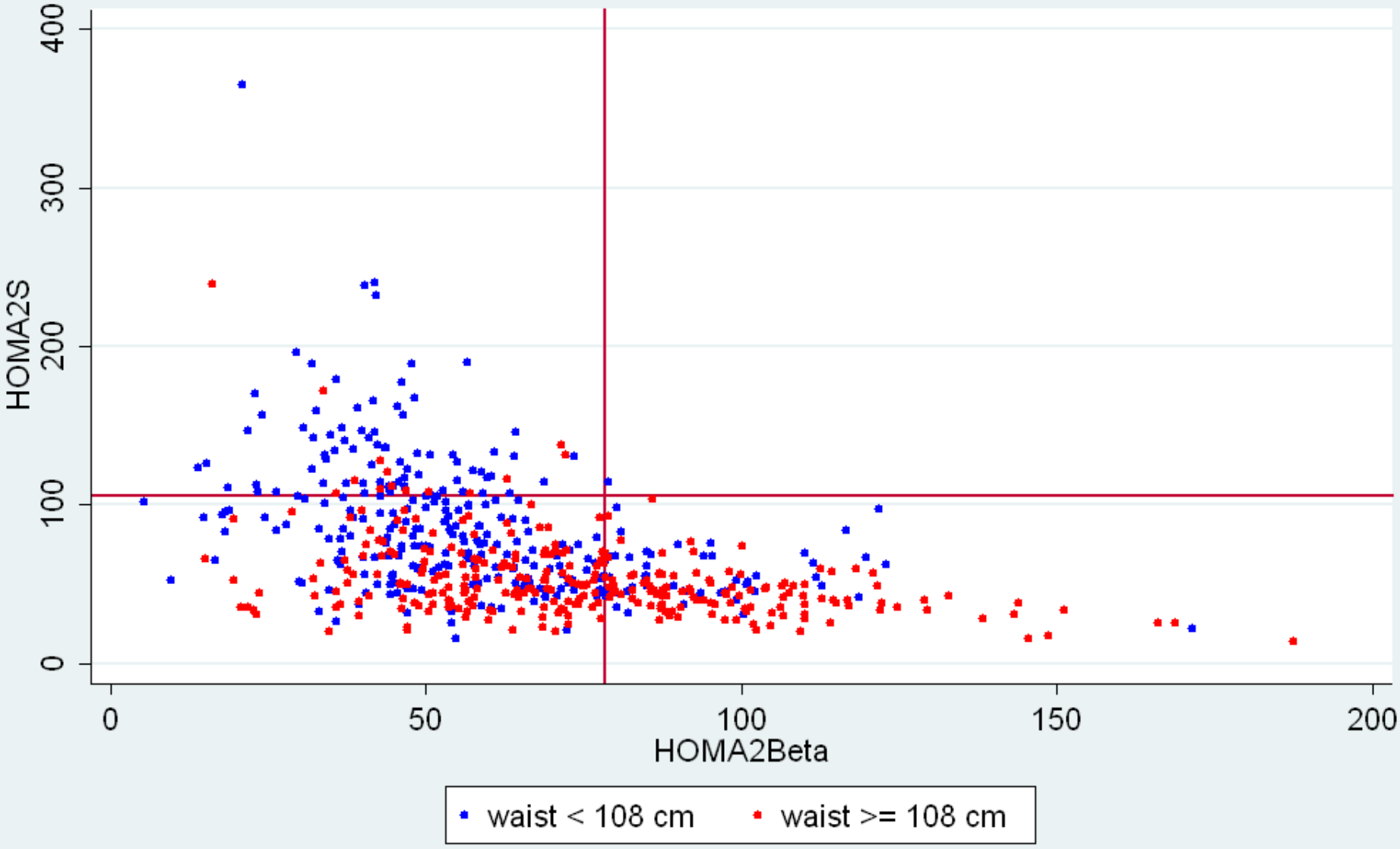
HOMA and waist circumference Women



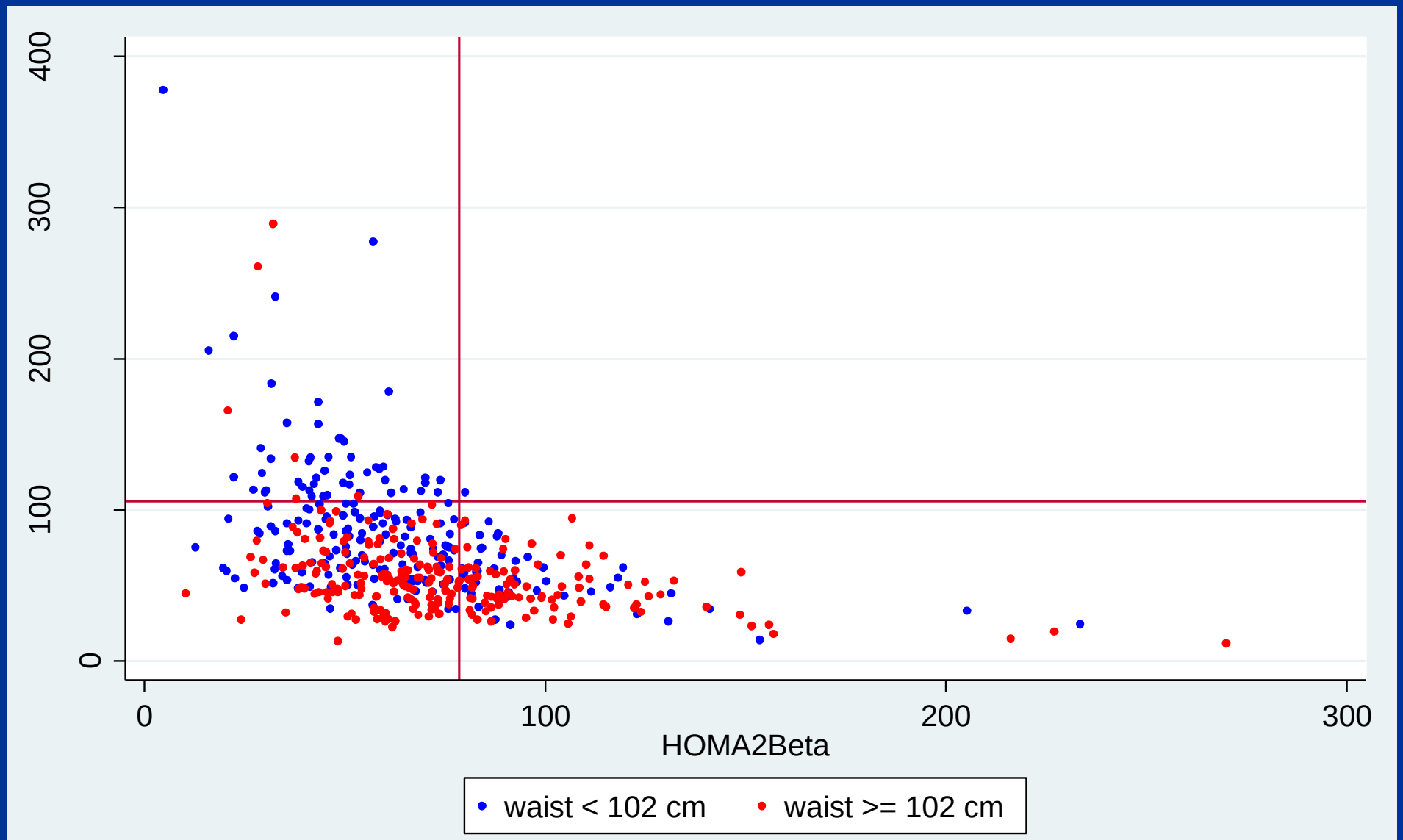
HOMA and waist circumference Men



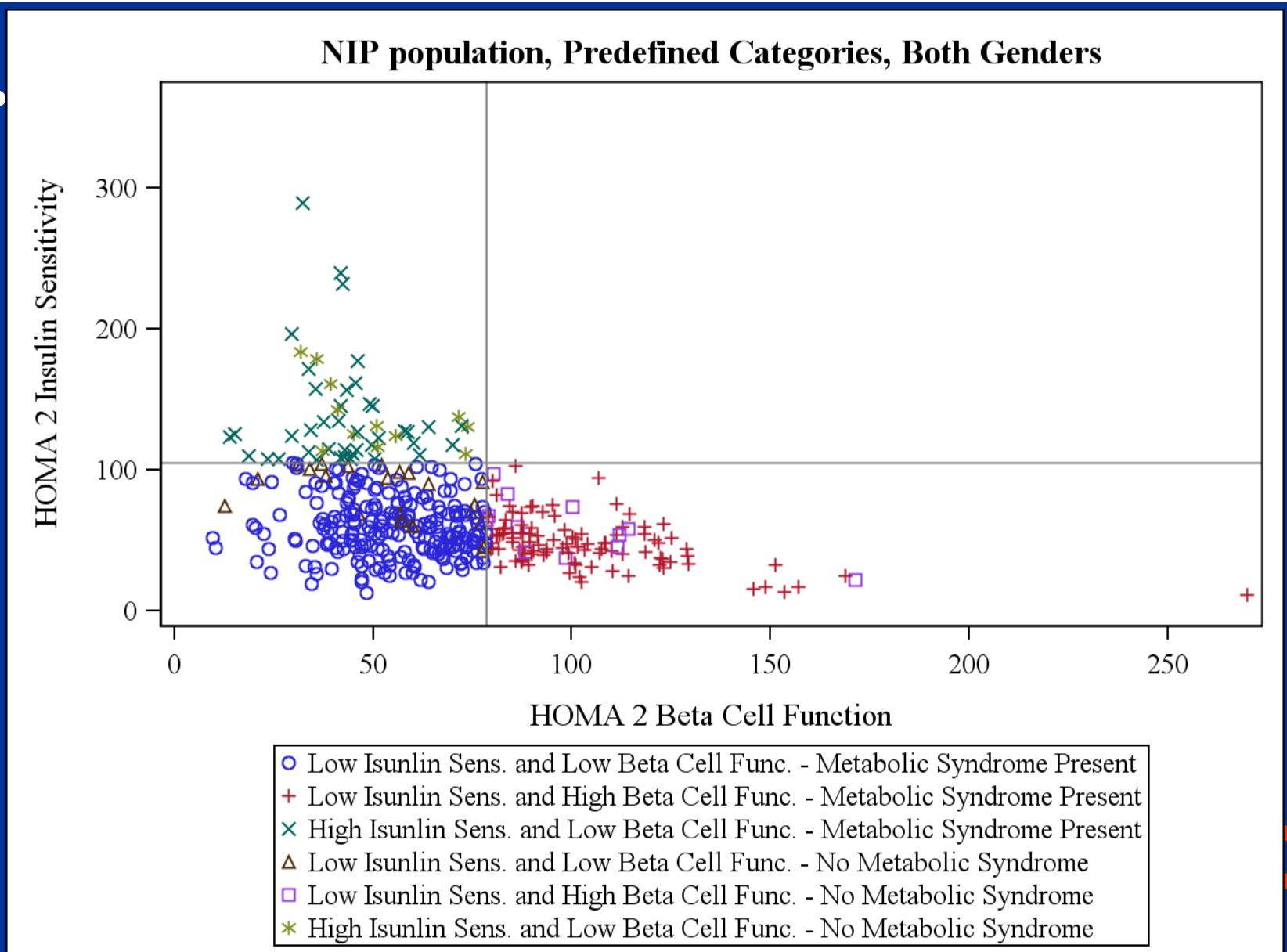
HOMA and waist circumference Men



HOMA and waist circumference Women



HOMA and metabolic syndrome



Anthropomorphics

	Classical T2D	Hyperinsulinemic	Insulinopenic
BMI (median, quartiles)	30.5 (27.4-34.6)	33.5 (29.3-37.7)	26.9 (23.8-30.9)
Waist circ. (cm, median, quartiles)	106 (98-116)	113 (101-122)	95 (88-103)
Weight gain (kg, median, quartiles)	28.0 (18.0 -39.0)	34.0 (24.0 – 44.0)	20.0 (14.0 – 30.0)

Comorbidity

	Classical T2D	Hyperinsulinemic	Insulinopenic
Cardiovascular disease	98 (18.4%)	63 (25.1%)	16 (13.0%)
Myocardial infarction	27 (5.1%)	24 (9.6%)	5 (4.1%)
Cerebrovascular disease	35 (6.6%)	20 (8.0%)	2 (1.6%)
Heart failure	12 (2.2%)	14 (5.6%)	1 (0.8%)

Summary

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	Classical T2D	Hyperinsulinemic	Insulinopenic
HOMA2-Beta (%, median, q)	56.9 (45.4-67.1)	93.7 (85.1-109.9)	44.2 (36.7-53.7)
HOMA2-S (%, median, q)	60.5 (46.0 - 78.5)	45.4 (37.3–55.7)	126.8 (112.6-145.9)
BMI (kg/m2, median, q)	30.5 (27.4-34.6)	33.5 (29.3-37.7)	26.9 (23.8-30.9)
Waist circ (cm, median, q)	106 (98-116)	113 (101-122)	95 (88-103)
Weight gain	28.0 (18.0 -39.0)	34.0 (24.0 – 44.0)	20.0 (14.0 – 30.0)
MI	27 (5.1%)	24 (9.6%)	5 (4.1%)

What is Insulinopenic T2D?

- Patients with low beta cell function, who do not suffer from T1D or LADA.
- They are normal weight to slightly overweight, insulin sensitive and do not have increased risk of CVD.

What is Hyperinsulinemic T2D?

- Patients with increased beta cell function and severe insulin resistance.
- They are obese and have high CV risk.

Conclusion 1

- T2D is a heterogeneous disease
- Several specific causes of hyperglycemia is hidden behind the clinical diagnosis T2D e.g. secondary diabetes, Prednisolon induced diabetes and LADA.

Conclusion 2

Furthermore T2D subjects can be divided in three pathophyciological phenotypes based

1. Classical T2D: Insulin resistance and relativily reduced beta cell function.
2. Insulinopenic T2D: Normal to improved insulin sensitivity, but absolutely beta cell insufficiency.
3. Hyperinsulinemic T2D: Severe insulin resistance and increased beta cell function.

Conclusion 3

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We recommend to measure both GAD antibodies and fasting C-peptide in newly diagnosed diabetics in order to do a proper classification of T2D phenotypes.

Coworkers

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