Associations between metabolic signature of gestational diabetes mellitus and adverse birth outcomes in China: a prospective birth cohort study

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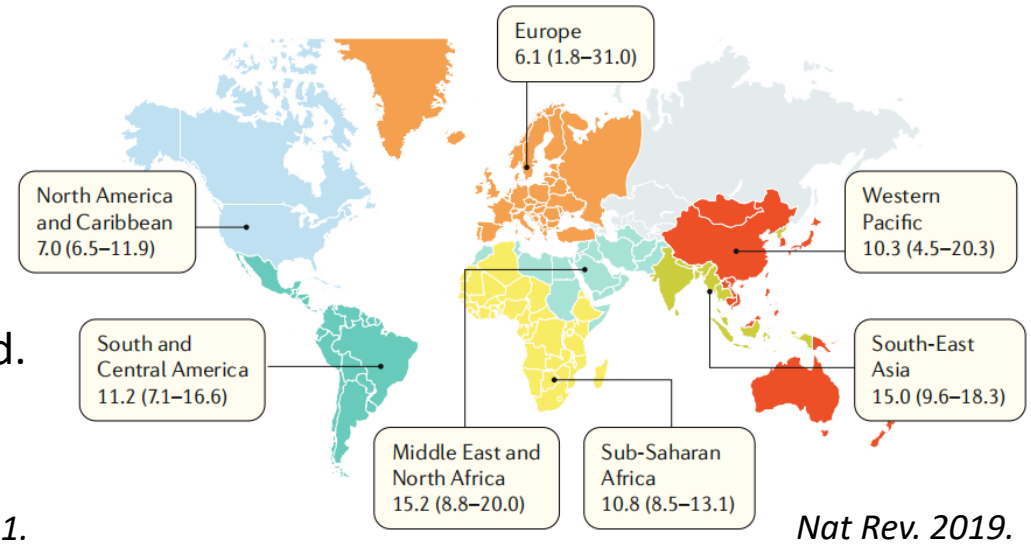
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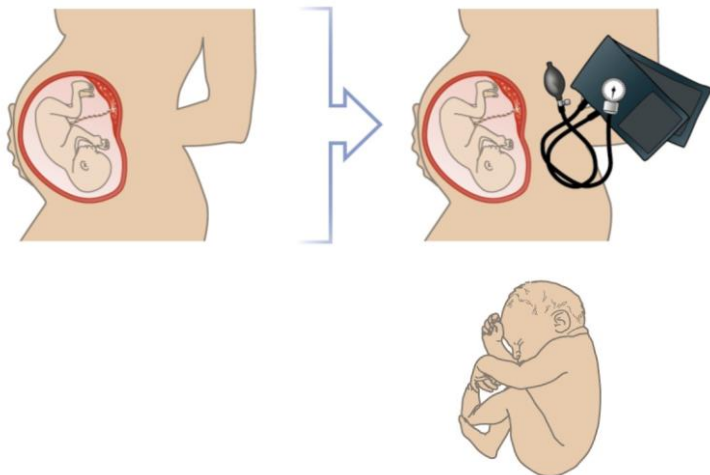
Introduction

Gestational Diabetes Mellitus, GDM

- Abnormal glucose with onset or first recognition in pregnancy, characterized as a metabolic disorder.

- Global prevalence is around **16.7%**, showing an ascending trend.

- Significantly increases the risk of adverse maternal and child health outcomes.

IDF Atlas 10th edition. 2021.

Europe
6.1 (1.8–31.0)

North America
and Caribbean
7.0 (6.5–11.9)

Western
Pacific
10.3 (4.5–20.3)

South and
Central America
11.2 (7.1–16.6)

South-East
Asia
15.0 (9.6–18.3)

Middle East and
North Africa
15.2 (8.8–20.0)

Sub-Saharan
Africa
10.8 (8.5–13.1)

Nat Rev. 2019.

short-term adverse outcomes

- cesarean section
- preeclampsia
- stillbirth
- congenital malformation
- large for gestational age
- premature delivery

long-term adverse outcomes
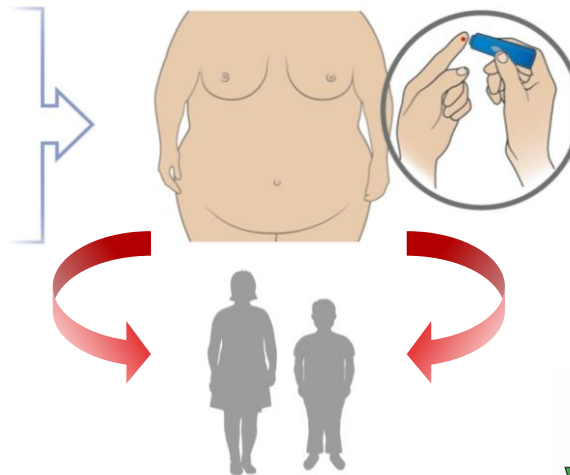
- type 2 diabetes
- obesity
- cardiovascular disaease

Endocr Rev. 2022 Sep 26;43(5):763-793.

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Introduction

Blood metabolomics

- **Blood circulation** reflects physiological and pathological states through numerous metabolites

- **Metabolomics**, downstream in regulatory networks, amplifies subtle gene and protein level variations.

- Recently, it has been employed to analyze **population heterogeneity** in health and disease.
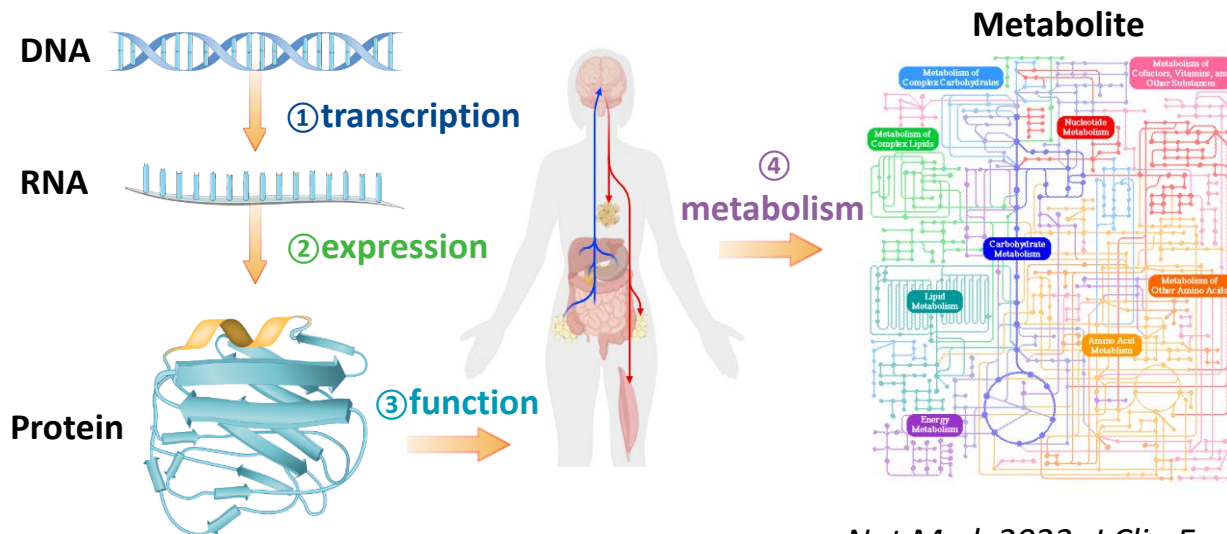
- GDM-specific metabolic profile not only illustrates the pathological characteristics of GDM but is also associated with **adverse birth outcomes**.
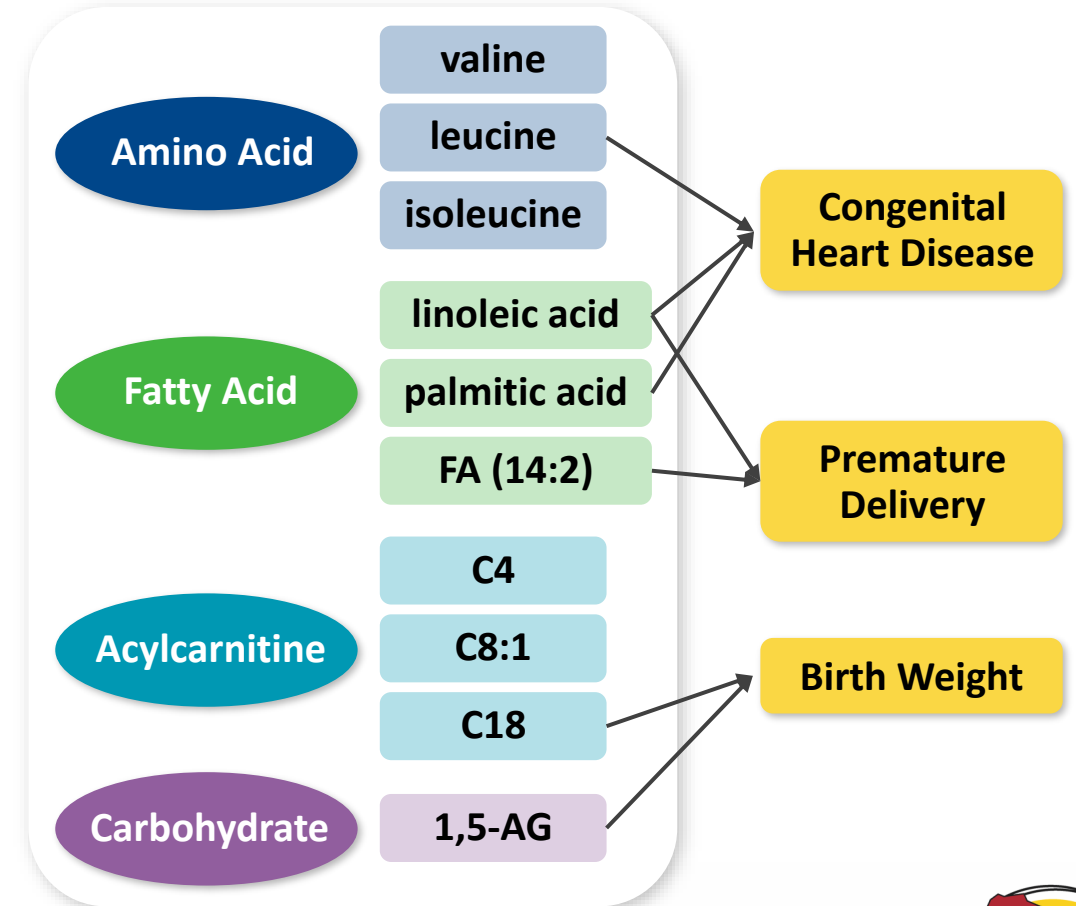
Nat Med, 2023; J Clin Endocrinol Metab, 2022; Diabetes Care, 2010. Cell Metab, 2019; PLoS Med, 2019; Cell Rep Med, 2023; Adv Sci, 2022.

Hypothesis
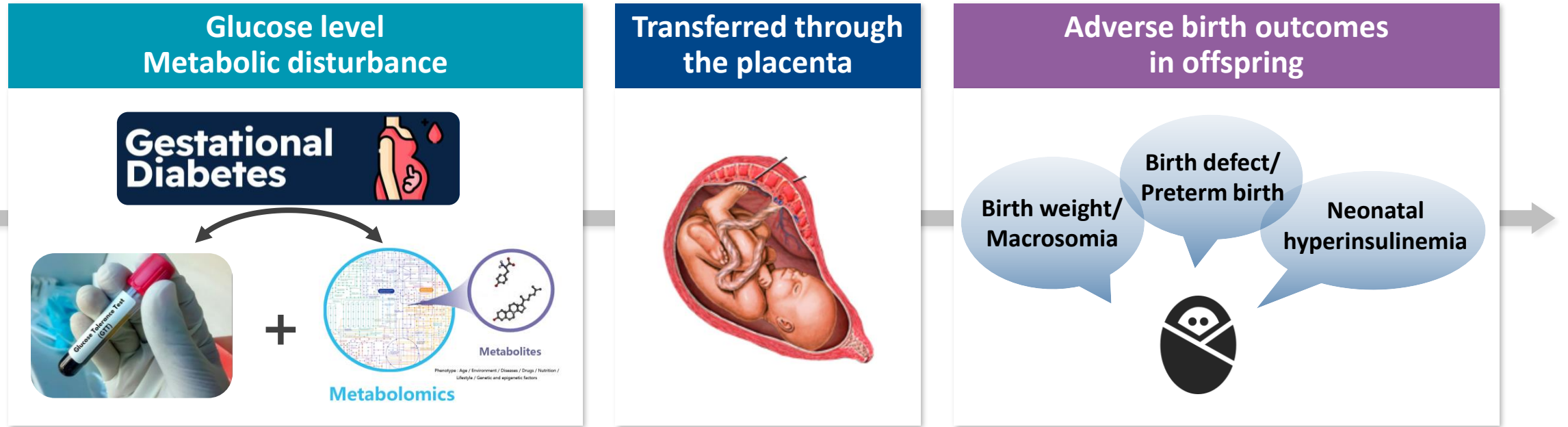
- **Our study aimed to identify the metabolic signatures of gestational diabetes (GDM), stratify pregnant women by glycemic and metabolic profiles, and further investigate the inter-group heterogeneity and their associations with adverse birth outcomes.**

Research methodology

A prospective cohort study conducted within Jiangsu Birth Cohort, established by Nanjing Medical University

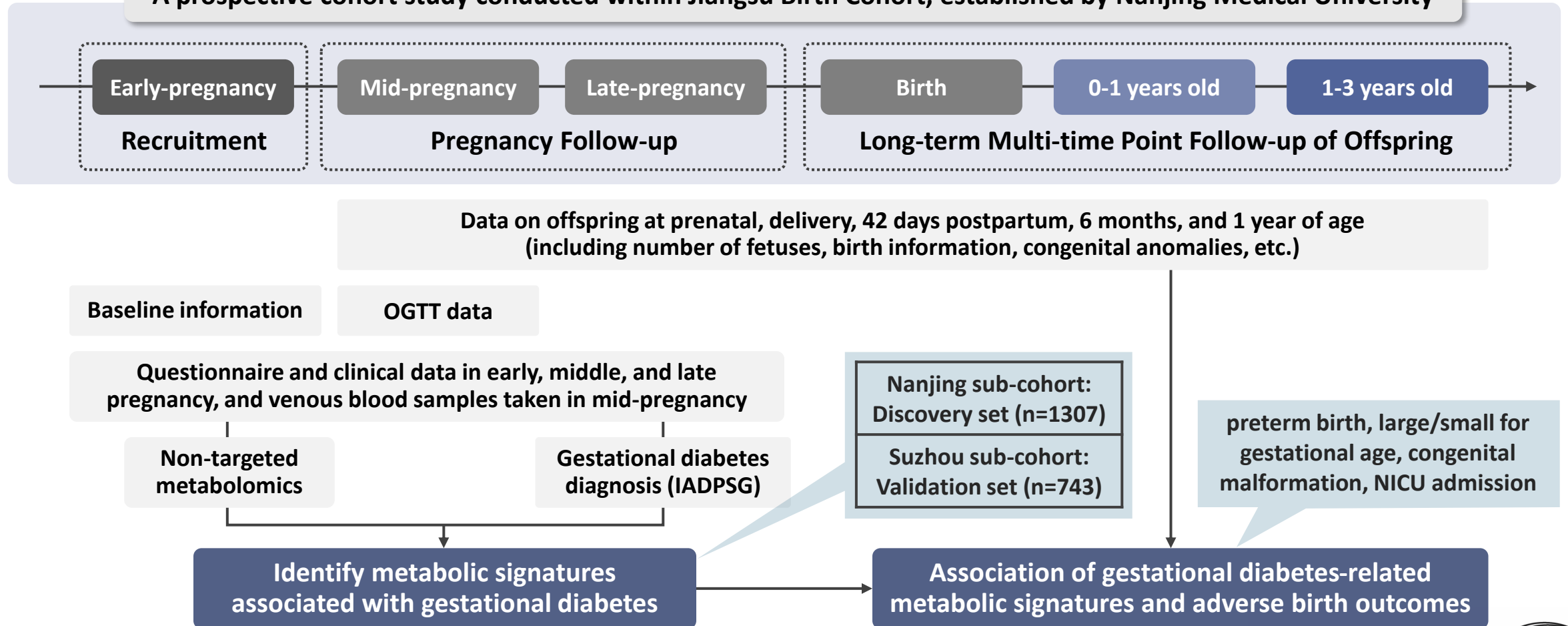| Early-pregnancy	Mid-pregnancy	Late-pregnancy	Birth	0-1 years old	1-3 years old

Recruitment | **Pregnancy Follow-up** | **Long-term Multi-time Point Follow-up of Offspring**

Data on offspring at prenatal, delivery, 42 days postpartum, 6 months, and 1 year of age
(including number of fetuses, birth information, congenital anomalies, etc.)

Baseline information

OGTT data

Questionnaire and clinical data in early, middle, and late pregnancy, and venous blood samples taken in mid-pregnancy

Non-targeted metabolomics

Gestational diabetes diagnosis (IADPSG)

Nanjing sub-cohort:
Discovery set (n=1307)

Suzhou sub-cohort:
Validation set (n=743)

preterm birth, large/small for gestational age, congenital malformation, NICU admission

Identify metabolic signatures associated with gestational diabetes

Association of gestational diabetes-related metabolic signatures and adverse birth outcomes

All data manipulation and statistical analyses were performed using R software (version 4.1.0)

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Profound perturbation of metabolome in GDM
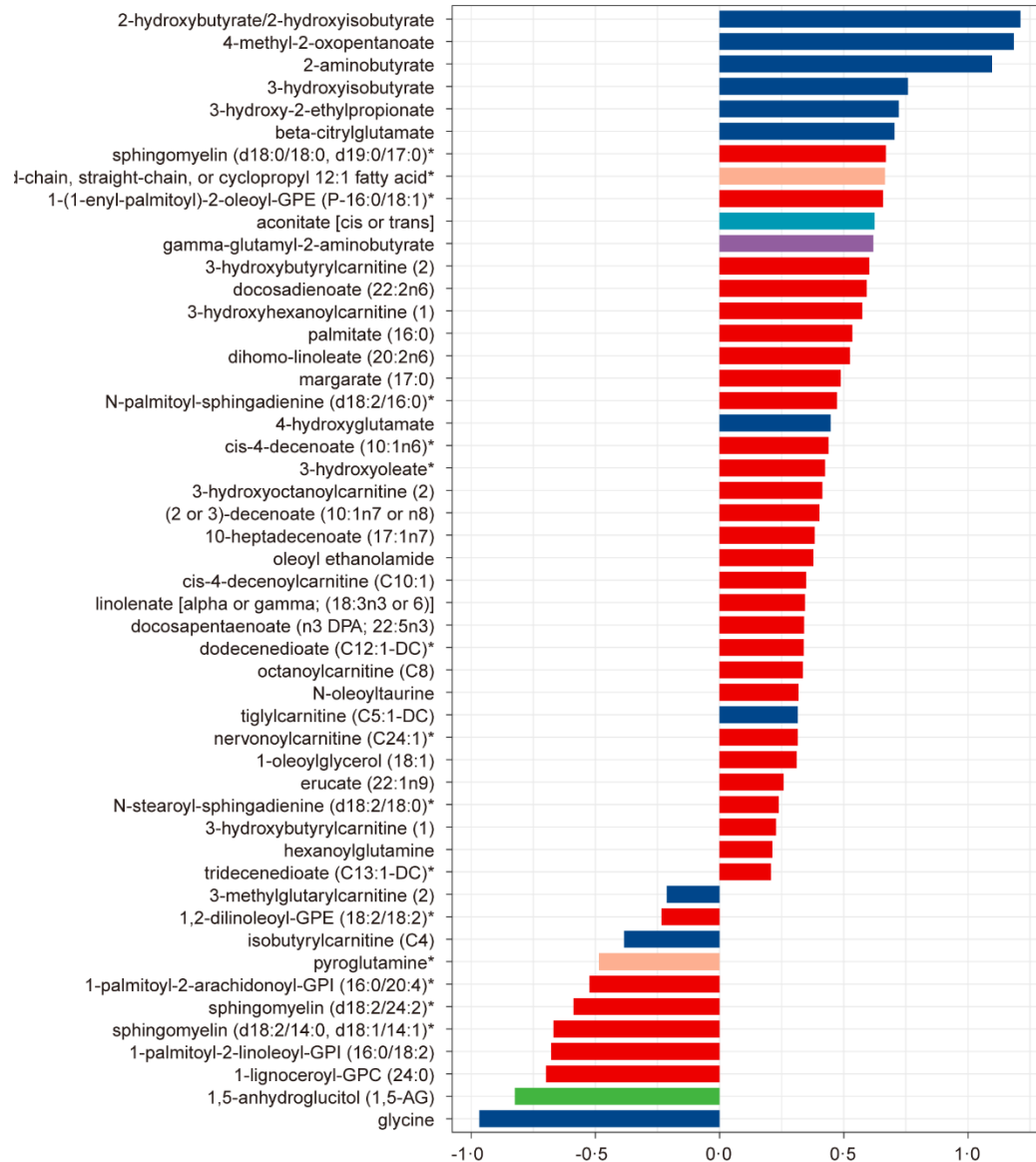
- **705 plasma metabolites** included (detection >80%)

- GDM-associated differential metabolites were identified in the **Nanjing sub-cohort** (175 GDM, 13.4%)

- Reassessing the association in the **Suzhou sub-cohort**

Legend:
- Amino Acid
- Carbohydrate
- Energy
- Lipid
- Partially Characterized Molecules
- Peptide

Pie chart values: 22.0%, 2.0%, 2.0%, 68.0%, 2.0%, 4.0%
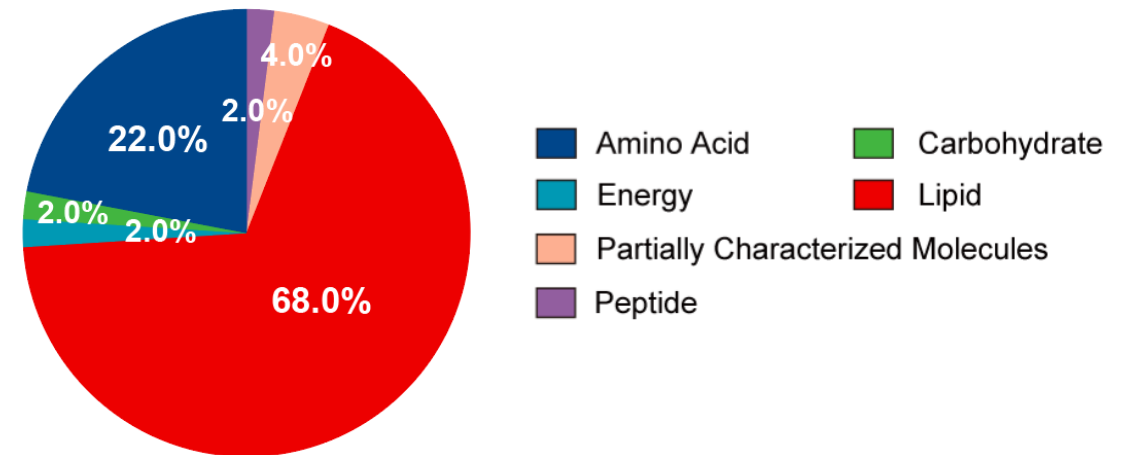
- **50 differential metabolites** constitute GDM metabolic signature

- Mainly **lipids** (n=34, 8.5% of all lipids) and **amino acids** (n=11, 6.5% of all AAs)

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Metabolic heterogeneity within normoglycemia and hyperglycemia

- We integrated data from the Nanjing and Suzhou sub-cohorts to develop an **elastic net** regression model predicting GDM using 50 GDM-related metabolites.

- This metabolomics-based model was subsequently used to define **mGDM**, the metabolite signature representing GDM.


	non-mGDM	mGDM
non-GDM	normoglycemic-non-mGDM n=1122	normoglycemic-mGDM n=611
GDM	hyperglycemic-non-mGDM n=77	hyperglycemic-mGDM n=240
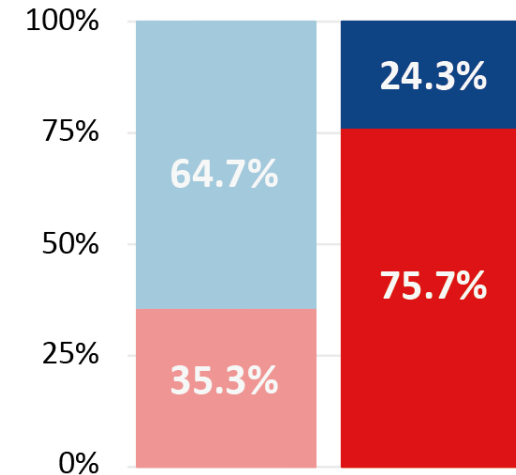
- Participants were categorized into four groups characterized by **distinct glycemic and metabolic profiles**.

- The misclassification rate was approximately **30%**, with 33.6% of individuals (688 mismatched, 1362 matched) inconsistent with OGTT-diagnosed GDM.

Characterization of metabolic GDM

- Compare the differences in **clinical indicators** and **demographic characteristics** among four groups
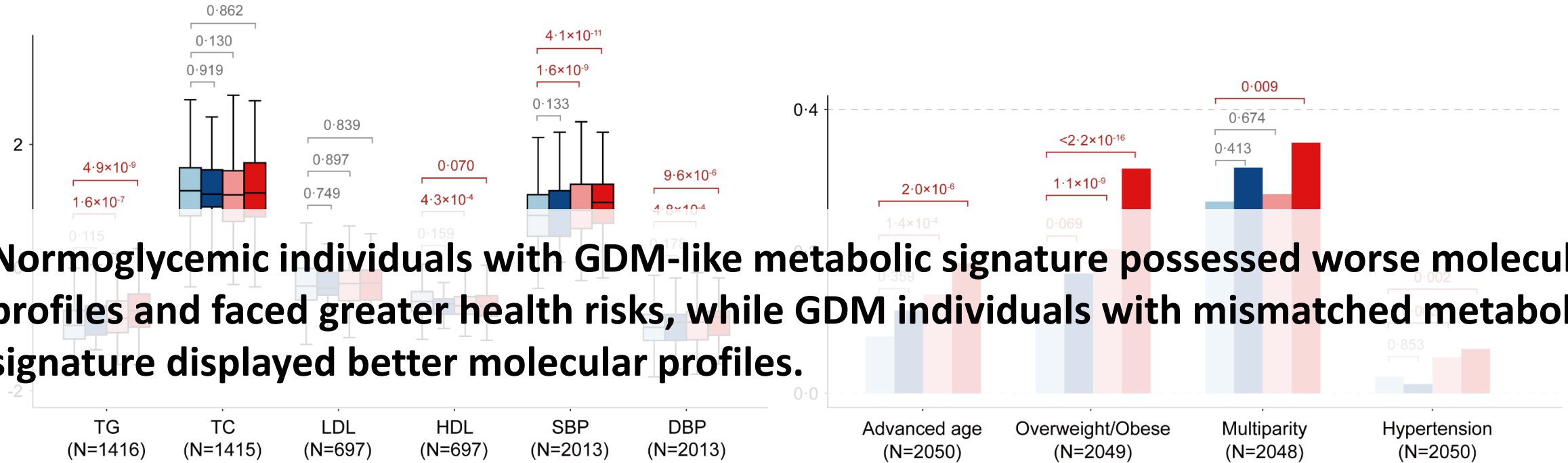
- **Normoglycemic individuals with GDM-like metabolic signature possessed worse molecular profiles and faced greater health risks, while GDM individuals with mismatched metabolic signature displayed better molecular profiles.**

🟥🟥 **mGDM Group (Mid-Pregnancy)**:

- **Elevated**: Triglycerides (TG), systolic/diastolic blood pressure (SBP/DBP)
- **Decreased**: High-density lipoprotein (HDL)
- **Characteristics**: Advanced maternal age (>35 years), pre-pregnancy overweight/obesity (≥24 kg/m²), gestational hypertension

Legend:
- 🟦 normoglycemic-non-mGDM
- 🟦 hyperglycemic-non-mGDM
- 🟥 normoglycemic-mGDM
- 🟥 hyperglycemic-mGDM

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Associations between GDM metabolic signature and birth outcomes

Reference: normoglycemic-non-mGDM	case (%)	Crude model		Adjusted model			P-trend
		RR (95%CI)	P	RR (95%CI)	P		
Preterm birth	22 (2.0)						
hyperglycemic-non-mGDM	0 (0.0)	-	-	-	-		
normoglycemic-mGDM	21 (3.4)	1.78 (0.97,3.26)	0.062	**1.99 (1.06,3.74)**	**0.032**		**0.010**
hyperglycemic-mGDM	10 (4.2)	**2.17 (1.02,4.65)**	**0.045**	**2.39 (1.07,5.35)**	**0.034**		
Large for gestational age	84 (7.5)						
hyperglycemic-non-mGDM	9 (11.7)	1.64 (0.79,3.39)	0.186	1.43 (0.67,3.04)	0.356		
normoglycemic-mGDM	96 (15.7)	**2.30 (1.69,3.14)**	**<0.001**	**2.04 (1.47,2.82)**	**<0.001**		**<0.001**
hyperglycemic-mGDM	47 (19.6)	**3.01 (2.04,4.44)**	**<0.001**	**2.26 (1.49,3.43)**	**<0.001**		
Congenital malformation	46 (4.1)						
hyperglycemic-non-mGDM	3 (3.9)	0.95 (0.29,3.12)	0.930	0.98 (0.29,3.28)	0.978		
normoglycemic-mGDM	28 (4.6)	1.12 (0.69,1.82)	0.635	1.15 (0.70,1.88)	0.586		0.091
hyperglycemic-mGDM	17 (7.1)	**1.78 (1.00,3.17)**	**0.049**	**1.92 (1.04,3.52)**	**0.036**		
NICU admission	103 (9.2)						
hyperglycemic-non-mGDM	6 (7.8)	0.84 (0.35,1.97)	0.682	0.78 (0.32,1.85)	0.567		
normoglycemic-mGDM	73 (11.9)	1.34 (0.98,1.84)	0.069	1.29 (0.93,1.79)	0.124		**0.013**
hyperglycemic-mGDM	36 (15.0)	**1.75 (1.16,2.63)**	**0.007**	**1.72 (1.12,2.63)**	**0.014**		

- **Hyperglycemic-non-mGDM**: **No increased risk** versus normoglycemic.
- **Normoglycemic-mGDM**: Nearly **2-fold increased risk** of preterm birth and large-for-gestational-age.
- **Hyperglycemic-mGDM**: **Highest risks** for all included birth outcomes.

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Conclusion

Metabolic heterogeneity	Characterization	Adverse Birth Outcomes
Individuals were stratified into four groups characterized by distinct glycemic and metabolic profiles.	Individuals with GDM metabolic signatures (i.e., mGDM) exhibited suboptimal clinical and demographic profiles.	Individuals with GDM metabolic signatures (i.e., mGDM) showed an increased risk of adverse birth outcomes.

Interpretation: By integrating blood glucose levels and metabolomics, this study represents a significant step towards more precise and clinically relevant stratification of pregnant women, paving the way for precision medicine in GDM.

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Day Time Scenery of Nanjing

Thanks for your attention! ☺

Night Time Scenery of Nanjing

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