Etched

Early Tracking of Childhood Health Determinants

Between Maternal and Fetal Glucose and Metabolic Biomarkers in the **ETCHED** Pregnancy Cohort

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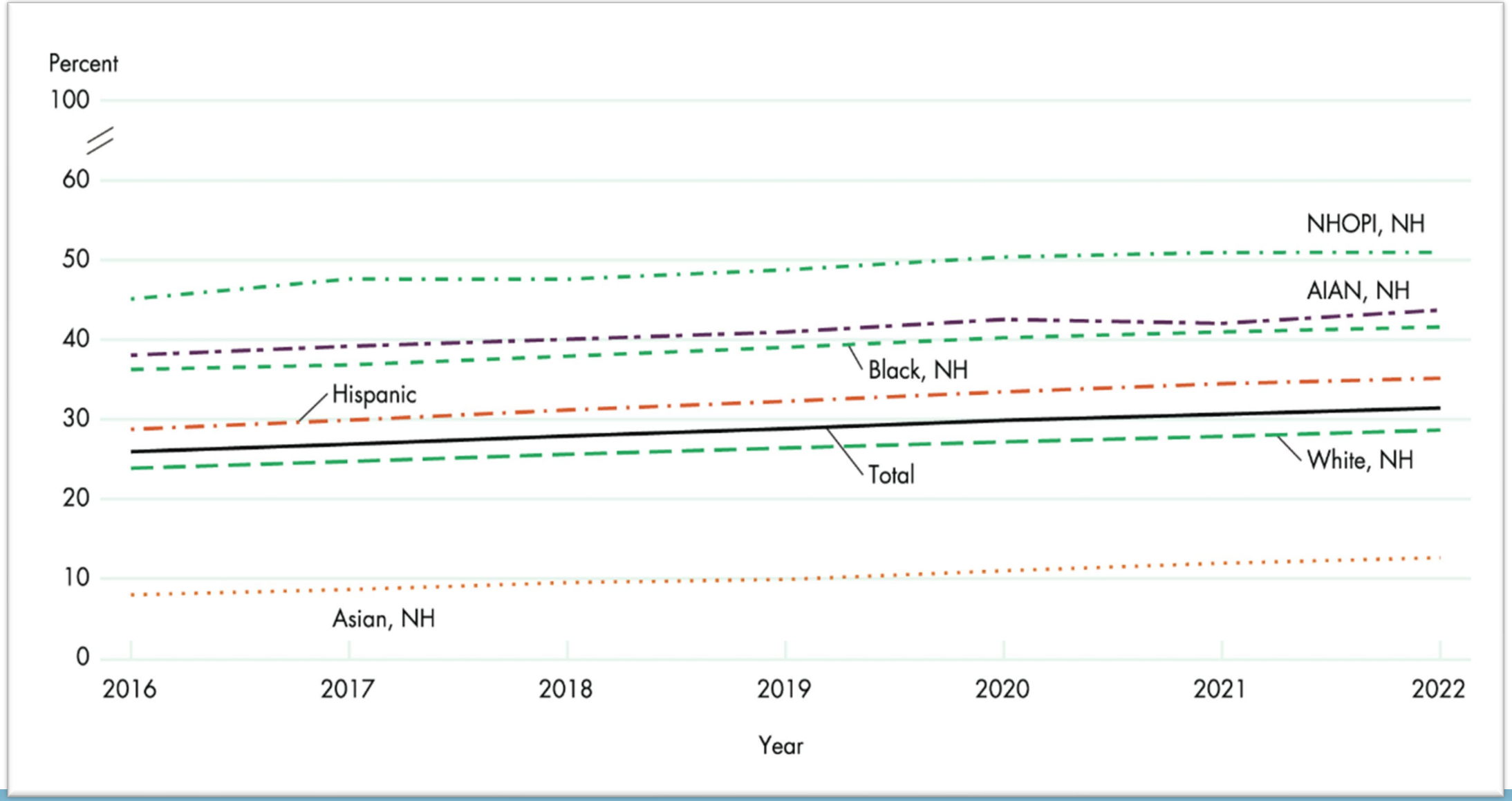
National Institutes of Health, IRP

NIH National Institute of Diabetes and Digestive and Kidney Diseases

PRESENTATION OUTLINE

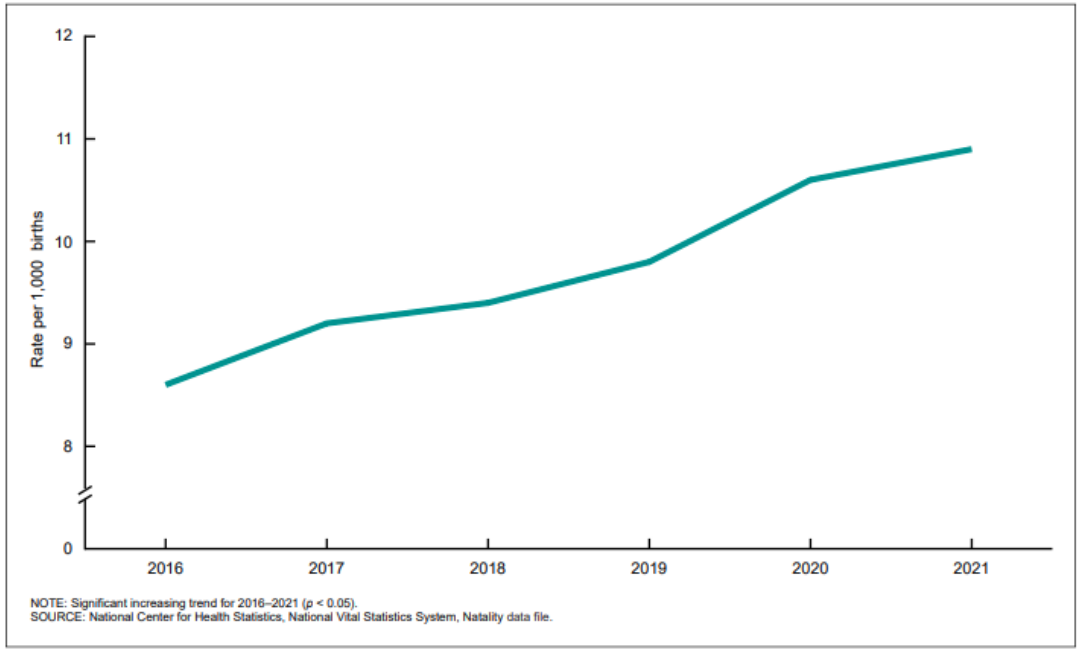
- Problem of obesity and diabetes in reproductive age women in the United States
- Prior studies at NIDDK Phoenix, on diabetes in pregnancy
- Introduction to the ongoing life course **ETCHED study**
- Presentation of data on ***Association Between Maternal and Fetal Glucose and Metabolic Biomarkers***

Percentage of women with pregestational obesity by race/Hispanic ethnicity, 2016-2022

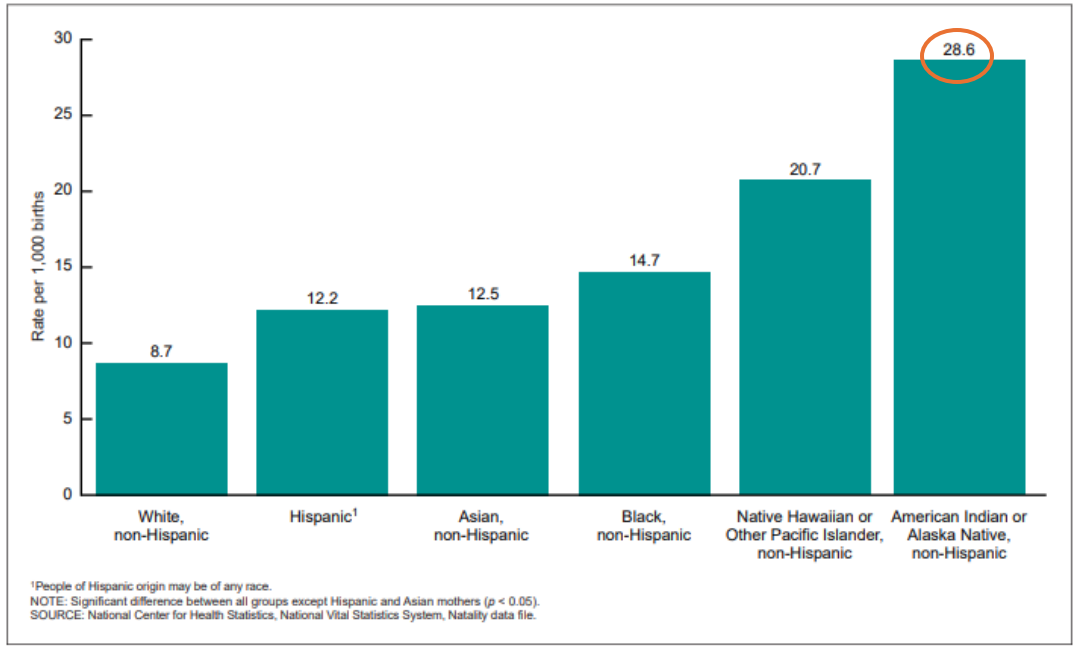


SOURCE: *National Center for Health Statistics, National Vital Statistics System, Natality.*

Rate of prepregnancy diabetes (Type 1 and 2): *United States, 2016–2021*

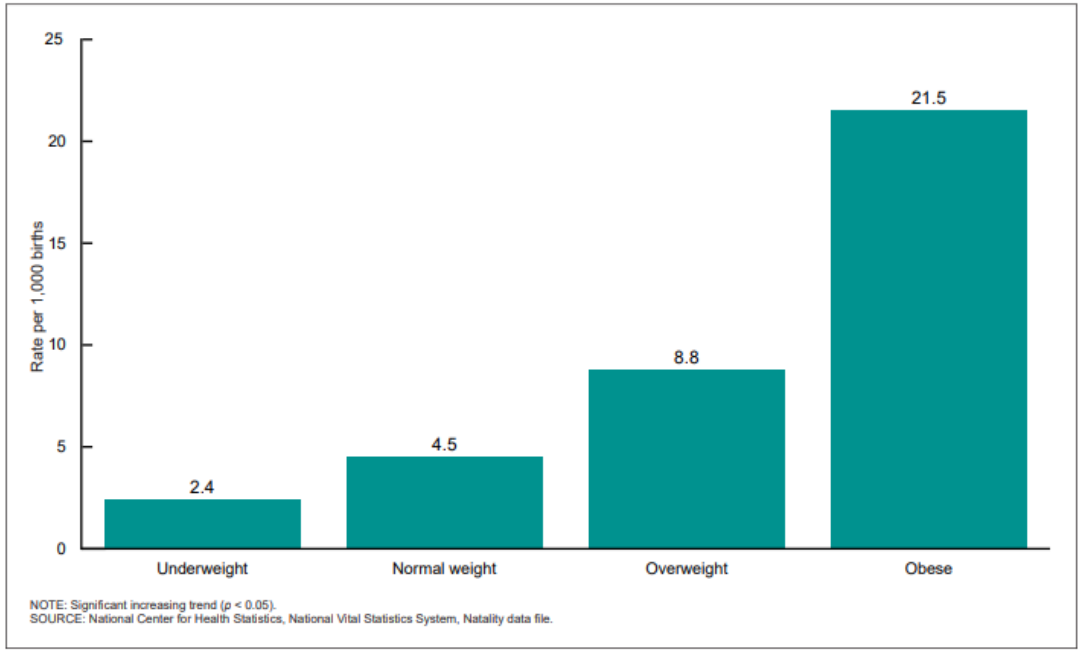


Rate of prepregnancy diabetes: *By race & Hispanic origin of mother, US 2021*

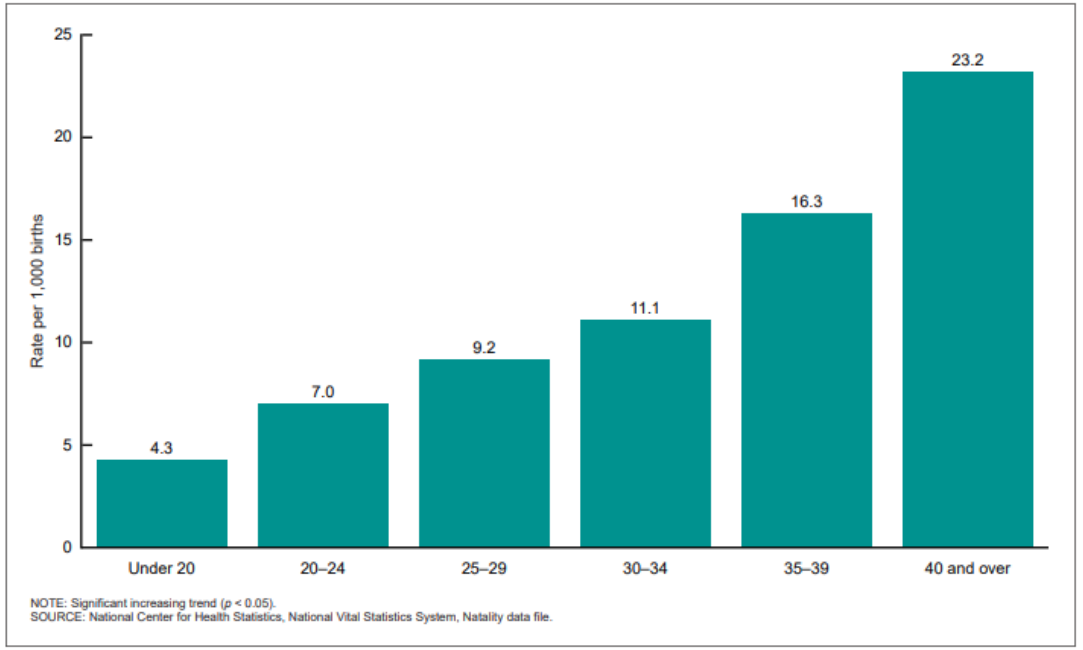


Source: National Vital Statistics Reports, Vol. 72, May 31, 2023

Rate of prepregnancy diabetes:
By BMI categories, United States 2021

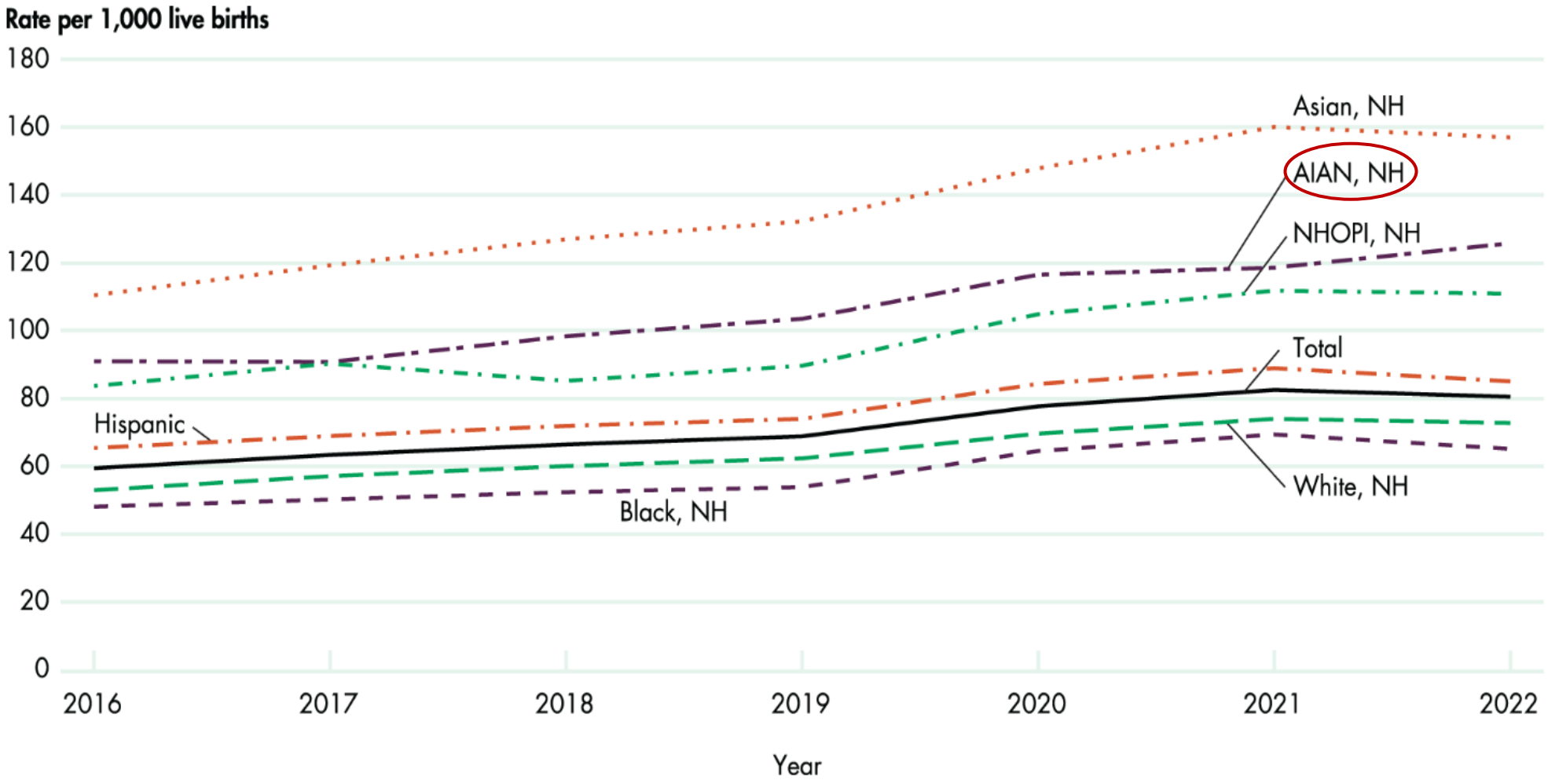


Rate of prepregnancy diabetes:
By maternal age, United States 2021



Source: National Vital Statistics Reports, Vol. 72, May 31, 2023

RATE OF GESTATIONAL DIABETES BY MATERNAL RACE AND HISPANIC ORIGIN 2016-2022



NOTE: NH = non-Hispanic origin; AIAN = American Indian or Alaska Native; NHOPI = Native Hawaiian or Other Pacific Islander. The 1997 U.S. Office of Management and Budget standards for data on race and ethnicity were used to classify people into one of the following five racial groups: White, Black or African American, Asian, American Indian or Alaska Native, or Native Hawaiian or Other Pacific Islander. All categories are single race. Data on race and Hispanic origin are collected and reported separately. People of Hispanic origin may be of any race.

SOURCE: National Center for Health Statistics, National Vital Statistics System, Natality.

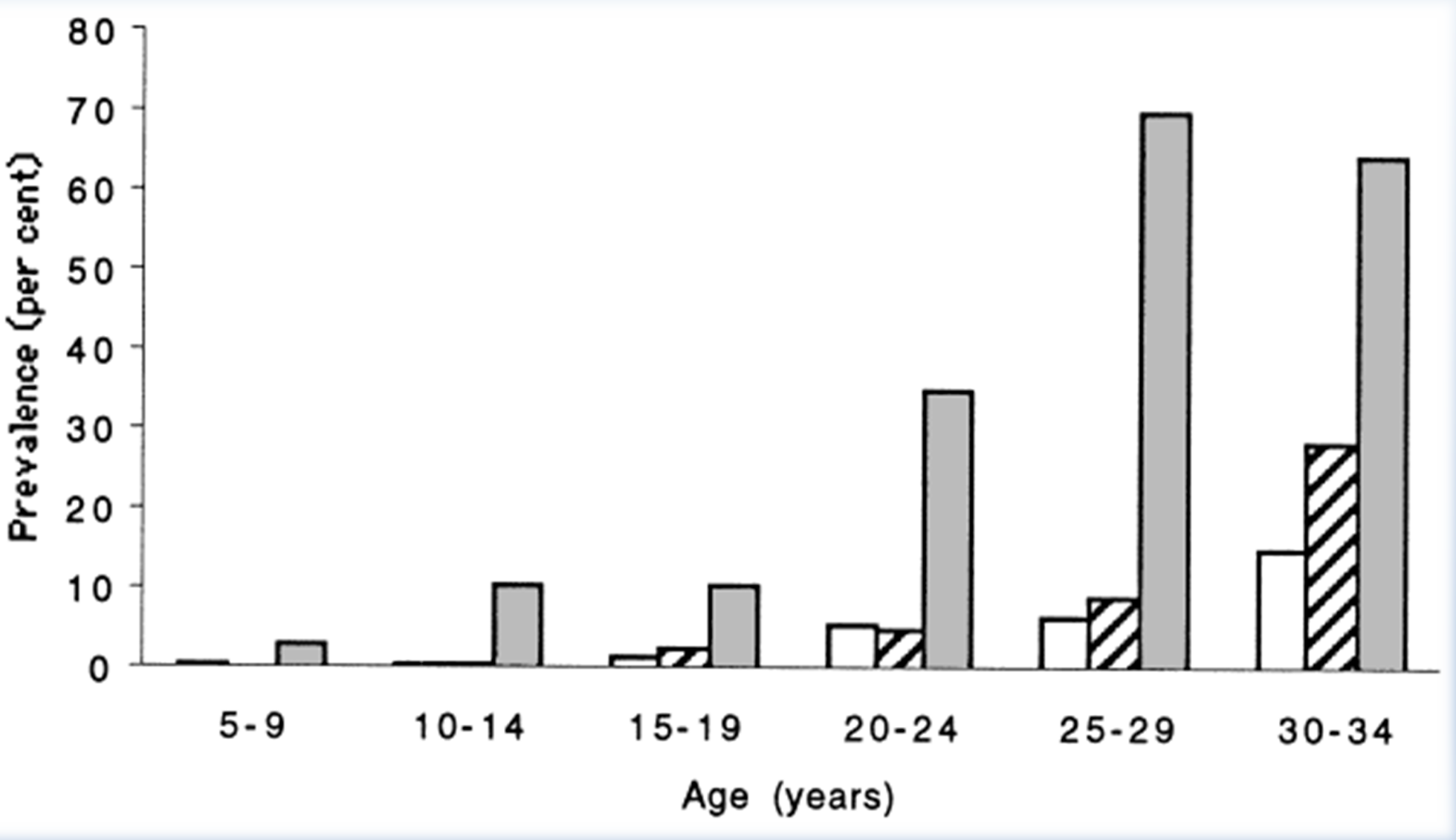
SOURCE: *National Center for Health Statistics, National Vital Statistics System, Natality.*

RATE OF GESTATIONAL DIABETES BY MATERNAL AGE 2016-2022

SOURCE: National Center for Health Statistics, National Vital Statistics System, Natality.

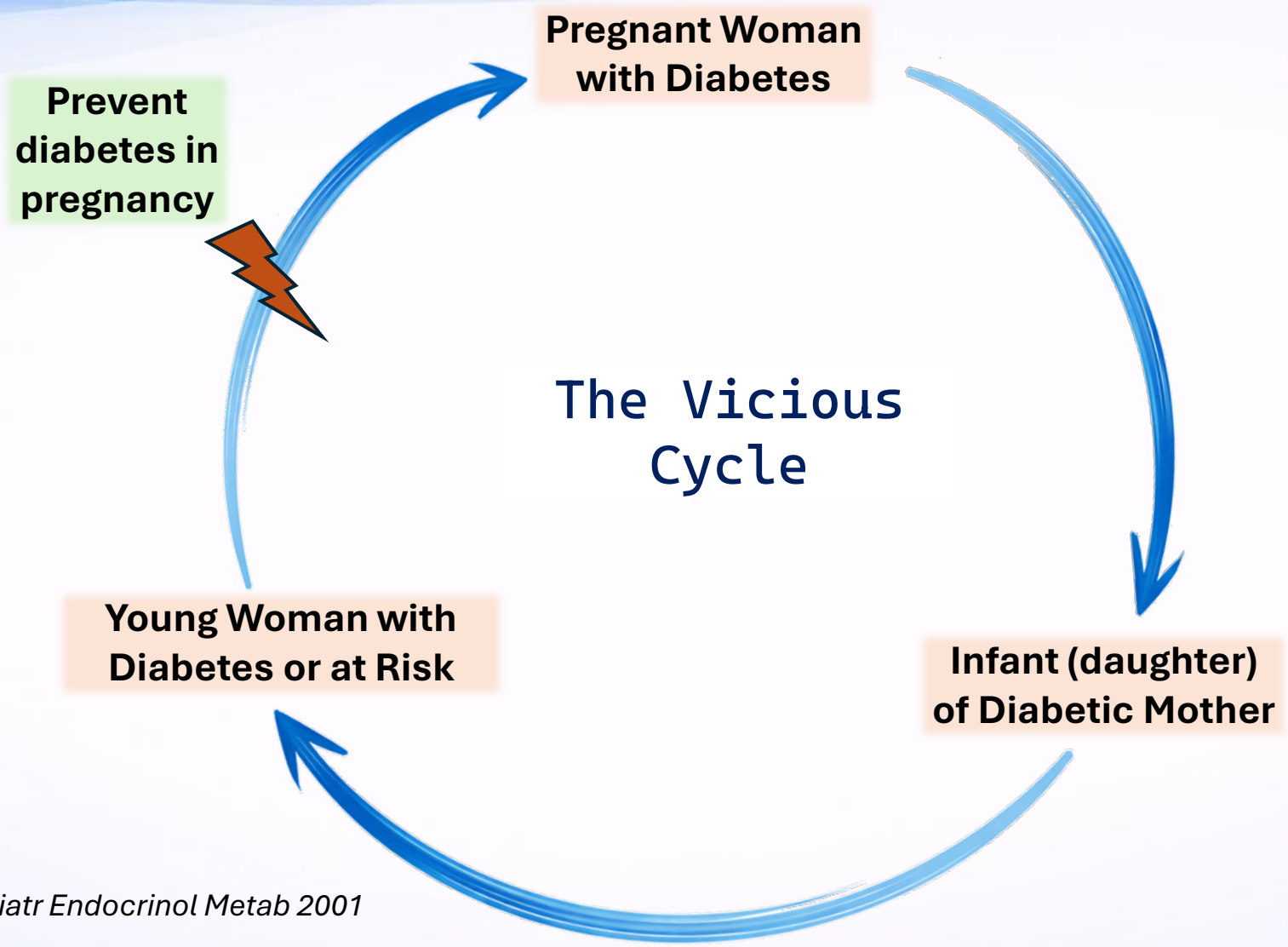
SOURCE: *National Center for Health Statistics, National Vital Statistics System, Natality.*

Prevalence of T2D by mother's diabetes status during and following pregnancy in AI/AN study participants in southwestern US



Dabelea et al. J. Matern. Fetal Med 2000

Transgenerational Amplification of Obesity and Type 2 Diabetes



Dabelea et al. J Pediatr Endocrinol Metab 2001

Developmental Origins of Health and Disease (DoHAD)

Barker's Hypothesis

Critical period theory

Fetal programming during intrauterine life plays a role in the etiology of chronic diseases later in life

A Life course perspective…

Life-events and biological, and environmental processes during the entire lifespan (*allostatic load*) can modify effects of intrauterine exposures

Early Tracking of Childhood Health Determinants (ETCHED) Study

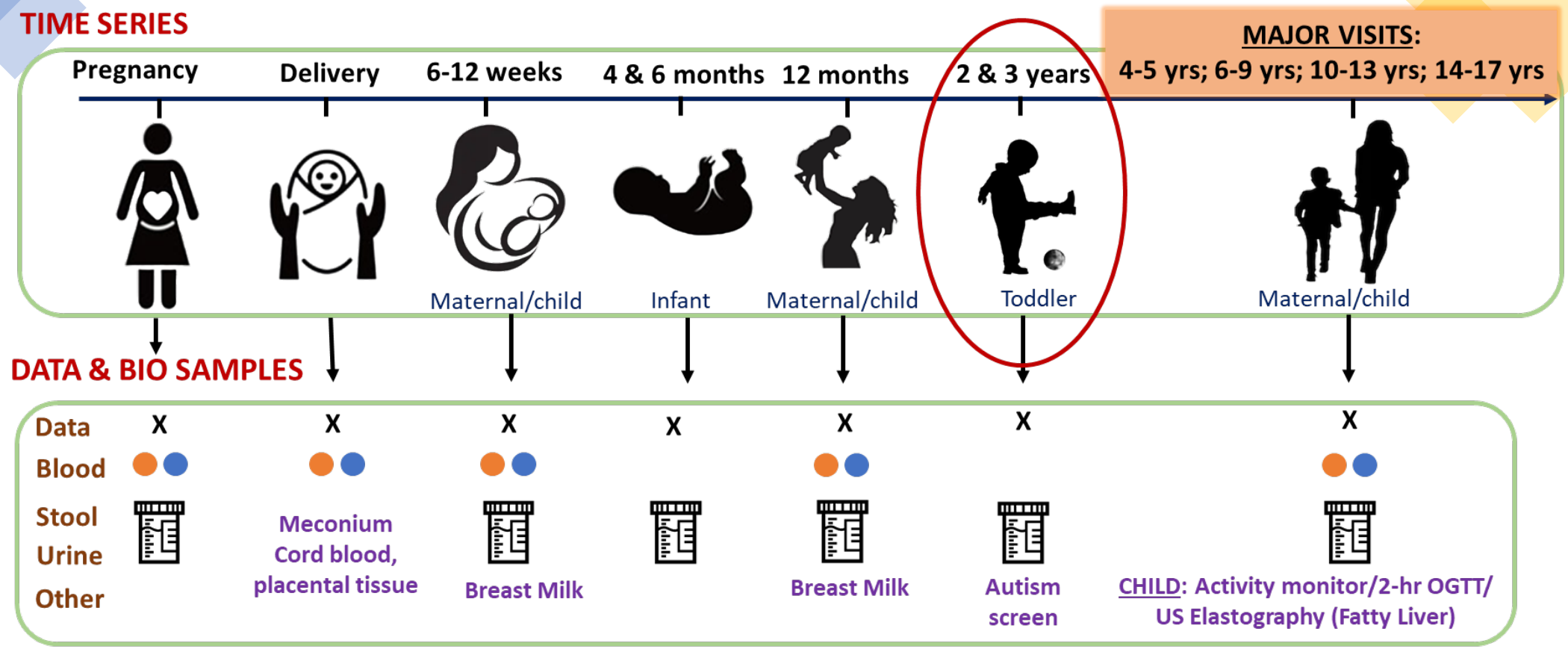
*ETCHED is a life course study aimed at establishing a longitudinal cohort of maternal/child dyads (Hispanic and American Indian/Alaska Native), to study the role of a combination of **biological** and **environmental** factors in childhood obesity and metabolic risk*

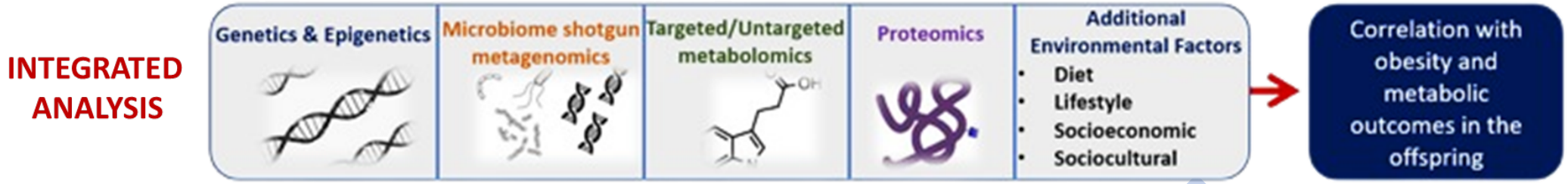
- **Enrollment (Ongoing):** 5-years, started in April 2022
- **Follow-up** of mother/child dyad: 18-years postpartum
- **Site:** Valleywise Health Medical Center, Phoenix, AZ
- **Total duration of study:** 23-years
- **Total study visits: 1,283** *(up to April 2026)*

ETCHED is supported by the NIH, NIDDK IRP

	PRENATAL			POSTPARTUM (PP) 1-year				PP 2-year		PP 3-year
STUDY VISITS	Baseline	2 & 3rd trim	Delivery	12-wk PP Mother/ Infant	4-mth Infant	6-mth Infant	12-mth Mother/ Infant	18-mth Infant	24-mth Mother/ Infant	36-mth Infant
NO.	**193**	**49**	**179**	**136/120**	**115**	**116**	**86/89**	**68**	**51/57**	**24**

ETCHED STUDY VISIT TIMELINE





Maternal Measures

DEMOGRAPHIC/SOCIO-ECONOMIC HISTORY

- Demographic data
- Family structure, size, employment, income

CLINICAL HISTORY

- Detailed medical and obstetric history

ANTHROPOMETRICS

- Height, weight, waist circumference (non-pregnant)
- Blood pressure measurement

SURVEYS/QUESTIONNAIRES

- Unmet Social Support
- Modifiable Activity Questionnaire
- Pittsburgh Sleep Quality Index
- Adverse Childhood Experience (at baseline)
- BLOCK-2000
- Food Insecurity Questionnaire
- Eating Behaviors (EARLY)
- Cohen's Perceived Stress Scale
- Short Acculturation Scale for Hispanic (SASH)
- Cultural considerations survey

CLINICAL LAB TESTS

- **Blood:** CBC, HbA1c, fasting glucose/insulin, folate, LFT, serum lipids, HbA1c, OGTT (postpartum) DNA/RNA
- **Urine** urinalysis, ACR
- **Stool** for microbiome
- **Placental tissue**
- **Cord blood**
- **Breastmilk**

IMAGING

- **Fibroscan** For Metabolic Liver Disease (PP)

ADDITIONAL BIOMARKERS

- Leptin, Adiponectin
- TNF-alpha
- IL-6, IL-8
- APO-C3
- FGF 21
- RBPH
- C-Peptide
- Cortisol
- Hs CRP
- Fructosamine
- Cystatin C
- ApoA-1, Apo-B, Apo-E

ETCHED Ancillary Studies

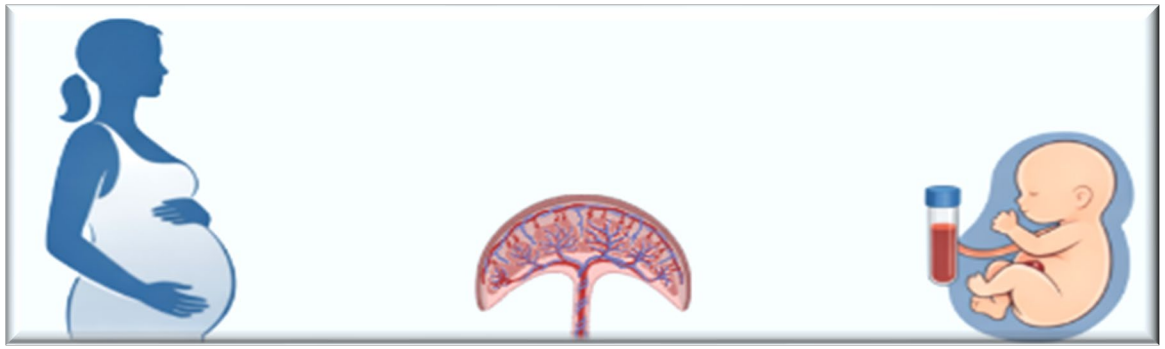
Photo Courtesy : Flores Family

Maternal and Fetal Glycemia

Assess the relationship between maternal blood glucose measures and fetal glucose exposure by reporting the strength and significance of correlations with fetal biomarkers

Pederson's Hypothesis: *Maternal glucose homeostasis and fetal response*

HAPO Study: *A strong continuous association observed between maternal glucose levels below the diabetes diagnostic criteria, and APO including higher neonatal adiposity and glucose intolerance*



Maternal glycemia → **Placental transfer** → **Fetal glycemia**

Association Between Maternal and Fetal Glycemia in the ETCHED cohort

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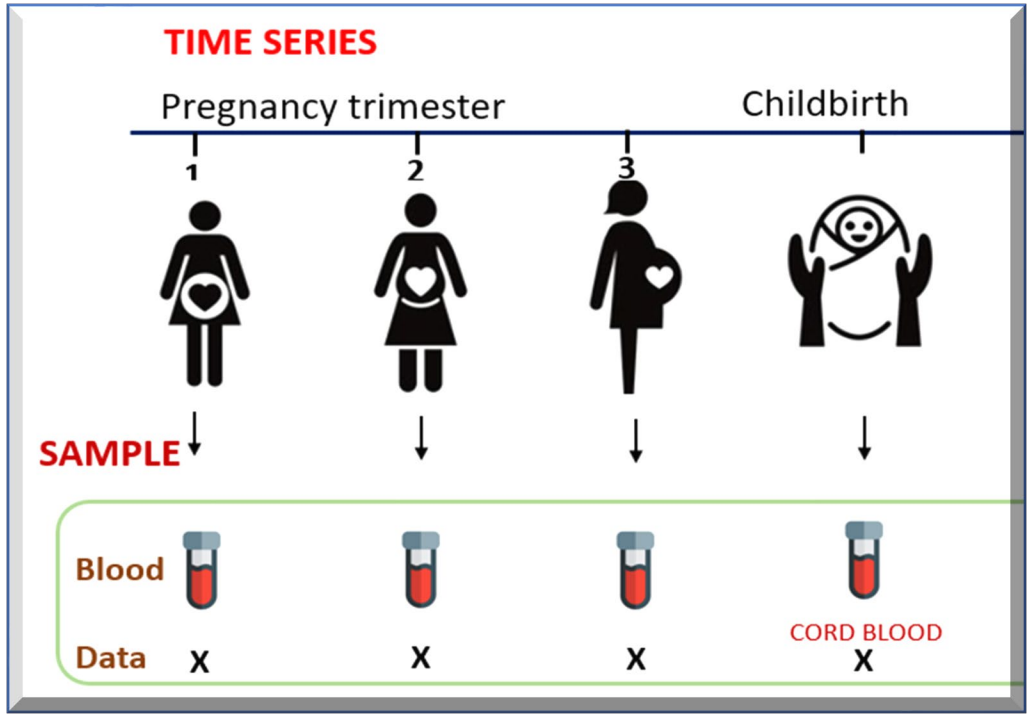
STUDY OBJECTIVE

To examine the relationship between ***glycemic*** and ***metabolic*** biomarkers including adipocytokines in ***prenatal***, and ***matched fetal cord blood*** samples in the ETCHED pregnancy cohort



Study Hypothesis: *Fetal cord blood **total glycated hemoglobin (GlyHB)** and **fructosamine**, indicating both long– and intermediate–term glucose metabolism, will be associated with the maternal levels of these metabolic markers reflecting prolonged in–utero fetal glucose exposure*

Inclusion and Exclusion Criteria

(ETCHED a Life Course Study)

Inclusion Criteria

1. Pregnant women aged 18 years or older
2. American Indian or Hispanic by self-report
3. Agree to continue with research study participation (both mother and their offspring) for at least 3 years after delivery

Exclusion Criteria

1. Women who are incarcerated or are unable to consent.
2. Women whose fetus is not viable or are not planning to continue the pregnancy.

Metabolic Biomarkers in the Current Analysis

Selected Glycemic markers and Adipocytokines (both Maternal and Fetal)

Fructosamine *Glycated serum proteins (product of non-enzymatic reaction), Identifies short-term metabolic changes*

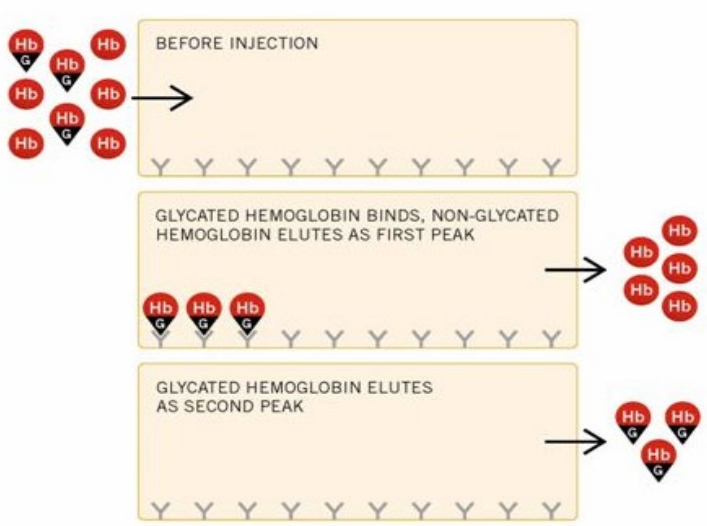
Glycated hemoglobin *GHb by the affinity method using boronic acid measures all glycated hemoglobins*

C-peptide and Insulin

Leptin and Adiponectin

FGF21, RBP4, APOC3 associated with obesity and diabetes

NIDDK Phoenix Lab (Clinical and Research)



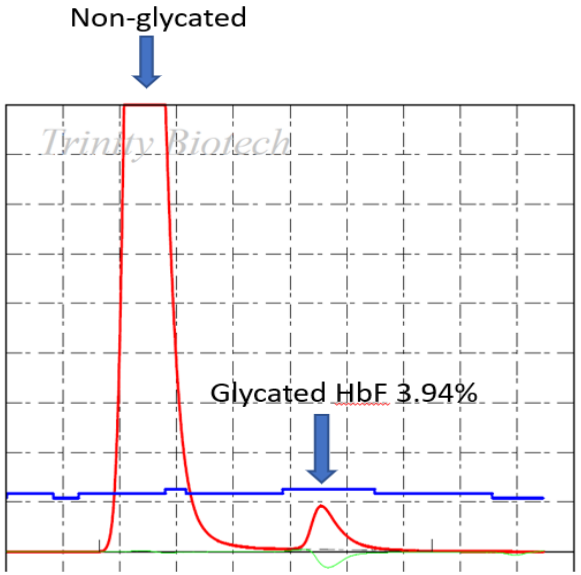


Photo courtesy Trinity Biotech

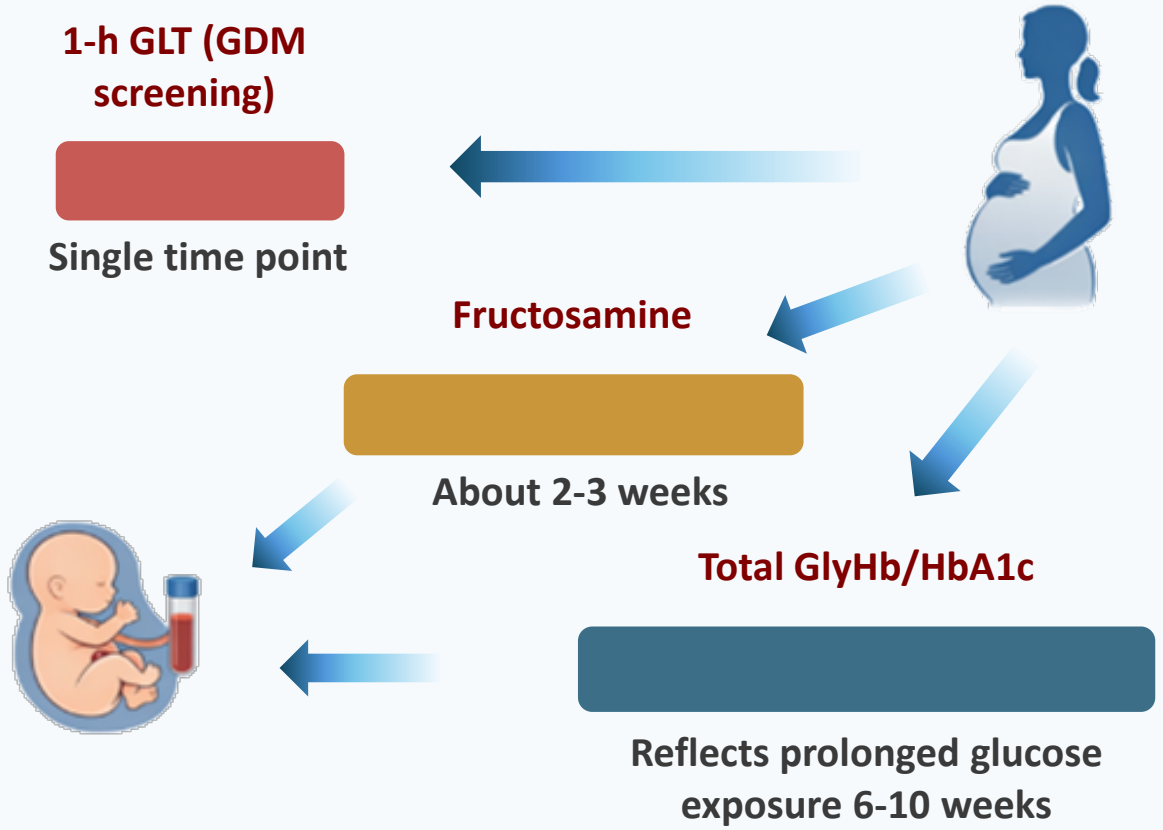
Glycated hemoglobin measurement in maternal prenatal, and fetal cord blood plasma samples:

- Fetal hemoglobin (α2, γ2) is the major Hgb in the red cells during fetal life.
- Total glycated hemoglobin was measured in whole blood by the **boronate affinity chromatography HPLC method** on the Premier Hb9210^{TM} (Trinity Biotech).
- This methodology can detect all the glycated hemoglobin species present, regardless of hemoglobin variants such as HbF.
- Matched maternal and fetal cord blood samples were run at **the NIH CC**

METHODS

Primary outcome

Fetal cord blood glycated proteins as markers of sustained mid and late-gestation glycemic exposure



Results

Data from **85 matched maternal–neonatal dyads** from singleton pregnancies (*August 2022–August 2025*), who had fetal cord blood available for analysis.

Demographic and **clinical data** were collected; anthropometric measurements

Pregestational weight by self-report, was verified by additional medical record review

Delivery data included *maternal weight, delivery mode, and perinatal complications*.

Cord blood was collected at delivery

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Early Tracking of Childhood Health Determinants

MATERNAL COHORT DESCRIPTION

Maternal baseline characteristics	Total	Diabetes in pregnancy present	Diabetes in pregnancy absent	*p value*
	(N=85)	*(N=24)*	*(N=61)*	
Maternal age in years (Median, IQR)	29.50 (24.75–34.25)	31.50 (26.00–34.25)	28.50 (23.75–34.25)	0.217
Maternal ethnicity (n, %)				
Hispanic	76 (89.4)	22 (91.7)	54 (88.5)	0.974
Maternal race, self–reported (n, %)				0.563
○ White	21 (24.6)	6 (25.0)	15 (24.6)	
○ American Indian/Alaska Native	14 (16.5)	4 (16.6)	10 (16.4)	
○ Asian	1 (1.2)	0 (0.0)	1 (1.6)	
○ More than one race	1 (1.2)	1 (4.2)	0 (0.0)	
○ Unknown/not declared	48 (56.5)	13 (54.2)	35 (57.4)	
Maternal education (n, %)				0.655
○ College degree or similar	21 (24.7)	7 (29.2)	14 (23.0)	
○ High School, completed and/or in part	52 (61.2)	15 (62.5)	37 (60.7)	
○ Less than High School	9 (10.6)	2 (8.3)	7 (11.5)	
○ Not reported	3 (3.5)	0 (0.0)	3 (4.9)	
Family size (Median, IQR)	4.00 (3.00–6.00)	4.50 (4.00–5.25)	4.00 (3.00– 6.00)	0.359
Annual household income (n, %)				0.346
○ <$25,000	46 (54.1)	12 (50.0)	34 (55.7)	
○ $25,000–<$50,000	19 (22.4)	5 (20.8)	14 (23.0)	
○ $50,000–<$75,000	9 (10.6)	4 (16.7)	5 (8.2)	
○ ≥$75,000	3 (3.5)	2 (8.3)	1 (1.6)	
○ Not reported	8 (9.4)	1 (4.2)	7 (11.5)	

MATERNAL COHORT DESCRIPTION

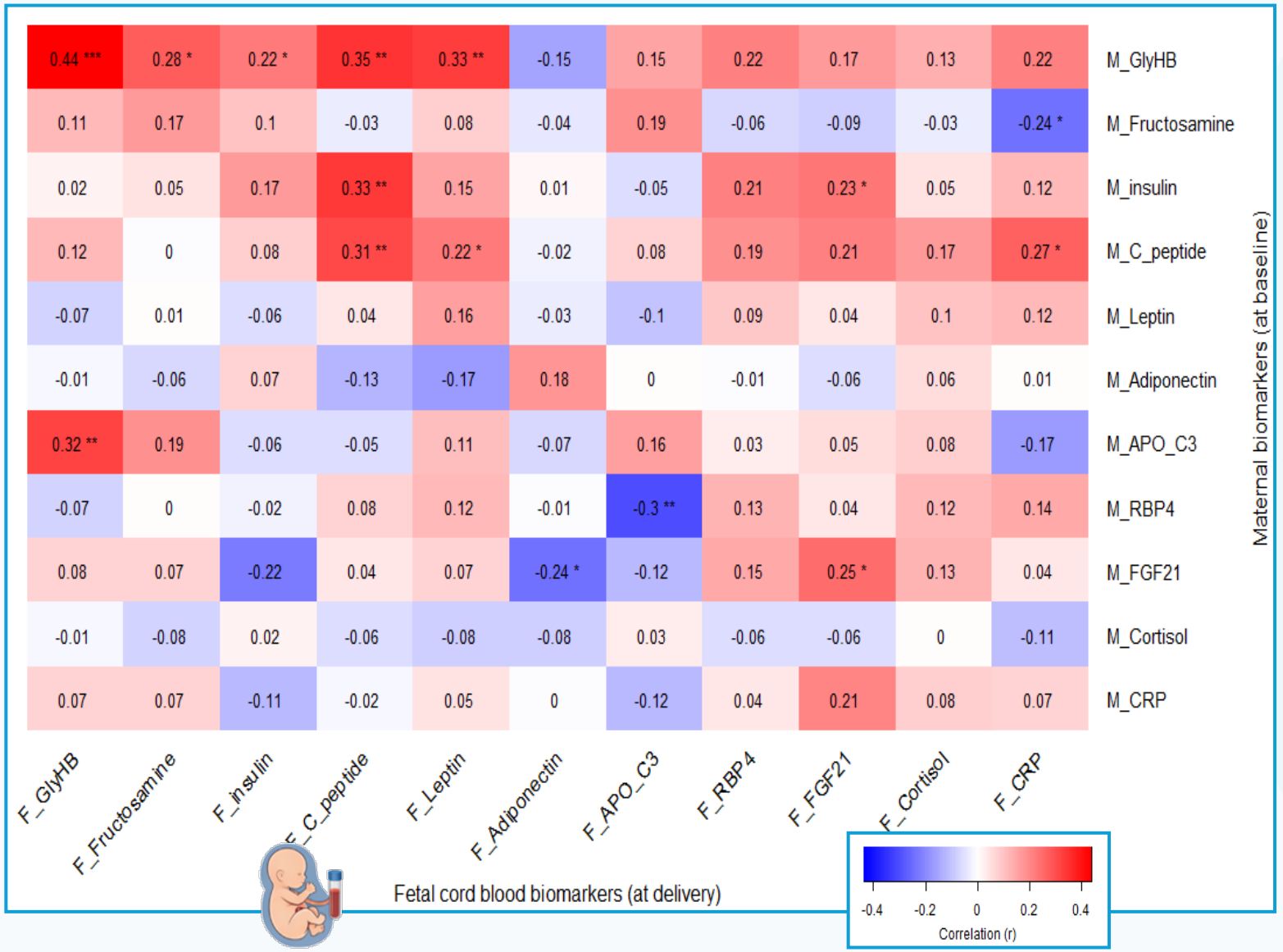
Maternal baseline characteristics	Total	Diabetes in pregnancy present	Diabetes in pregnancy absent	*p value*
	(N=85)	*(N=24)*	*(N=61)*	
Pregestational BMI, kg/m² (Median, IQR)	31.81 (26.98–38.29)	35.00 (29.52–40.10)	30.86 (24.85–36.24)	**0.012***
Pregestational BMI categories (n, %)				0.118
○ Underweight	1 (1.2)	0	1 (1.6)	
○ Healthy weight	14 (16.5)	0	14 (23.0)	
○ Overweight	21 (24.7)	7 (29.2)	14 (23.0)	
Obesity				
○ Class 1 Obesity	20 (23.5)	5 (20.8)	15 (24.6)	
○ Class 2 Obesity	15 (17.6)	6 (25.0)	9 (14.8)	
○ Class 3 Obesity (severe obesity)	14 (16.5)	6 (25.0)	8 (13.1)	
Mean Arterial Pressure, mm Hg (Median, IQR)	78.50 (74.17–85.21)	82.58 (75.17–86.42)	78.33 (74.17–85.00)	0.392
○ Chronic hypertension	11 (12.9)	7 (29.2)	4 (6.6)	**0.036†**
○ Gestational hypertension	12 (14.1)	2 (8.3)	10 (16.4)	
○ Preeclampsia	4 (4.7)	2 (8.3)	2 (3.3)	
○ Chronic hypertension with superimposed preeclampsia	3 (3.5)	0	3 (4.9)	

NEONATAL COHORT DESCRIPTION

Neonatal characteristics	Total	Maternal Diabetes in pregnancy present	Maternal Diabetes in pregnancy absent	*p value*
	(N=85)	***(N=24)***	***(N=61)***	
Offspring sex (n, %)				0.255
Male	36 (42.4)	13 (54.2)	23 (37.7)	
Female	49 (57.6)	11 (45.8)	38 (62.3)	
Birthweight in grams (Median, IQR)	3430.00 (2930.0–3680.0)	3470.00 (2967.5–3715.0)	3410.00 (2930.0–3630.0)	0.773
Birthweight categories (n, %)				0.768
▪ AGA	65 (76.5)	18 (75.0)	47 (77.0)	
▪ SGA	9 (10.6)	2 (8.3)	7 (11.5)	
▪ LGA	11 (12.9)	4 (16.7)	7 (11.5)	
Delivery Mode				0.858
• Cesarian Section	26 (30.6)	7 (29.2)	19 (31.1)	
• Normal Spontaneous Vaginal Delivery	59 (69.4)	17 (70.8)	42 (68.9)	
Major congenital anomalies present (n, %)	4 (4.7%)	1 (4.2)	3 (4.9)	1.00[†]
Gestational age at delivery, weeks (Median, IQR)	39.00 (38.00–39.00)	38.50 (37.00–39.00)	39.00 (38.00–40.00)	**0.005**[*]

RESULTS

Among 85-paired maternal-neonatal dyads.



Strong positive association with maternal GlyHB

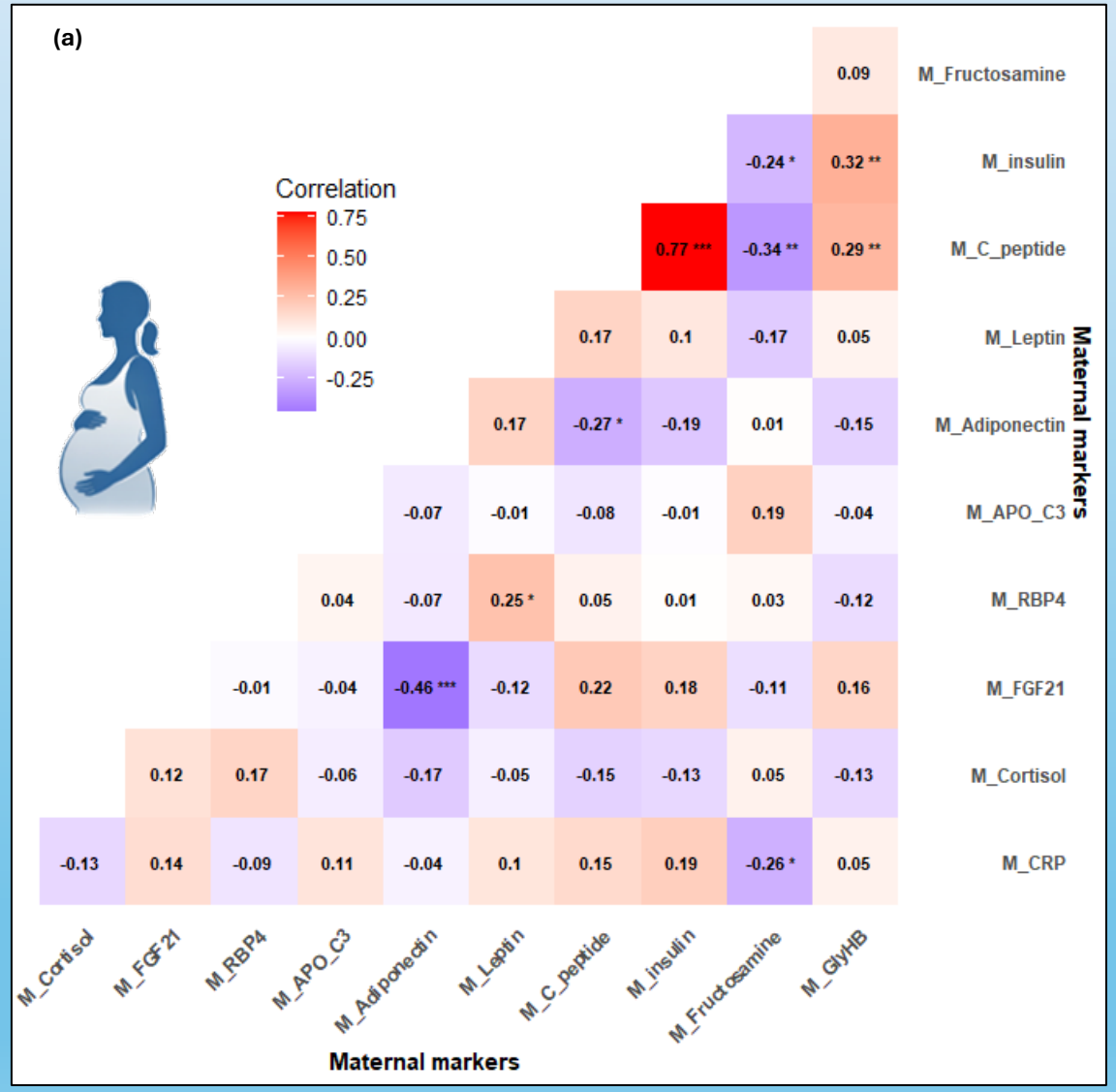
Fetal GlyHB
r = 0.44, p < 0.001

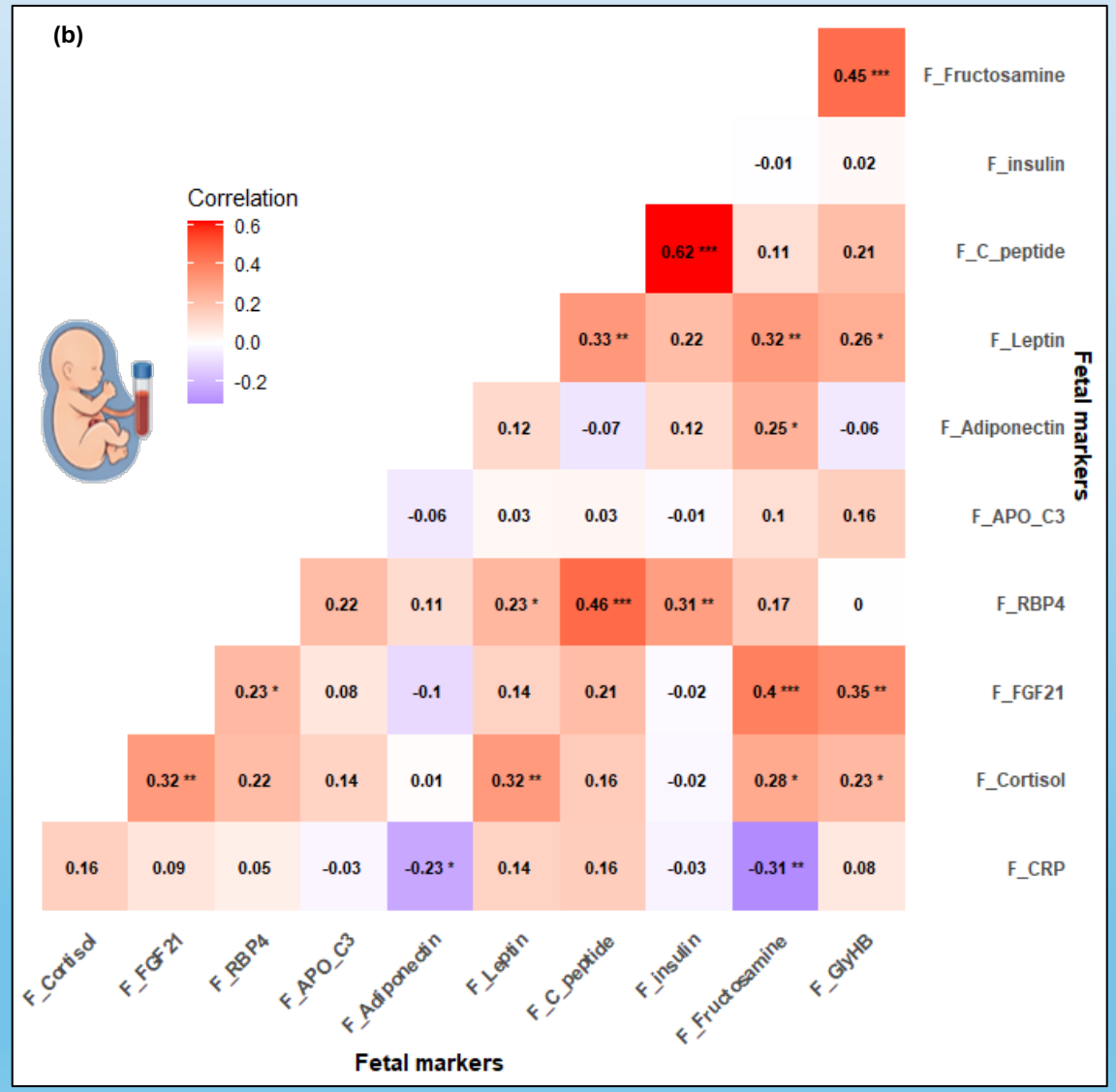
Fetal fructosamine
r = 0.28, p < 0.05

Fetal insulin and C-peptide
r = 0.22, p < 0.01 and 0.34, p < 0.05

Fetal leptin
r = 0.33, p < 0.01

Correlations between Maternal and Fetal Cord Blood Biomarkers





Spearman's partial correlation matrix between (a) maternal prenatal biomarkers, adjusted for pregestational BMI, gestational age at baseline, and presence of diabetes; (b) fetal cord blood biomarkers, adjusted for maternal pregestational BMI, gestational age at baseline, presence of diabetes, gestational age at delivery, neonatal birthweight and sex.

Metabolic Biomarkers Measured	Prenatal Biomarker Levels		*p* value
	Median (IQR)		
	Diabetes in pregnancy present	Diabetes in pregnancy absent	
	N=24	N=61	
C–peptide (ng/mL)	3.9 (2.5–6.4)	3.5 (2.3–5.4)	0.364
Cortisol (ug/dL)	16.8 (11.9–20.3)	17.1 (14.3–19.9)	0.770
hs–CRP (mg/dL)	0.8 (0.4–1.2)	0.7 (0.4–1.0)	0.548
Fructosamine (umol/L)	137.5 (121.0–155.3)	131 (116.0–145.0)	0.110
Total GlyHB (%)	5.8 (5.3–6.2)	5.2 (5.0–5.5)	**<0.001***
APO C–3 (mg/dL)	10.9 (9.5–15.2)	7.7 (6.1–11.0)	**0.002***
RBP4 (ug/mL)	26507.6 (21745.0–32157.8)	27255.0 (22742.5–32408.5)	0.781
FGF21 (pg/mL)	188.1 (66.8–348.2)	127.2 (38.3–221.2)	0.196
Insulin (mcU/mL)	26.1 (14.0–56.2)	20.8 (12.3–34.2)	0.153
Leptin (ng/ml)	39.7 (28.0–59.3)	32.0 (18.7–49.3)	0.219
Adiponectin (ug/ml)	5.5 (4.2–6.4)	5.4 (4.1–7.7)	0.519

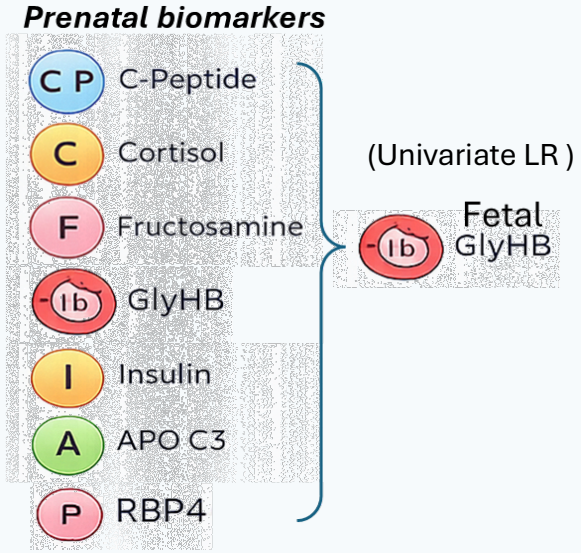
 Metabolic Biomarkers Measured	Fetal Cord Blood Biomarker Levels		*p* value
	Median (IQR)		
	Diabetes in pregnancy present	Diabetes in pregnancy absent	
	N=24	N=61	
C–peptide (ng/mL)	0.8 (0.7–1.1)	0.8 (0.5–1.1)	0.500
Cortisol (ug/dL)	7.1 (5.9–8.7)	8.7 (7.1–11.4)	0.057
hs–CRP (mg/dL)	0.02†	0.02†	0.224
Fructosamine (umol/L)	142.0 (122.5–165.5)	138 (120.0–145.5)	0.170
Total GlyHB (%)	4.0 (3.8–4.2)	3.7 (3.6–3.8)	**<0.001***
APO C–3 (mg/dL)	1.9 (1.2–2.3)	1.7 (1.3–2.0)	0.659
RBP4 (ug/mL)	14188.5 (11783.3–17541.3)	14719.0 (12390.0–17748.0)	0.507
FGF21 (pg/mL)	10.3 (4.9–24.9)	20.5 (10.1–36.8)	0.059
Insulin (mcU/mL)	5.8 (5.1–6.4)	5.1 (2.9–5.9)	0.058
Leptin (ng/ml)	9.7 (5.9–14.6)	8.9 (5.5–14.5)	0.578
Adiponectin (ug/ml)	26.9 (18.1–32.9)	29.4 (24.4–35.5)	0.109

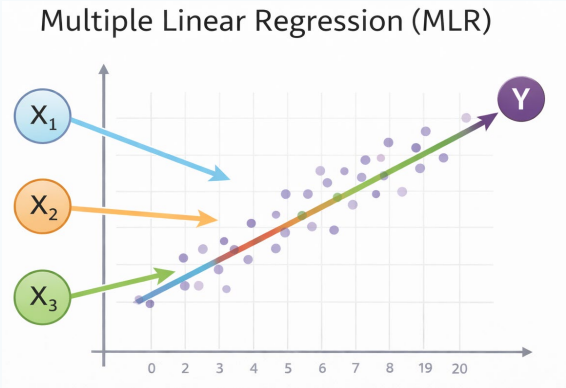
RESULTS

Maternal GlyHB is a key independent predictor of fetal GlyHB

Adjusted multivariable linear regression model

Per 1SD higher maternal GlyHB, fetal GlyHB increased by 0.385 SD after covariate adjustment





0.469
model R^2

Maternal GlyHB — **Fetal cord blood GlyHB**

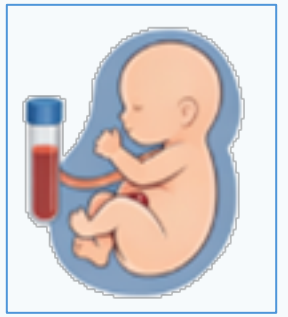
P < 0.0001
Overall model significance

No significant predictor emerged when fetal fructosamine was used as an outcome

RESULTS

Did maternal adiposity moderate this relation?

Pregestational BMI interaction



Maternal GlyHB

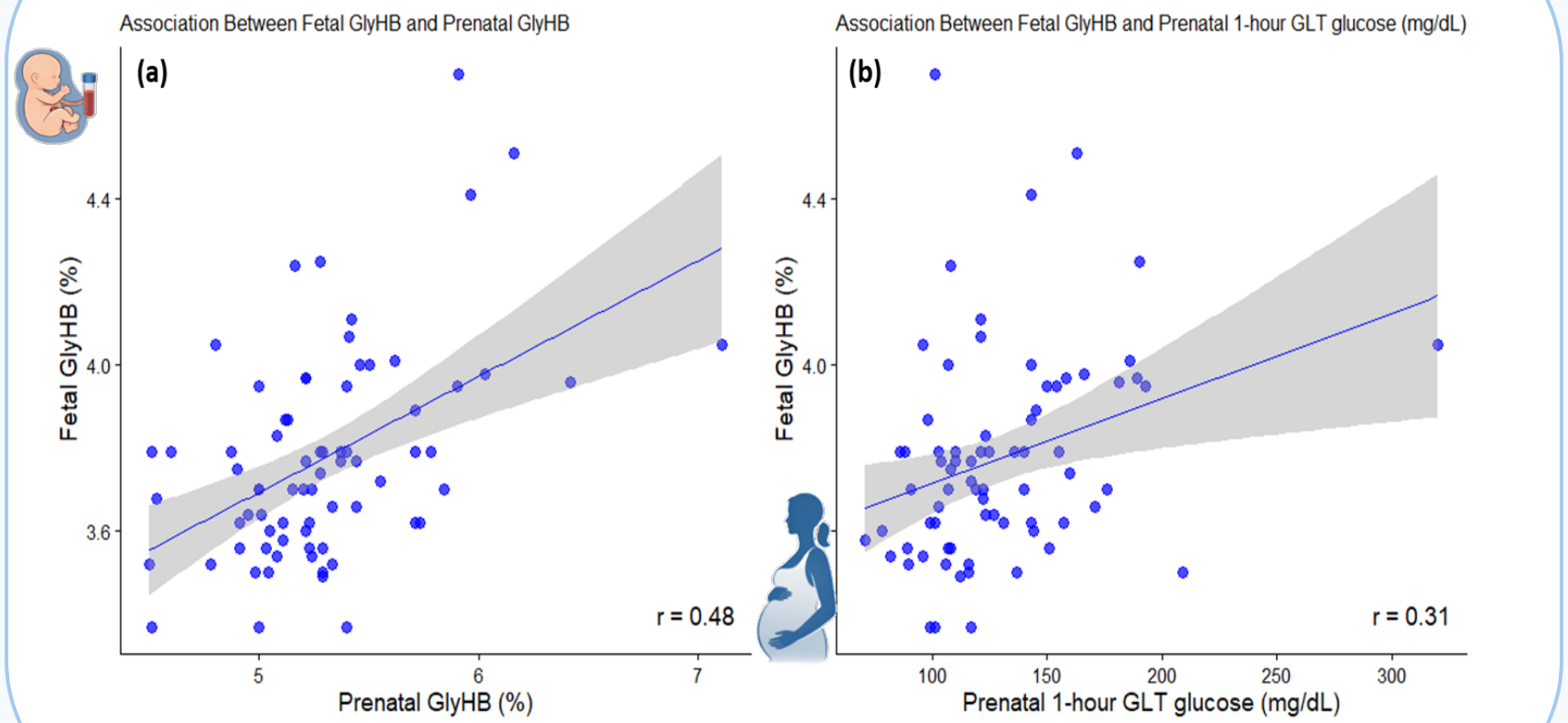
Fetal cord blood GlyHB

Pregestational BMI does not mitigate the effects in the relationship between maternal prenatal, and fetal cord GlyHB levels

RESULTS

Maternal Total GlyHB correlates with fetal sustained glycemic measure

N=73



Maternal prenatal GlyHB

$R = 0.48$, $p < 0.001$

1-h GLT glucose

$r = 0.31$, $p < 0.008$

Difference in correlation

$\Delta r = 0.17$, $p < 0.067$

Strengths and Limitations

Strengths

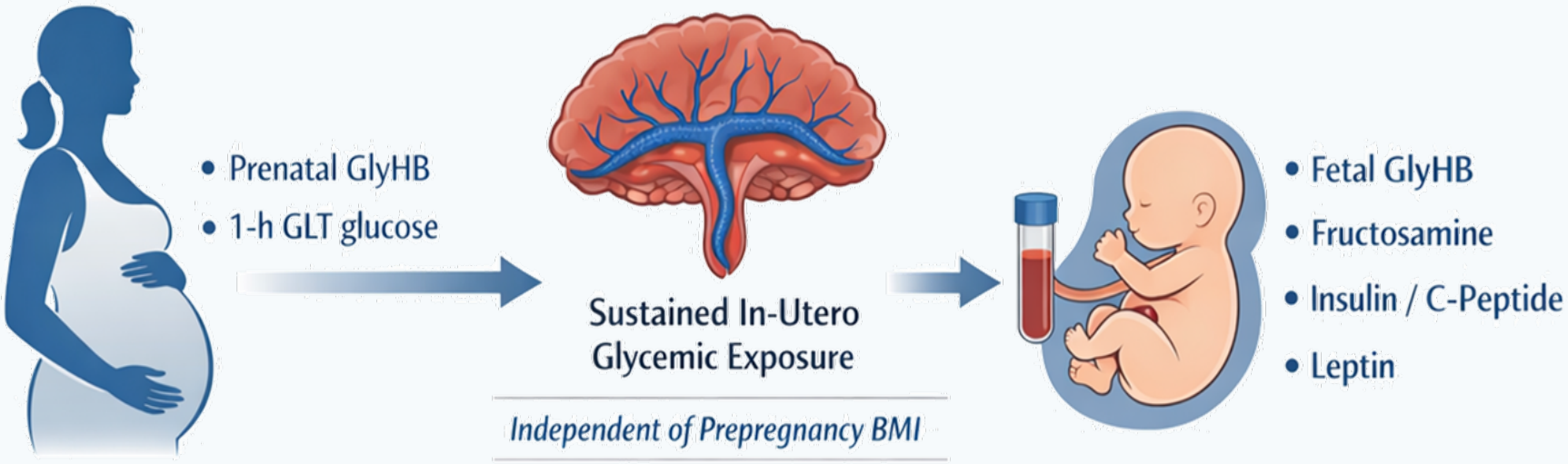
- Simultaneous availability of targeted prenatal and fetal cord blood metabolic biomarkers, measured using identical analytical methods.
- Provide a robust snapshot of the offspring's metabolic profile at birth.
- A large number of maternal and neonatal metabolic biomarkers were investigated and novel associations found.

Limitations

- Single site design and its focus on a specific population with a high prevalence of obesity and diabetes, which may limit generalizability.

SUMMARY

Maternal Prenatal Glycemia and Fetal Metabolic Biomarkers



- **Maternal GlyHB** associated with fetal GlyHB & metabolic markers.
- Associations independent of pregestational BMI.
- Prenatal GlyHB ≈ 1-h GLT for fetal GlyHB.

Prenatal GlyHB is a clinically relevant marker of sustained in-utero glycemic exposure.

Thank You

Acknowledgments

- We wish to thank the study patients for their participation.
- We also acknowledge the laboratory staff at NIDDK, Phoenix Research lab **and**
- The Department of Laboratory Medicine, ***Dr. Sack's Lab***, NIH Clinical Center, Bethesda, MD, for their assistance with biomarker analysis.
- NIDDK IRP for overall support

DECRS Lab, NIDDK, Phoenix