Lactation and Future Risk of Cardiometabolic Diseases in Women

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Background - Lactation and Health Risks in Women

Excess Health Risk for Women Associated with Not Breastfeeding (AHRQ Report 2010)	
Health Outcomes	Excess Risk %
Breast cancer	4
Ovarian cancer	27

- ***Insufficient/limited data to estimate excess risk for type 2 diabetes and cardiovascular disease in women***
- **Cancer – search for genetic markers: estrogen receptors; long latency period from exposure for cancer**

Lactation Association with Metabolic and Cardiovascular Risk Factors and Disease Outcomes in Women

Objectives:

1. ***Describe and evaluate the evidence basis for lactation* and future** **cardiometabolic disease in women (i.e., The Metabolic Syndrome, Diabetes, Hypertension and Cardiovascular disease).**

2. ***Discuss the importance of antecedent cardiometabolic risk factors to causal inferences*** **in lactation and cardiometabolic disease risk across the childbearing years.**

3. ***Identify the contribution of pregnancy-related risk factors*** **(i.e., gestational diabetes, HDP) as early harbingers of cardio-metabolic disease risk in women, and research gaps.**

Pregnancy and Lactation – A Reproductive Continuum for Risk of Diabetes and Cardiovascular Disease in Women

- ***Pregnancy and lactation form a single continuum*** *within the reproductive cycle where alterations in physiologic demands may have lasting consequences for future metabolic and cardiovascular disease outcomes in women.*

- *The **postpartum period** may be <u>a critical period</u> for early disease prevention in women, with **lactation** playing a prominent and unique role within a limited time window.”*

Windows Into Early Cardiometabolic Risk

The Continuum From Before, During, and After Pregnancy

Before conception

Preconception Risk

Obesity, Metabolic Subclinical Risk

Dyslipidemia
Prediabetes, Diabetes, Hypertension

Pregnancy

Metabolic Stress

Superimposed on Risk

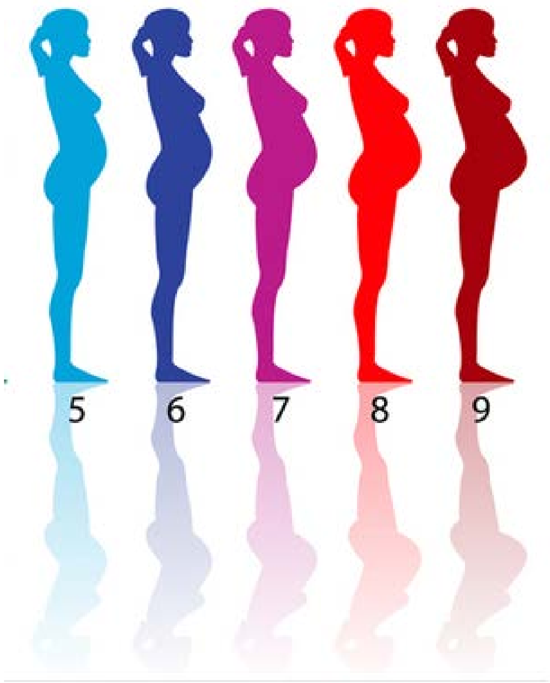
Universal screening for Gestational Diabetes, Preeclampsia, HTN
Complications/outcomes

Postpartum/ Postnatal

Lactation –Milk Production

Higher Energy demands;
Mobilizes fat mass
Cardiometabolic risk factors
Less atherogenic lipids,
Glucose, insulin, Diabetes
Lasting effects on disease?

Normal Pregnancy Metabolic Demands



– Blood lipids

+200% TG, +50% LDL-C

– Insulin resistance

(1.5-fold insulin secretion)

– Accelerated starvation – wider glycemic excursions

– Fat mass gain (+2-6 kg): (subcutaneous + visceral)

– Greater Inflammation

Normal Cardiovascular Adaptations of Pregnancy

Hemodynamic parameter	Normal Changes	Manifestation
Blood volume	+ 40-50%	Hemodilution
Red cell mass	+ 25%	Physiologic anemia
Heart rate	+ 10-15 beats/min	Work
Cardiac Output	+ 30-50%	Increased size
Blood pressure	- 10 mm Hg	Mid gestation
Systemic vascular resistance	----------	Placental perfusion

Pregnancy-related Complications and Future Cardiometabolic Diseases in Women

- Pre-pregnancy **Obesity** (25% of U.S. women)
- **Gestational Diabetes Mellitus – GDM phenotypes**

  Glucose intolerance with first recognition during pregnancy

  (7 - 8%) 2-step method; 3-hr 100 g OGTT

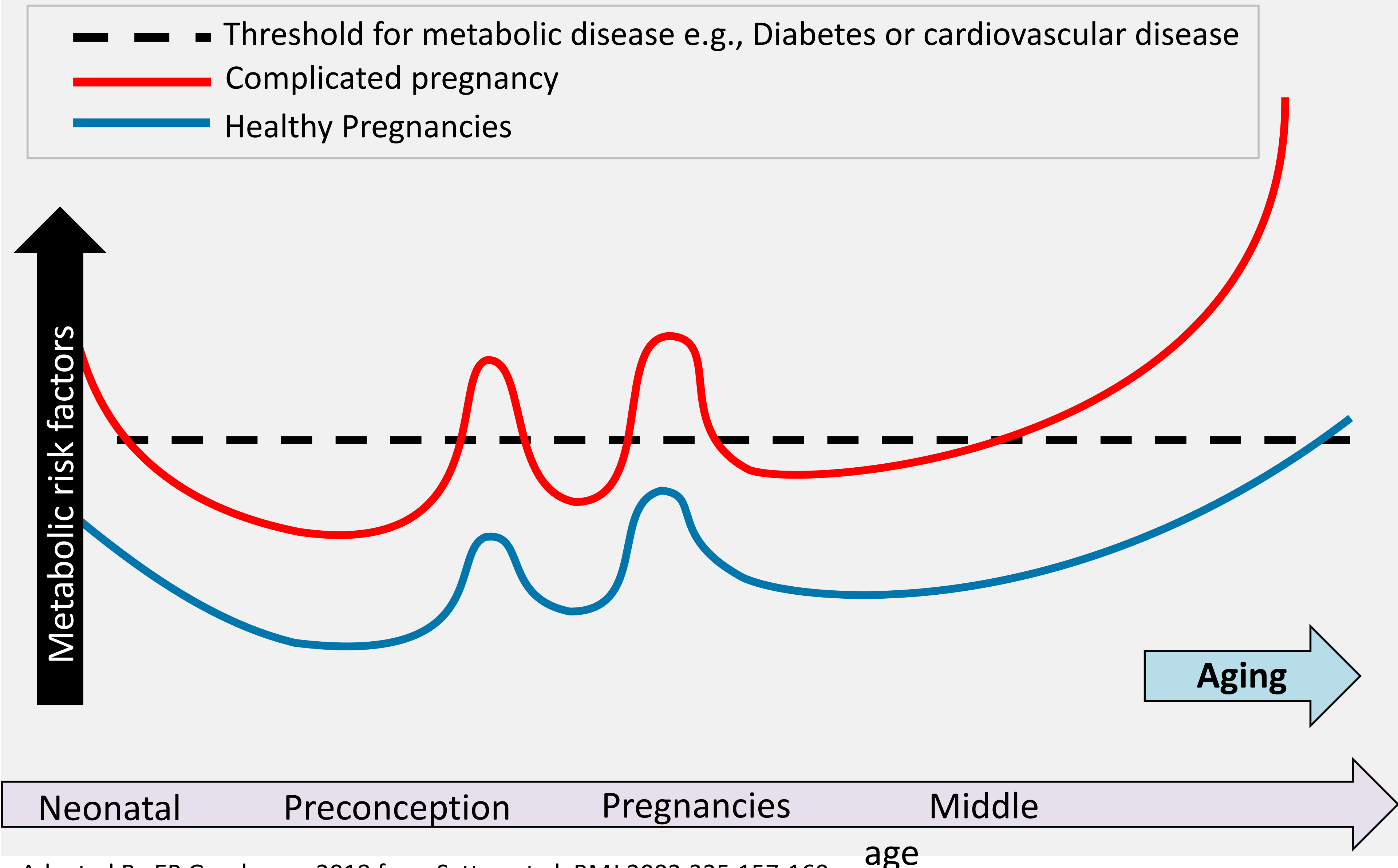
  (18 - 20%) 1 step method; 2-hr 75 g OGTT

- **Hypertensive** Disorders of Pregnancy (3-5%)

  Preeclampsia/eclampsia, Gestational Hypertension

  Pre-gestational hypertension; superimposed

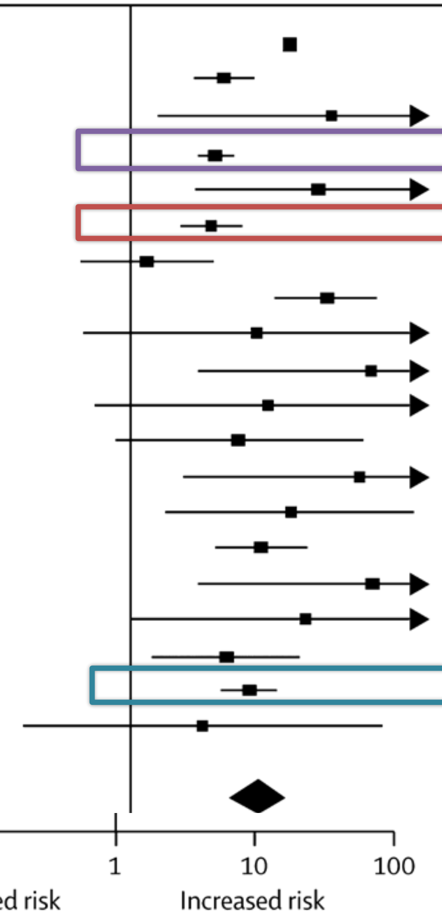
Life Course Model Reproductive Exposure and Disease Risk



Adapted By EP Gunderson 2018 from Sattar, et al. BMJ,2002:325:157-160

Bellamy, et al. Lancet 2009, Meta-analysis GDM and Risk of Type 2 Diabetes in Women; Summary Relative Risk = 7.4 (1.3 - 47.3)

	Country	T2DM/GDM	T2DM/no GDM	Relative risk (95% CI)
Feig et al,[18] 1995–2002	Canada	2874/21 823	6628/637 341	12·66 (12·15–13·19)
Lee H et al,[15] 1995–97	Korea	71/620	22/868	4·52 (2·83–7·21)
Madarasz et al,[21] 1995	Hungary	21/68	0/39	24·93 (1·55–400·64)
Gunderson et al,[22] 1985–206	USA	43/166	150/2242	3·87 (2·87–5·22)
Vambergue et al,[23] 1992	France	53/295	1/111	19·94 (2·79–142·47)
Lee A et al,[24] 1971–2003	Australia	405/5470	16/783	3·62 (2·21–5·93)
Ferraz et al[17]*	Brazil	6/70	7/108	1·32 (0·46–3·78)
Krishnaveni et al,[25] 1997–98	India	13/35	8/489	22·70 (10·09–51·08)
Morimitsu et al,[26] 1999–2001	Brazil	7/23	0/11	7·50 (0·47–120·11)
Järvelä et al,[5] 1984–94	Finland	23/435	0/435	47·00 (2·86–771·65)
Albareda et al,[27] 1966–93	Spain	44/696	0/70	9·07 (0·56–146·25)
Åberg et al,[28] 1991–99	Sweden	21/229	1/61	5·59 (0·77–40·66)
Linné et al,[16] 1964–65	Sweden	10/28	0/52	38·38 (2·33–631·74)
Bian et al,[29] 1964–65	China	15/45	1/39	13·00 (1·80–93·93)
Ko et al,[30] 1988–95	China	105/801	7/431	8·07 (3·79–17·19)
Osei et al,[31] 1990–91	USA	10/15	0/35	47·25 (2·95–757·28)
Damm et al,[32] 1978–85	Denmark	33/241	0/57	16·06 (1·00–258·06)
Benjamin et al,[33] 1961–88	New Mexico	14/47	3/47	4·67 (1·43–15·21)
O'Sullivan,[34] 1954–60 and 1962–70	USA	224/615	18/328	6·64 (4·19–10·52)
Persson et al,[35] 1961–84	Sweden	5/145	0/41	3·16 (0·18–55·76)
Total		**3997/31 867**	**6862/643 588**	**7·43 (4·79–11·51)**



Test for heterogeneity: τ^2=0·50, χ^2=126·67, df=19 (p<0·0001), I^2=85·0% (95

Test for overall effect: Z=9·39 (p<0·0001)

GDM, Type 2 Diabetes and CVD Outcomes

- **Type 2 Diabetes Associated with 2 to 4-fold higher risk of CVD**

- **GDM association with CVD risk for women without T2 Diabetes**

Ontario, Canada (Retnakaran et al. 2017, Diabetes Care)
White women
RR = **1.30**, 95%CI; (1.07 to 1.59)

NHS II Women (Tobias, et al. 2017, JAMA Internal Med)
White women
RR = **1.30**, 95%CI (0.99 to 1.71); Lifestyle adjusted 1.24

-- Data collection via surveys and/or hospital administrative data only
-- No systematic biochemical diabetes testing of women < age 45 y
-- Analysis does not include lactation duration history.

Lactation and Lower Cardiometabolic Disease: Hypothesis: Return to preconception metabolic state

During Lactation - Benefits
"Reset Maternal Metabolism"

- More rapid decline Triglycerides and LDL-C,
- Preserves higher HDL-C,
- Lower blood glucose,
- Lower fasting insulin,

Energy Balance:

- +298 kcal/day energy for milk production;
- Modest weight loss (1-2 kg) or weight gain – variable;
- Regional fat mobilization -- Hip and thigh

Gunderson, DOR 2020

Research Study Design – Limitations in Causal Inferences Lactation and Lasting Effects on Disease Risk in Women

1. Randomized trials – Limitations

- Individual randomization not desirable or ethical,
- Cluster randomization limitations – expensive, low statistical power clusters, n=30 clinics (cluster),
- Lacks an "unexposed" group, (all women breastfeed)

2. Prospective Epidemiologic Population-based

- Most self-report of disease events only
- Retrospective reproductive exposures
- No antecedent biochemical risk factor measurements
- Almost none have data on pregnancy complications

Lifetime Lactation and Odds of Hypertension in Women Meta-Analysis, *Qu et al., Breastfeeding Medicine, 2018*

7 published studies, n=444,759 women, self-report outcomes		
Lifetime duration	Pooled OR	95% CI
Any vs Never	0.93	(0.91, 0.95)
Never	1.00	referent
>0 to 6 months	0.88	(0.84, 0.93)
>6 to 12 months	0.89	(0.86, 0.92)
>12 months	0.88	(0.84, 0.93)

Weak inverse association (**7 to 12% reduction** in odds of HTN)

Threats to Internal Validity:

- **5 of 7 studies cross-sectional** or case-control (primarily self-report)
- **No graded association** with higher BF duration (biologic plausibility?)
- **No pregnancy complications or antecedent risk factors**
- Older Ages at follow up (**40 to 81**, 20 to 85, **50 to 79**, 20 to 60)

Lactation and HRs (95%CIs) CVD Hospitalization and Mortality New South Wales, Australia, *Nguyen et al. JAHA 2019*

Prospective 6-y follow up, n= 100,864, Linkage hospital/death records		
Breastfeeding duration	**CVD hospitalized**	**CVD Mortality**
Ever vs Never	**0.86 (0.78, 0.96)**	**0.66 (0.49, 0.89)**
None	1.00	1.00
< 6 months per child	**0.86 (0.71, 0.97)**	**0.69 (0.51, 0.94)**
>6 to 12 months per child	**0.85 (0.75, 0.97)**	**0.59 (0.41, 0.84)**
>12 months per child	**0.89 (0.71, 1.12)**	**0.67 (0.28, 1.57)**

Covariates: (self-report diabetes, or hypertension, lifestyle, SES, BMI)

Older age women, mean 60 years, Baseline: 2006-2009 questionnaire, self-report no CVD diagnosis or hospitalization in previous 6 years;

Average breastfeeding duration per child (months), 5.4 mos

No graded associations to substantiate biologic plausibility.

Lactation and HTN, CVD Risk Factors, CHD, CVD Events in Women: Prospective Studies

Prospective Follow up of Disease Events Self-report, ICD-10 Incident CVD, Stroke, or CVD Risk Factors	Relative Risk Reduction >12 mos., >4*mos. Or Ever vs. Never	Baseline Age y (Median)
HUNT Study (CVD Mortality)	**45%**	< 65 y
EPIC-CVD (In-person) CHD incidence	**29%**	53 y
Women's Health Initiative (Stroke)	**23%**	> 65 y
Nurses' Health Study (NHS) CHD	**13%**	40-65 y
China Kadoorie Biobank (CVD / Stroke)	**9% or 8%**	30-79 y

Women's Health Initiative (Risk Factors)	9 to 19%	63 y
Nurses' Health Study (NHS II) HTN	**22%**	51 y
PROBIT (cluster randomized) BP at 11.5 y	**No diff SBP (ns)**	38 y
Danish National Cohort (HTN or CVD)	**20-30%***	30 y

Risk Factors = hypertension, self-reported diabetes, hyperlipidemia, and prevalent and incident cardiovascular disease; All studies conducted retrospective assessment of Lactation history in women, except for PROBIT; BF >7 to 12 months, WEAK ASSOCIATIONS OLDER AGES

Breastfeeding and Risk of CHD (EPIC)

Peters et al. Eur J Prev Cardiol. 2016 November ; 23(16): 1755–1765

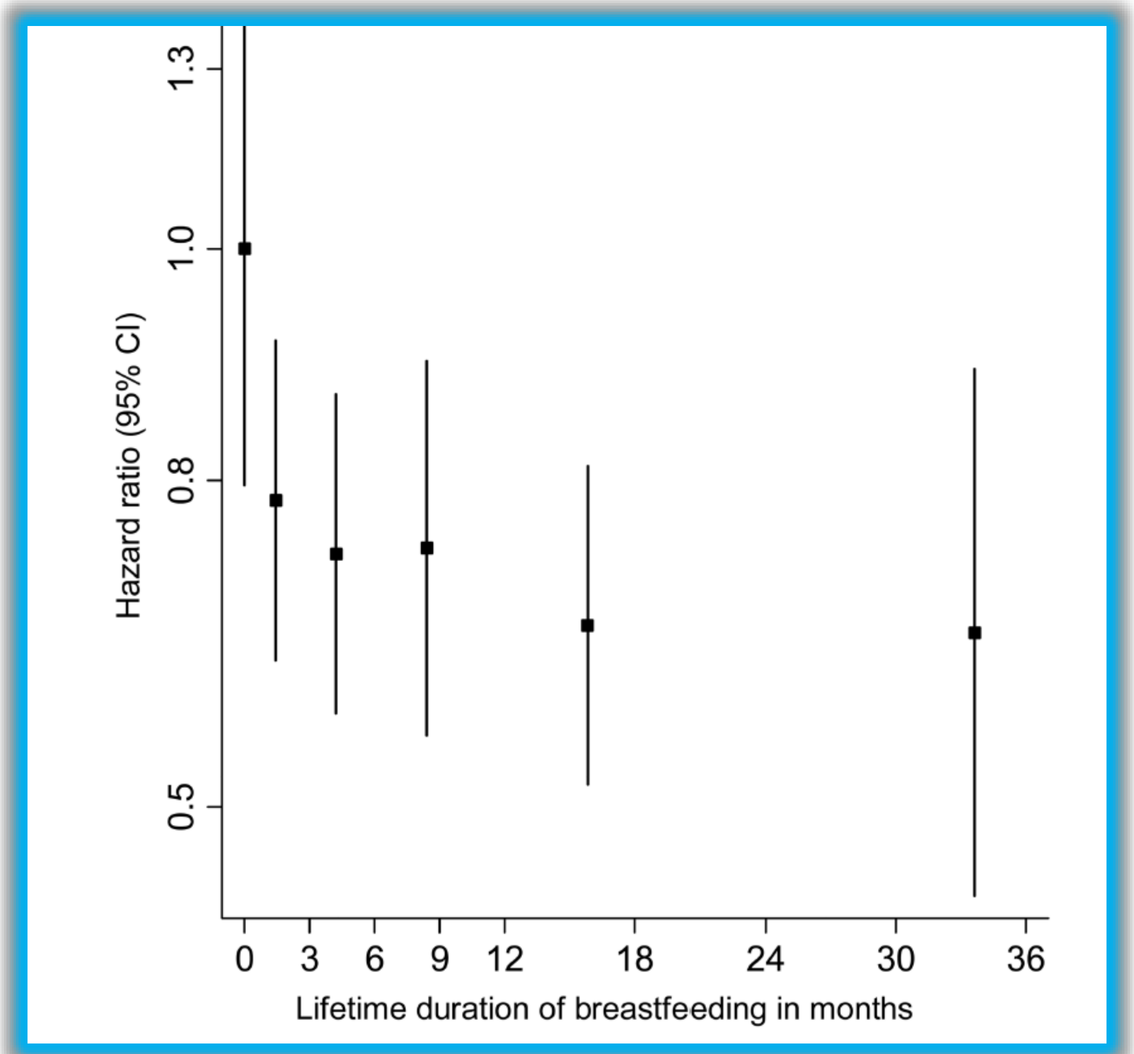


Figure 2. Adjusted hazard ratios (with group-specific 95% confidence intervals) for incident coronary heart disease associated with lifetime duration of breastfeeding in parous women. Categories are never, 0-<3 months, 3-<6 months, 6-<12 months, 12-<23 months, and 23 months or more. Adjusted for age at study entry, centre, level of attained education, smoking status, number of livebirths, high blood pressure, HDL cholesterol, total cholesterol, history of diabetes mellitus, and BMI.

Evidence for Lifetime Lactation (total months) and the Risk of Incident Type 2 Diabetes in Women

Prospective Studies Surveys, Self-report New Onset Diabetes Only	Relative Risk Reduction per 12 months	Baseline Age Median
Nurses' Health Study (NHS I)	15%	51 y
Women's Health Initiative (WHI)	5% to 7%	63 y
Shanghai Women's Health (SWHS)	3% to 4%	52 y
	per 6 months	
Northern European EPIC	20% (NS)	47 y

None of these studies assess history of GDM, except 1 retrospectively in NHS

(Stuebe et al., JAMA 2005, Villegas et al., Diabetologia 2008; Jager et al. Diabetologia 2014)

Research Study Methodology -- Limitations of the Body of Epidemiologic Evidence

Longitudinal Epidemiologic Studies of Lactation and T2D / CVD:

1. Internal Validity:

- **No antecedent metabolic or CVD risk** (before lactation),
- Self-report (diabetes, CVD);
- Women <45 y are **<u>not routinely</u>** tested for diabetes or CVD risk factors;
- **Exclusion of** young, **high risk women before baseline;**

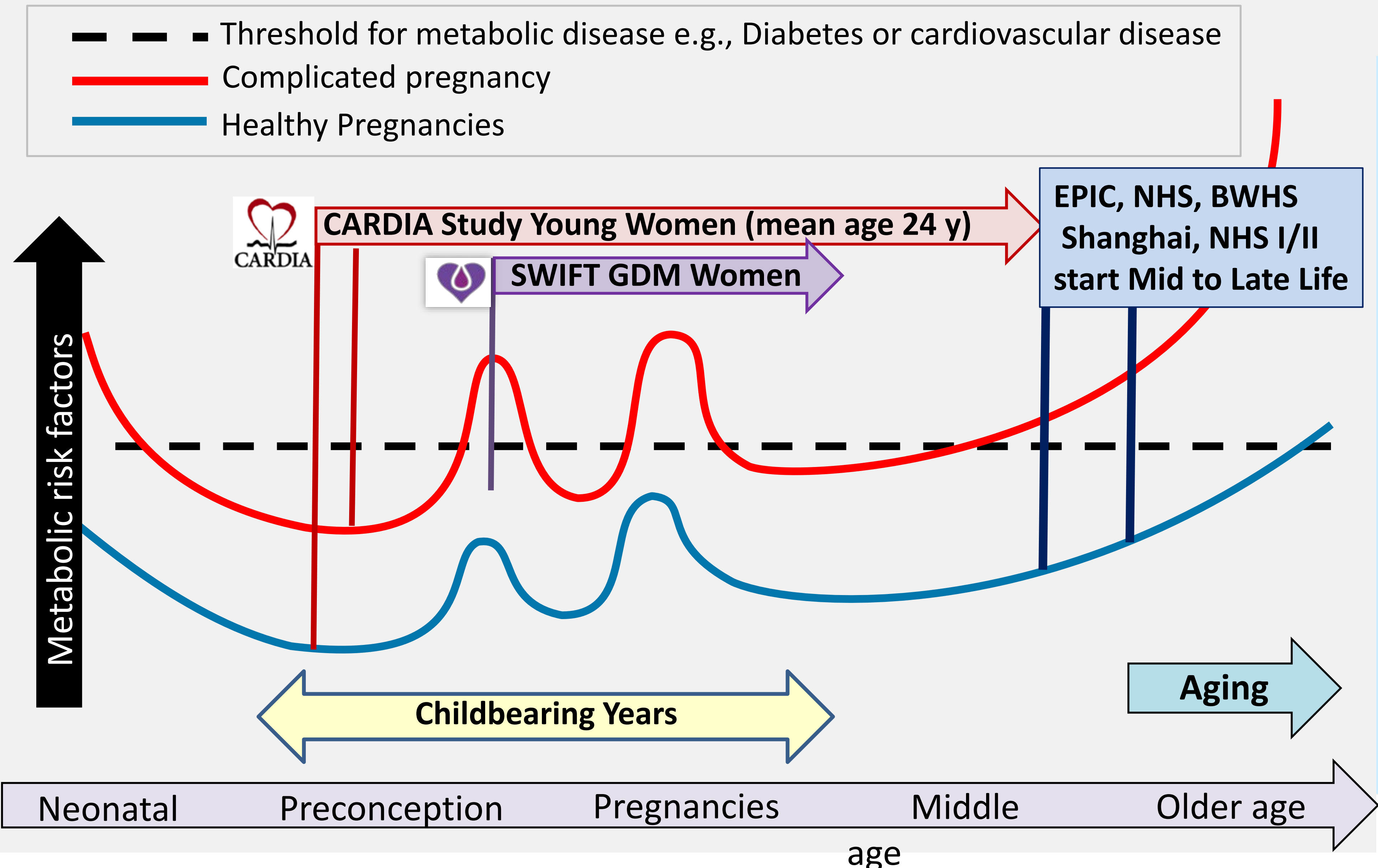
• **-** Weak or no graded association CVD (i.e., dose-response) Variable across cohorts, and by age subgroups

- Unknown pregnancy complications, or very low **GDM in older cohorts (never tested)**;

2. Limited **External Validity:**

- Northern European Ancestry or Asian women

Life Course Model Reproductive Exposure and Disease Risk



Adapted By EP Gunderson 2018 from Sattar, et al. BMJ,2002:325:157-160

Importance of Longitudinal Studies Across the Childbearing Years and Assessment of Antecedent Risk Factors -- Life Course Perspective

Evidence for Causal Inferences and Reduce Reverse Causation:

1. **Longitudinal studies that measure Antecedent metabolic risk factors both BEFORE and AFTER lactation (repeated measurements).**

2. **Establish equivalency of maternal risk status before lactation to address potential confounding and reverse causation;**

3. **Measure persistent effects rather than previous metabolic risk status or pregnancy complications that may determine lactation;**

4. **Preserve the unexposed group (no lactation); Randomization to "lactation support" *eliminates the "unexposed" group*, and underestimate effect,**
5. **Systematic testing for diabetes with research OGTTs -- repeated**

Examples of Studies with Robust Study Designs (Biochemical Data):
CARDIA risk factors measured Before Pregnancy AND After Lactation
SWIFT risk factors measured During Pregnancy AND After Lactation

Causal Inferences, Biological Plausibility, Temporality, and Selection bias and Ascertainment bias.

Research

JAMA Internal Medicine | Original Investigation

Lactation Duration and Progression to Diabetes in Women Across the Childbearing Years
The 30-Year CARDIA Study

Erica P. Gunderson, PhD, MPH, MS; Cora E. Lewis, MD, MSPH; Ying Lin, MS; Mike Sorel, MS; Myron Gross, PhD; Stephen Sidney, MD, MPH; David R. Jacobs Jr, PhD; James M. Shikany, DrPH; Charles P. Quesenberry Jr, PhD

IMPORTANCE Lactation duration has shown weak protective associations with incident diabetes (3%-15% lower incidence per year of lactation) in older women based solely on self-report of diabetes, studies initiated beyond the reproductive period are vulnerable to unmeasured confounding or reverse causation from antecedent biochemical risk status, perinatal outcomes, and behaviors across the childbearing years.

OBJECTIVE To evaluate the association between lactation and progression to diabetes using biochemical testing both before and after pregnancy and accounting for prepregnancy cardiometabolic measures, gestational diabetes (GD), and lifestyle behaviors.

Coronary Artery Risk Development in Young Adults

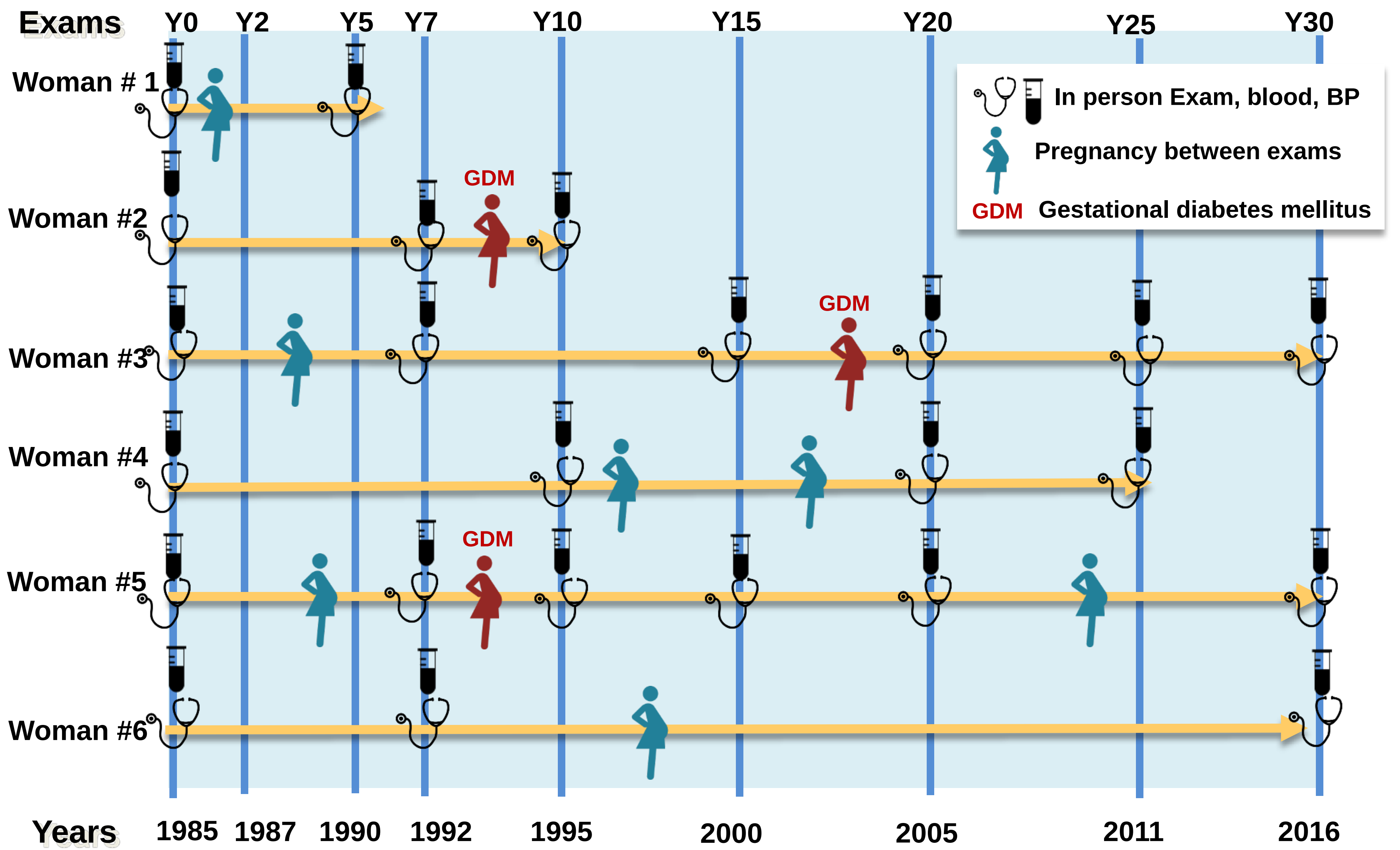
CARDIA

Cardiovascular Risk Factors and Childbearing 30-Year Prospective Cohort (1986-2016)

U.S. Multi-Center, 50% Black and White Women; (18-30 years of age, n= 2,787)

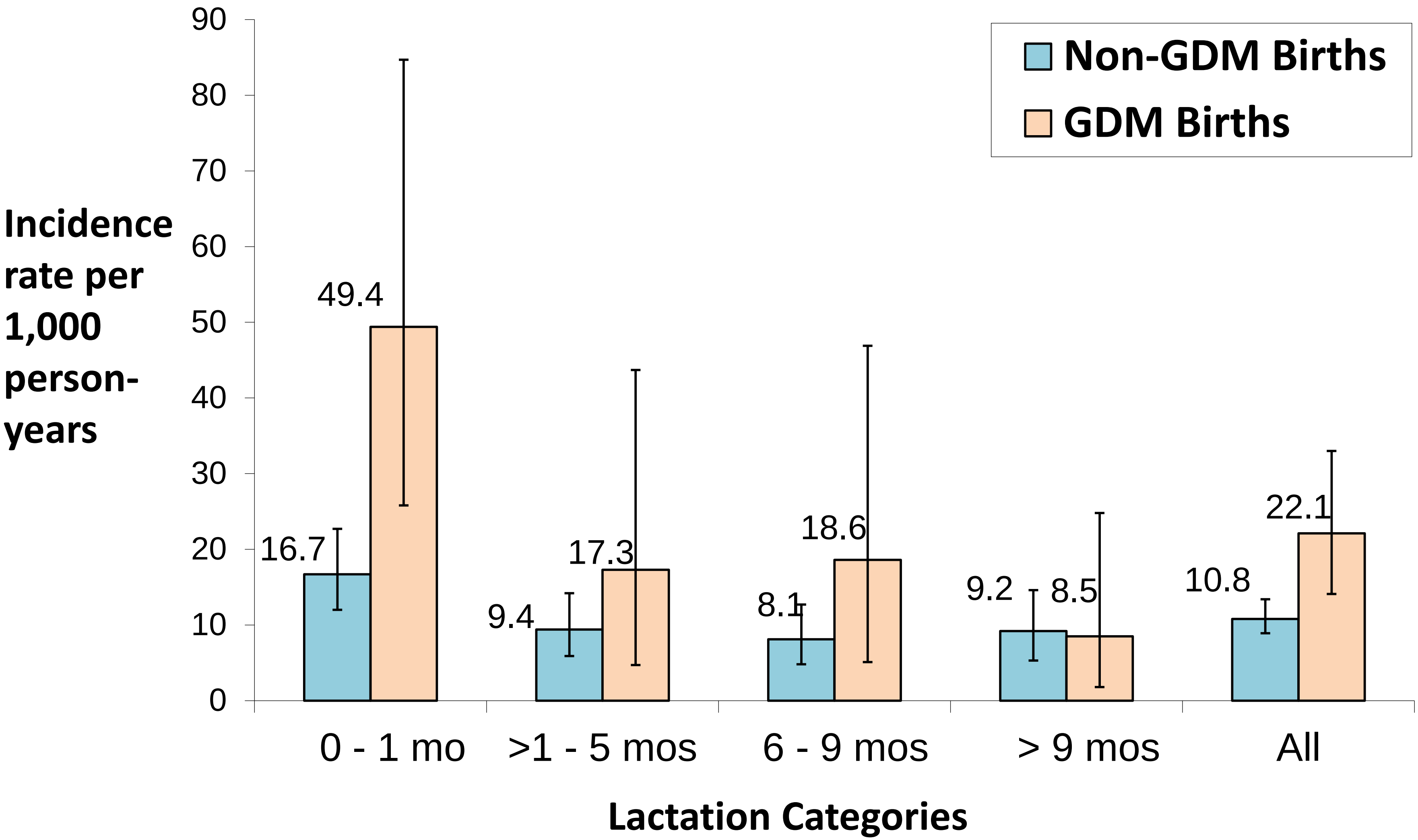
4 Centers: Alabama, Chicago, Minnesota, Oakland

9 Exams in 30-Year Follow up (every 2-5 years) (1986-2016) in Women age 18-30 y at baseline



Lactation Duration and Incidence of the Metabolic Syndrome, 20-Year Follow Up

Gunderson, et al. Diabetes, 2010



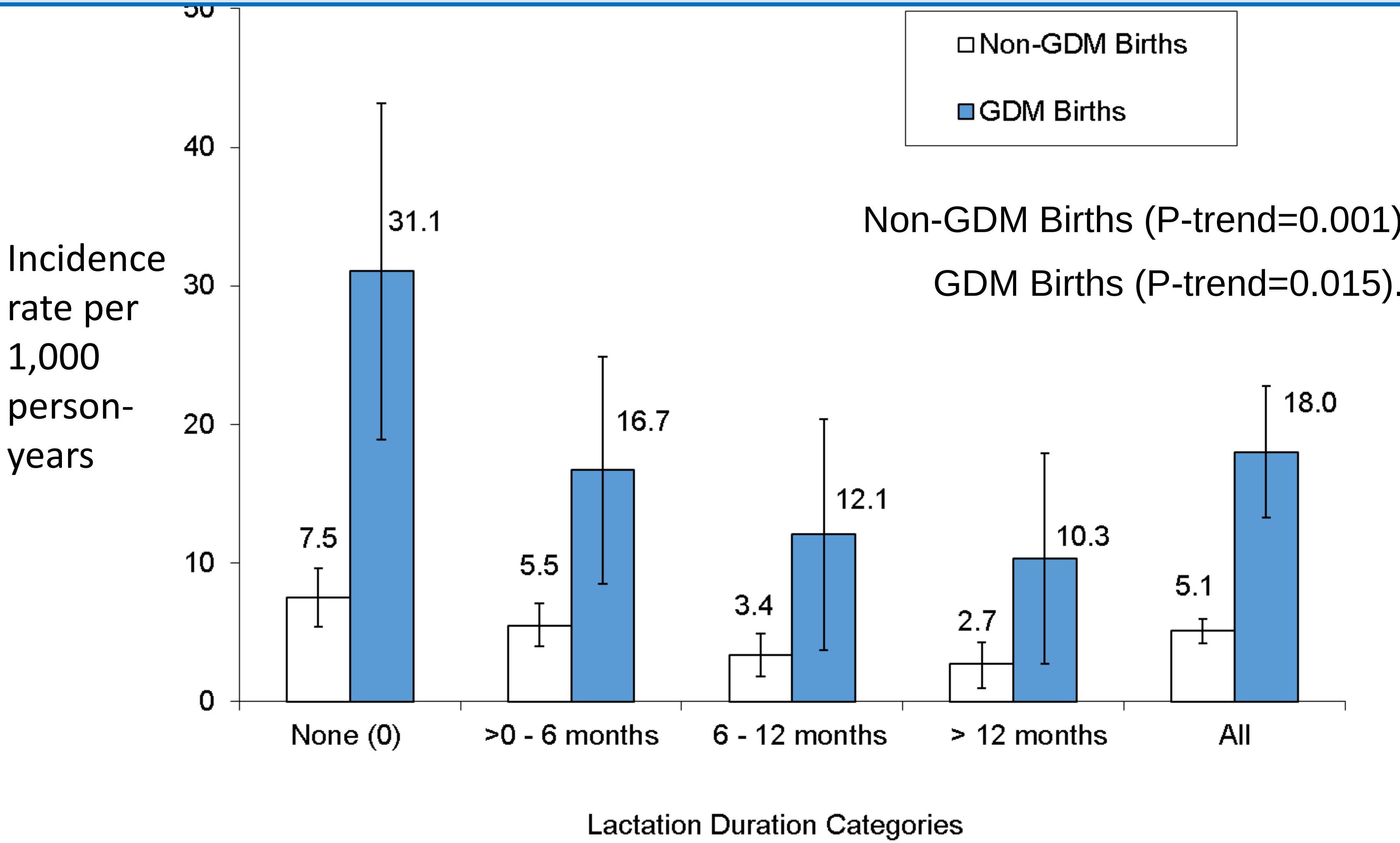
CARDIA 30-Year Follow Up: Antecedent Risk Factors, Lifestyle and Follow Up Characteristics Associated with Lactation Duration

Characteristics n = 1,238 women	Time-Dependent Lactation Categories				
	None (n = 322)	> 0 to 6 months (n = 418)	> 6 to 12 months (n = 268)	>12 months (n = 230)	P-value
Baseline Year 0:	Mean (SD), N (%) or Median (IQR) †				
Race (Black)	252 (78)	215 (51)	93 (35)	55 (24)	<.001
Parity (Nulliparous)	184 (57)	141 (34)	66 (25)	44 (19)	<.001
Age (years)	23 (4)	24 (4)	24 (4)	24 (4)	0.001
BMI (kg/m^2)	25.3 (6.3)	23.6 (4.7)	23.3 (4.4)	22.2 (3.7)	<.001
Waist circumference (cm)	76 (13)	72 (10)	71 (9)	70 (8)	<.001
Fasting Glucose, mg/dL	79 (8.3)	79 (7.8)	80 (7.2)	79 (7.4)	0.06
HDL-C, mg/dL	54 (13)	56 (12)	58 (13)	58 (12)	<.001
HOMA-IR †	1.9 (1.7)	1.8 (1.3)	1.6 (1.3)	1.5 (1.2)	<.001
Follow Up to Year 30:	Mean (SD) or N (%)				
Family history of Diabetes	172 (53)	188 (45)	119 (44)	83 (36)	<.001
History of GDM (ever)	43 (13)	43 (10)	34 (13)	35 (15)	0.30
Dietary Quality Score	59 (10)	68 (11)	72 (11)	72 (10)	<.001
Weight change, kg	20.7 (17.1)	19.6 (16.3)	15.8 (15.6)	15.5 (15.6)	<.001
Post-menopausal	166 (52)	230 (55)	161 (60)	127 (55)	0.23

Gunderson, et al. *JAMA Internal Medicine*, 2018

Lactation Duration and Incidence Rates of Diabetes Mellitus across 30 Years Follow Up by GDM Status

Gunderson, et al. *JAMA Internal Medicine*, 2018



Relative Hazards (95%CI) of Incident Diabetes Mellitus During 30-Year Follow up (1986-2016) Among Lactation Duration Categories

Gunderson et al. JAMA Internal Medicine, 2018

Multivariate Models	Time-Dependent Lactation Duration Categories				
Relative Hazards (95% CI) of Incident Diabetes, n=1,238	**None (n = 322)**	**> 0 to 6 months (n = 418)**	**> 6 to 12 months (n = 268)**	**>12 months (n = 230)**	**p-value trend**
Model 1 = Unadjusted	1.00 Referent	0.60 (0.43, 0.83)	0.36 (0.23, 0.57)	0.29 (0.17, 0.49)	< 0.001
Model 2 = M1 + Adjusted for race time-dependent Parity & GDM status during follow up.	1.00 referent	0.74 (0.53, 1.04)	0.55 (0.34, 0.87)	0.45 (0.26, 0.80)	0.003
Model 3 = M2 + age, baseline BMI, waist circumference, fasting glucose) & family history of diabetes.	1.00 referent	0.84 (0.60, 1.20)	0.56 (0.35, 0.91)	0.50 (0.27, 0.90)	0.006
Model 4 = M3 + time-dependent physical activity score and diet quality score during follow up	1.00 referent	0.81 (0.56, 1.19)	0.53 (0.31, 0.88)	0.53 (0.29, 0.98)	0.010
Model 5 = M4 + time-dependent weight change during follow-up	1.00 referent	0.75 (0.51, 1.09)	0.52 (0.31, 0.87)	0.53 (0.29, 0.98)	0.012

No evidence of effect modification by race, GDM status, or parity groups. All p-values >0.16

Annals of Internal Medicine

ORIGINAL RESEARCH

Lactation and Progression to Type 2 Diabetes Mellitus After Gestational Diabetes Mellitus

A Prospective Cohort Study

Erica P. Gunderson, PhD, MPH, MS, RD; Shanta R. Hurston, MPA; Xian Ning, MS; Joan C. Lo, MD; Yvonne Crites, MD; David Walton, MD; Kathryn G. Dewey, PhD; Robert A. Azevedo, MD; Stephen Young, MD; Gary Fox, MD; Cathie C. Elmasian, MD; Nora Salvador, MD; Michael Lum, MD; Barbara Sternfeld, PhD; and Charles P. Quesenberry Jr., PhD, for the Study of Women, Infant Feeding and Type 2 Diabetes After GDM Pregnancy Investigators*

Background: Lactation improves glucose metabolism, but its role in preventing type 2 diabetes mellitus (DM) after gestational diabetes mellitus (GDM) remains uncertain.

Objective: To evaluate lactation and the 2-year incidence of DM after GDM pregnancy.

Design: Prospective, observational cohort of women with recent GDM. (ClinicalTrials.gov: NCT01967030)

Setting: Integrated health care system.

Participants: 1035 women diagnosed with GDM who delivered singletons at 35 weeks' gestation or later and enrolled in the Study of Women, Infant Feeding and Type 2 Diabetes After GDM Pregnancy from 2008 to 2011.

Measurements: Three in-person research examinations from 6

ratios of 0.64, 0.54, and 0.46 for mostly formula or mixed/inconsistent, mostly lactation, and exclusive lactation versus exclusive formula feeding, respectively (*P* trend = 0.016). Time-dependent lactation duration showed graded inverse associations with incident DM and adjusted hazard ratios of 0.55, 0.50, and 0.43 for greater than 2 to 5 months, greater than 5 to 10 months, and greater than 10 months, respectively, versus 0 to 2 months (*P* trend = 0.007). Weight change slightly attenuated hazard ratios.

Limitation: Randomized design is not feasible or desirable for clinical studies of lactation.

Conclusion: Higher lactation intensity and longer duration were independently associated with lower 2-year incidences of DM after GDM pregnancy. Lactation may prevent DM after GDM delivery.

Annals of Internal Medicine, December 2015,
SWIFT - Study of Women, Infant Feeding and Type 2 Diabetes after GDM Pregnancy

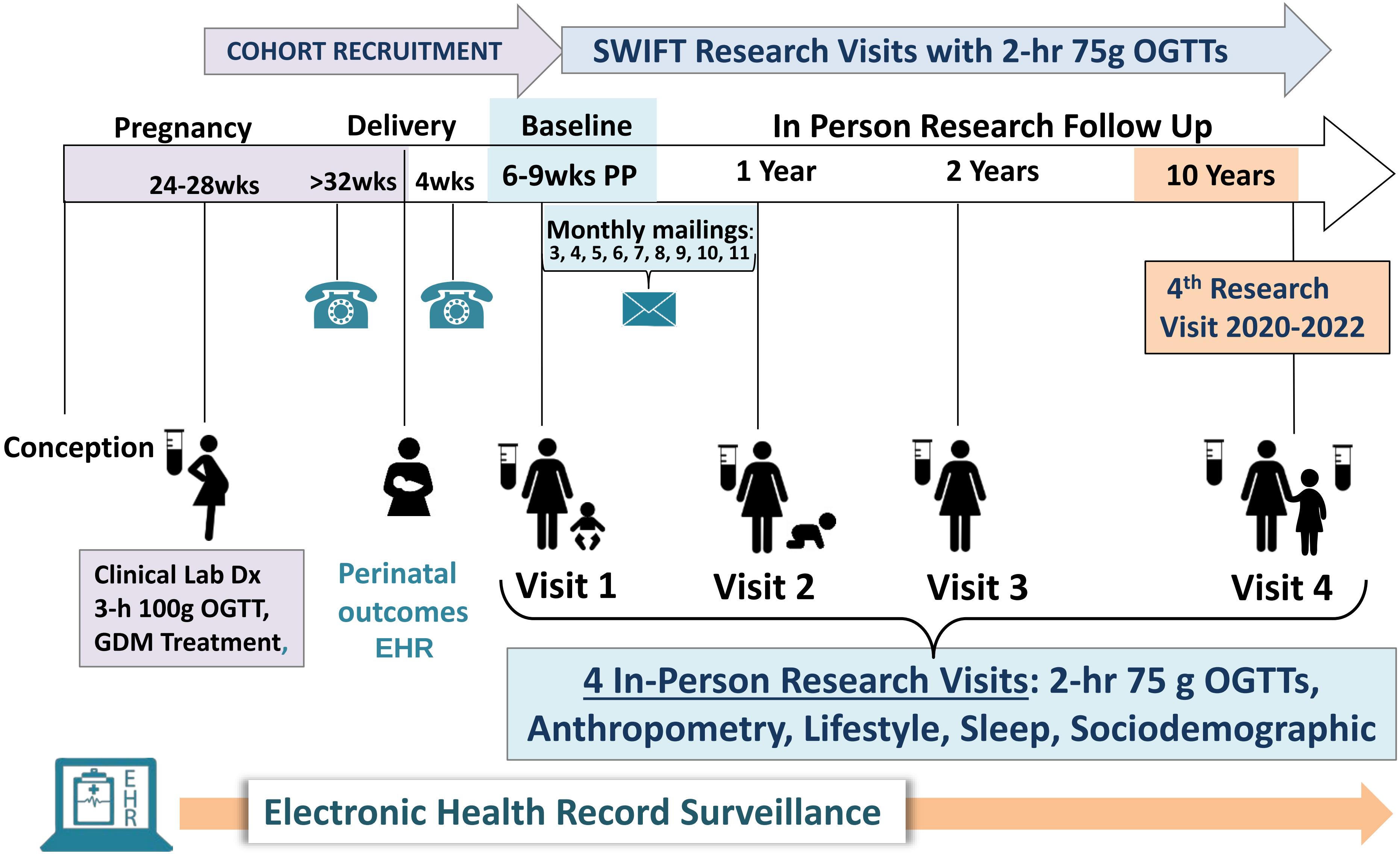
The Study of Women, Infant Feeding and Type 2 Diabetes After Gestational Diabetes

Mothers with GDM and their Infants

Longitudinal design from pregnancy

Glucose tolerance testing (2-h 75 g OGTTs) from 6-9 weeks through 2 years postpartum

Study Design: Longitudinal, Observational Pregnancy through 10 Years Post-baseline



Gunderson, EP; 2012 SWIFT Study Design;

SWIFT Moms & babies

Prospective GDM Postpartum Cohort Mothers and infants – longitudinal

Study Baseline

1,035 women with GDM with deliveries in 2008-2011

Research 2-hr 75 g OGTT at baseline 6-9 wks postpartum

GDM – All followed from early (6-9 wks) postpartum

1,010 women (No diabetes based on 2-h OGTT)

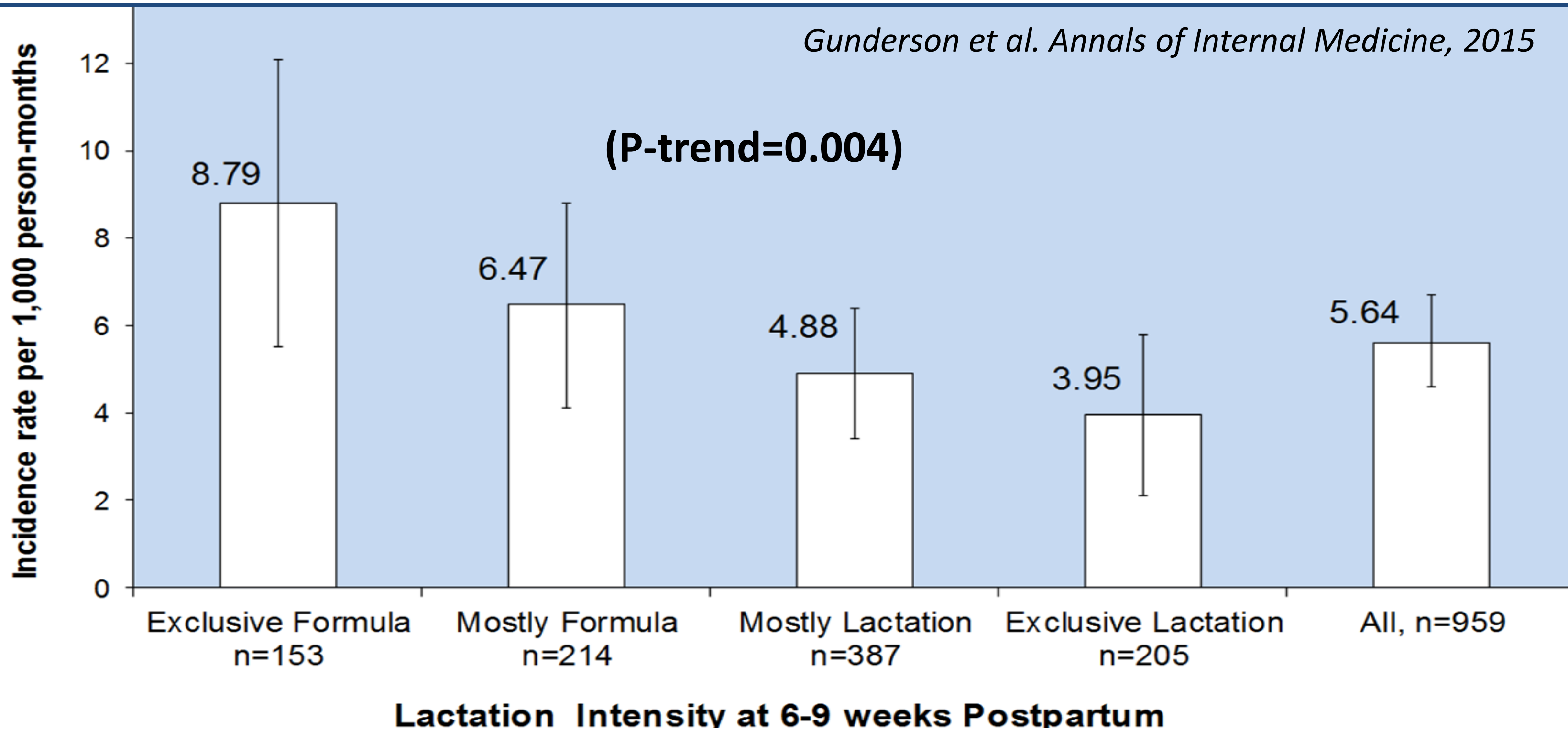
Annual Follow Up with Research OGTTs and EMR Lab

959 (95%) had annual 2-hr 75 g OGTTs and/or EMR Data

113 (12%) with incident DM in 2 years post-baseline

197 (19.7%) with incident DM up to 8 years post-baseline

Diabetes Incidence Rates (95%CI) per 1,000 person-months by Lactation Intensity Groups at 6-9 weeks Postpartum in Women with GDM



Lactation Intensity Groups	Sample, N	Incident DM, n	Person-months (p-mos)	Incidence rate, (n/p-mos)	(95%CI)
Exclusive formula	153	27	3,071	8.79	5.47-12.1
Mostly formula/mixed/inconsist	214	29	4,481	6.47	4.11-8.83
Mostly Lactation	387	40	8,191	4.88	3.37-6.39
Exclusive Lactation	205	17	4,300	3.95	2.07-5.83
All	959	113	20,043	5.64	4.60-6.68

Antecedent Risk Factors (Prenatal) among Lactation Intensity Groups at 6 to 9 weeks postpartum

Characteristics/prenatal n= 959 women	Exclusive FF	Mostly FF or Mixed	Mostly BF (≤6oz FF/d)	Exclusive BF	P-value
Mean (SD) or N (%)	N=153	N=214	N=387	N=205	
Pre-pregnancy BMI	31 (8)	30 (8)	29 (7)	28 (6)	<.001
3-hr OGTT z-score sum	0 (2.3)	0.3 (2.6)	0 (2.8)	−0.2 (2.6)	0.24
GDM Treatment, n %					0.89
Diet	108 (71)	141 (66)	263 (68)	143 (70)	
Oral meds	43 (28)	65 (30)	105 (27)	57 (28)	
Insulin	2 (1)	8 (4)	19 (5)	5 (2)	
Race/ethnicity, n %					<.001
Black race	22 (14)	19 (9)	20 (5)	11 (5)	
White (not Hispanic)	34 (22)	43 (20)	79 (20)	69 (34)	
Hispanic ethnicity	48 (31)	68 (32)	118 (31)	58 (28)	
Asian / other	49 (33)	84 (39)	170 (44)	67 (33)	
Family History DM, n %	70 (46)	103 (48)	204 (53)	96 (47)	0.89
Cesarean section delivery	61 (40)	74 (35)	113 (29)	57 (28)	<0.05

Gunderson et al. Annals of Internal Medicine, 2015

Relative Hazards (95%CI) of 2-Yr Incident Diabetes by Lactation Duration (n=113 Incident DM, N=959 Women GDM)

Gunderson et al. Annals of Internal Medicine, 2015

Time-Dependent Lactation Duration Categories

Weibull Regression: Proportional Hazards Models	Adjusted Hazards Ratio (95% CI) of Incident Diabetes				
	0 to 2 months N=189	**>2 to 5 months** N=190	**>5 to 10 months** N=208	**>10 months** N=372	**P-trend**
Age adjusted:	**1.00 Referent**	**0.64 (0.36-1.13)**	**0.44 (0.22-0.88)**	**0.38 (0.20-0.71)**	**0.0008**
++Maternal and Perinatal Risk Factors Newborn outcomes £	**1.00 Referent**	**0.55 (0.31-1.01)**	**0.50 (0.25-0.99)**	**0.43 (0.23-0.82)**	**0.007**
+Postpartum Lifestyle Behaviors §	**1.00 Referent**	**0.54 (0.30-0.99)**	**0.55 (0.28-1.09)**	**0.43 (0.22-0.82)**	**0.0096**
+Potential Mediator: Weight change: delivery to 1 Year	**1.00 Referent**	**0.48 (0.25-0.90)**	**0.65 (0.33-1.24)**	**0.47 (0.24-0.91)**	**0.037**

Addition of the following selected groups of covariates in succession to the age adjusted model: * Maternal and Perinatal Risk Factors: Race/ethnicity, Education, Pre-pregnancy BMI, GDM Treatment, Prenatal 3-hour 100 g OGTT z-score sum, Gestational age at GDM diagnosis, and Subsequent Birth (1 vs. 0). £ Maternal and Perinatal Risk Factors plus Newborn outcomes: LGA vs not LGA (referent), hospital length of stay > 3 days, and NICU admission. § All Covariates above Plus Postpartum Lifestyle Behaviors: Total physical activity (Met-hours per wk), Glycemic index and % Kcal from animal fat (>median). Note: Covariate data is complete except for lifestyle behaviors missing for 5 women and 1 Year weight change missing for 35 women

Summary of the Evidence
Lactation and Reduction in Type 2 Diabetes Risk in Women

<u>**Lactation (increasing intensity and duration) :**</u>

- **Better early postpartum** glucose tolerance after GDM, even obese women**.**

- **Biologic Plausibility - Graded and strong relative risk reductions in 2-year and 30-year** incidence of T2 diabetes in women (Both Non-GDM & GDM).

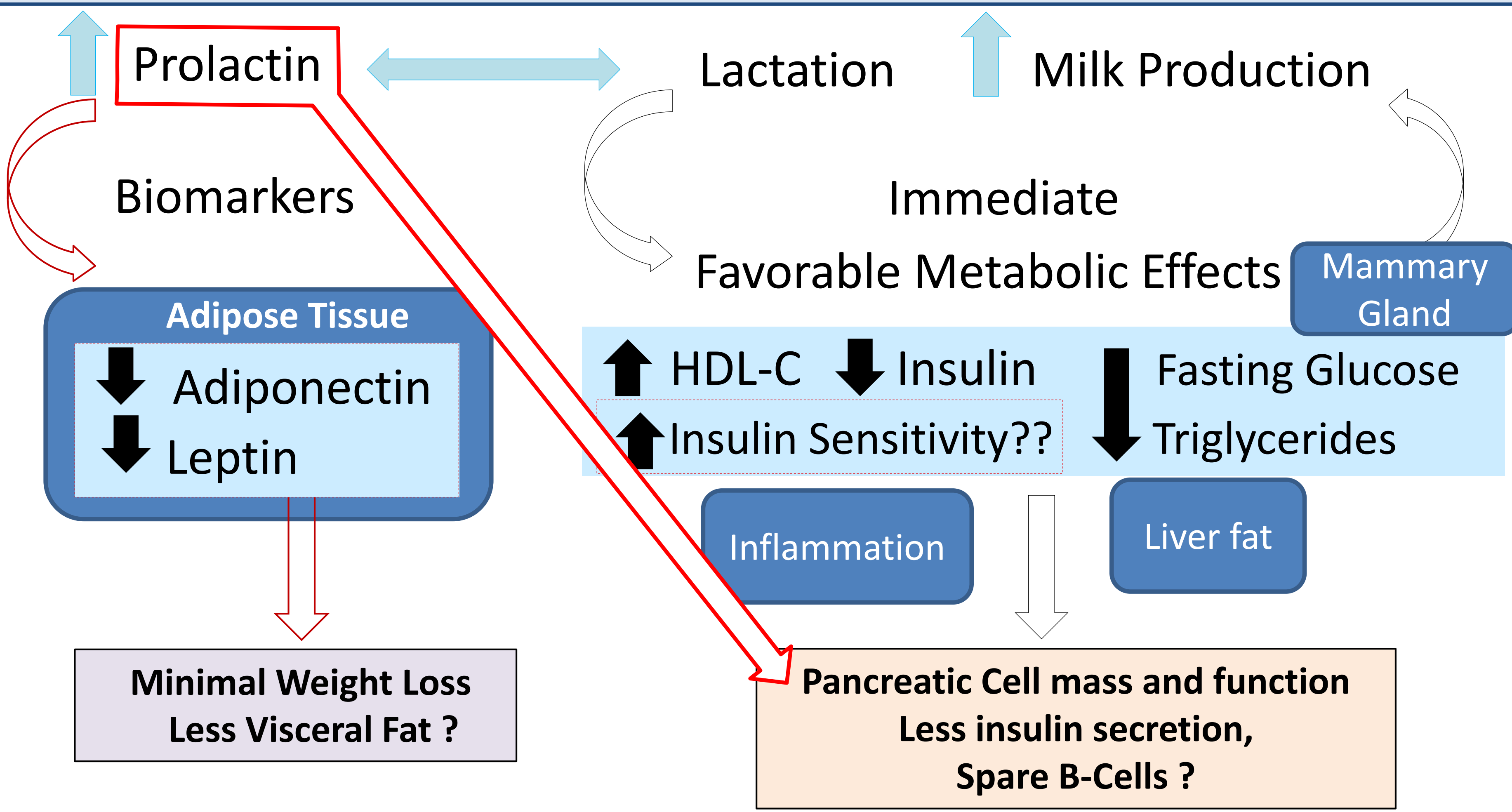
- **Persistent after accounting for "Antecedent Risk Factors" (Biochemical: GDM severity, blood glucose, insulin resistance, perinatal outcomes), and Follow up Behaviors: diet, physical activity, and Sociodemographic.**

- **Before, during and after** pregnancy and through later life

- **Antecedent metabolic risk** profiles **lessen potential for reverse causation**

Gunderson et al. Diabetes Care, 2012, Gunderson et al. Annals Internal Medicine, 2015, Gunderson et al. JAMA Internal Medicine, 2018

What is the Mechanism? Lactation May Counterbalance the Adverse Effects of Pregnancy



Lactation Metabolism and Return to Pre-pregnancy State

Gunderson et al. Metabolism. 2014 Jul; 63(7):941-50

Implications for Diabetes Prevention in Women
Lactation and the DPP Lifestyle have Similar Risk Reduction

DPP Lifestyle Intervention:

Randomized Mid-Life Adults with IGT to Diet and physical activity intervention

- **58% lower diabetes incidence for 5 kg weight loss**

CARDIA, SWIFT - Young Women Lactation and Risk of Diabetes:

Systematic testing for diabetes across childbearing years (short- and long-term)

- **Dose-response for lactation duration and intensity**
- **50% lower diabetes incidence: >5 months, or >6 months duration**

Lactation has Minimal effects on Weight Change

- **1-year weight loss + 1.2 kg greater exclusive BF vs. FF**
- **30-yr weight change with lactation similar for incident DM and not DM.**

Research gaps and Next steps

Mechanistic studies to elucidate pathways

Changes in biomarkers – metabolomics

Gunderson, et al. *JAMA Internal Medicine*, 2018

Implications for Prevention- Lactation and Health Outcomes in Women

<u>Bartick et al., 2017</u> **Annual excess deaths attributable to suboptimal breastfeeding total 3,340, 78% of which are maternal due to myocardial infarction (n = 986), breast cancer (n = 838), and diabetes (n = 473).**

"*Breastfeeding has a larger impact on women's health than previously appreciated*."

Research Needs and Recommendations
Lactation and Maternal Health Outcomes Cardiometabolic

<u>Research Rigor</u>

- ***Assess the longitudinal*** **continuum across childbearing years to *link changes in cardiometabolic risk factors prior to pregnancy or lactation and follow for*** **incident disease (new onset);**

- ***Crucial to Measure cardiometabolic risk factors prior to lactation in women in studying diabetes and cardiovascular disease*;**

- **Pregnancy complications included in future studies – *phenotype severity/ heterogeneity***
  - **GDM phenotype**
  - **Preeclampsia**
  - **Gestational hypertension**

- **Robust quantitative measures of lactation duration and intensity – dose-response evidence in studies across childbearing years,**
- **Mechanistic studies of post-weaning effects.**

CARDIA: Before, During and After Pregnancy up to 30 years

SWIFT: During and After Pregnancy up to 10 years

Preconception

Pregnancy

Postpartum

Prior Metabolic State

CARDIA

Measures blood Glucose, lipids, **Biomarkers**

- **before conception**
- **Inter - conception**

State of Metabolic Stress

SWIFT

GDM severity phenotype (treatment, z-score, GA Dx)

Longitudinal early PP

Serial measures (**n=1,035**)

Counterbalance of Lactation

CARDIA FBG, OGTTs across childbearing years

SWIFT prospective

Postnatal quantitative measures, OGTTs

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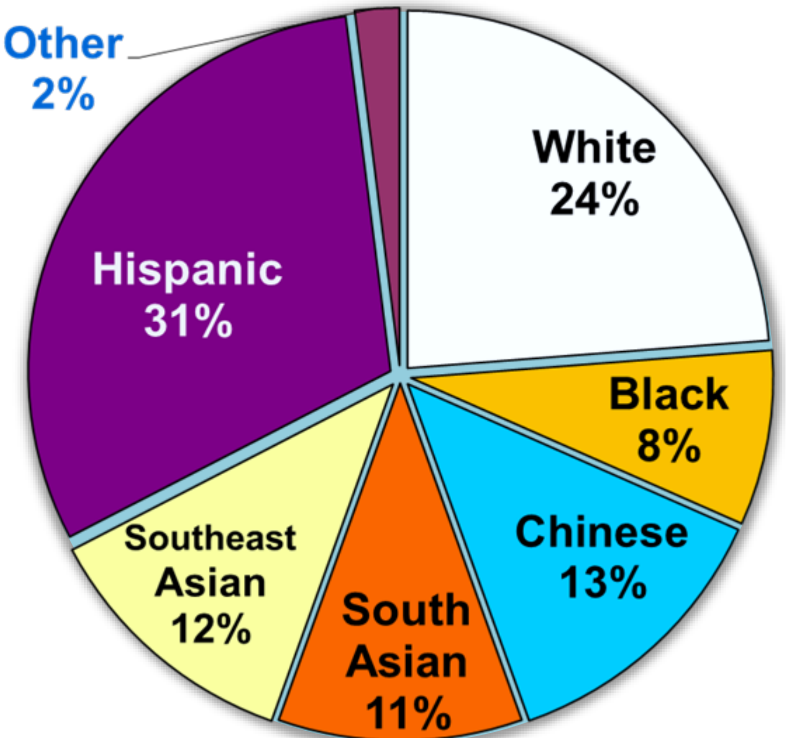
K01 DK059944 (GUNDERSON)

Racially Ethnically Diverse GDM Cohort

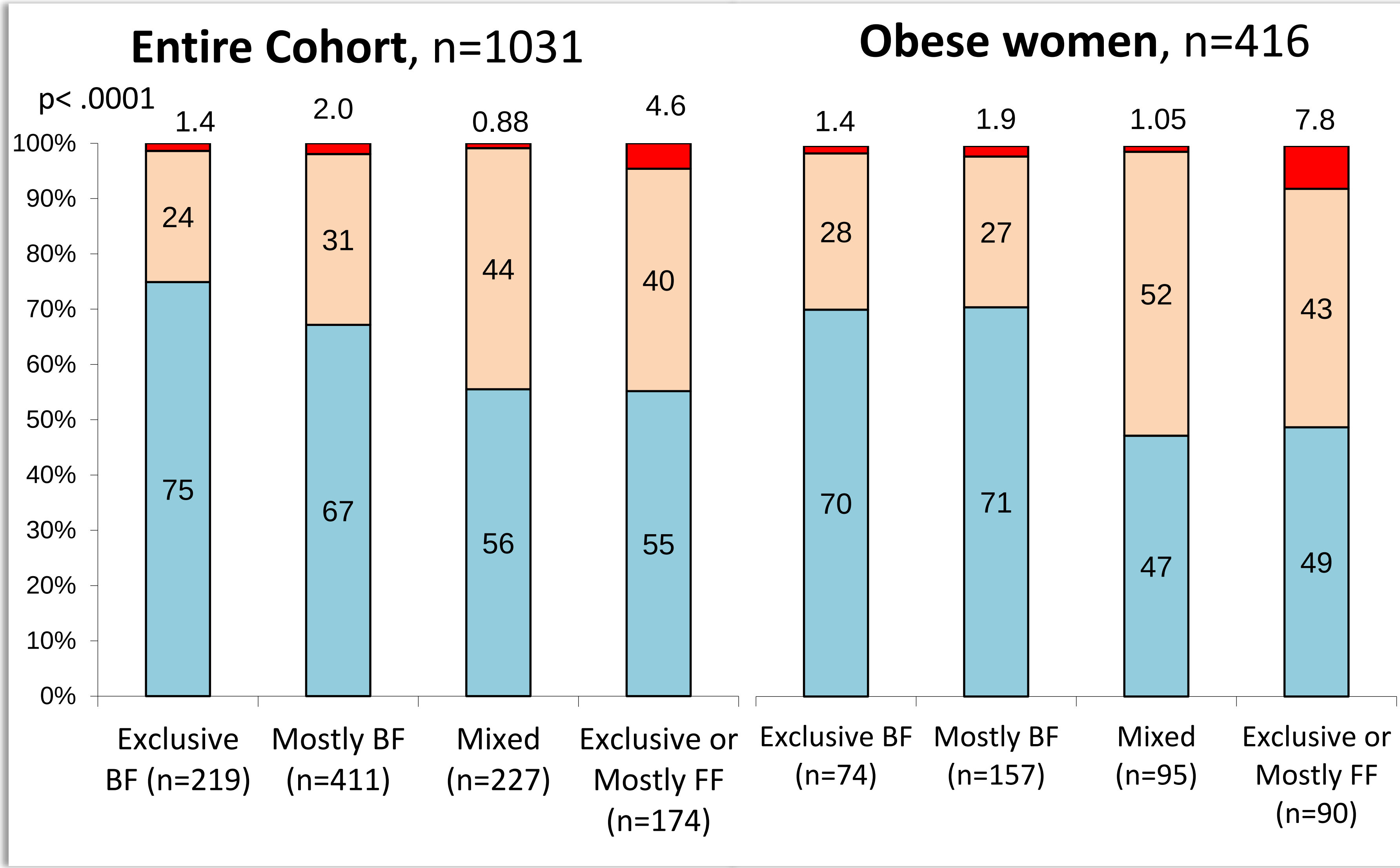
Singleton births ≥ 35 wks, GDM via 3-hr 100 g OGTT



Race/ethnicity
75% minority women

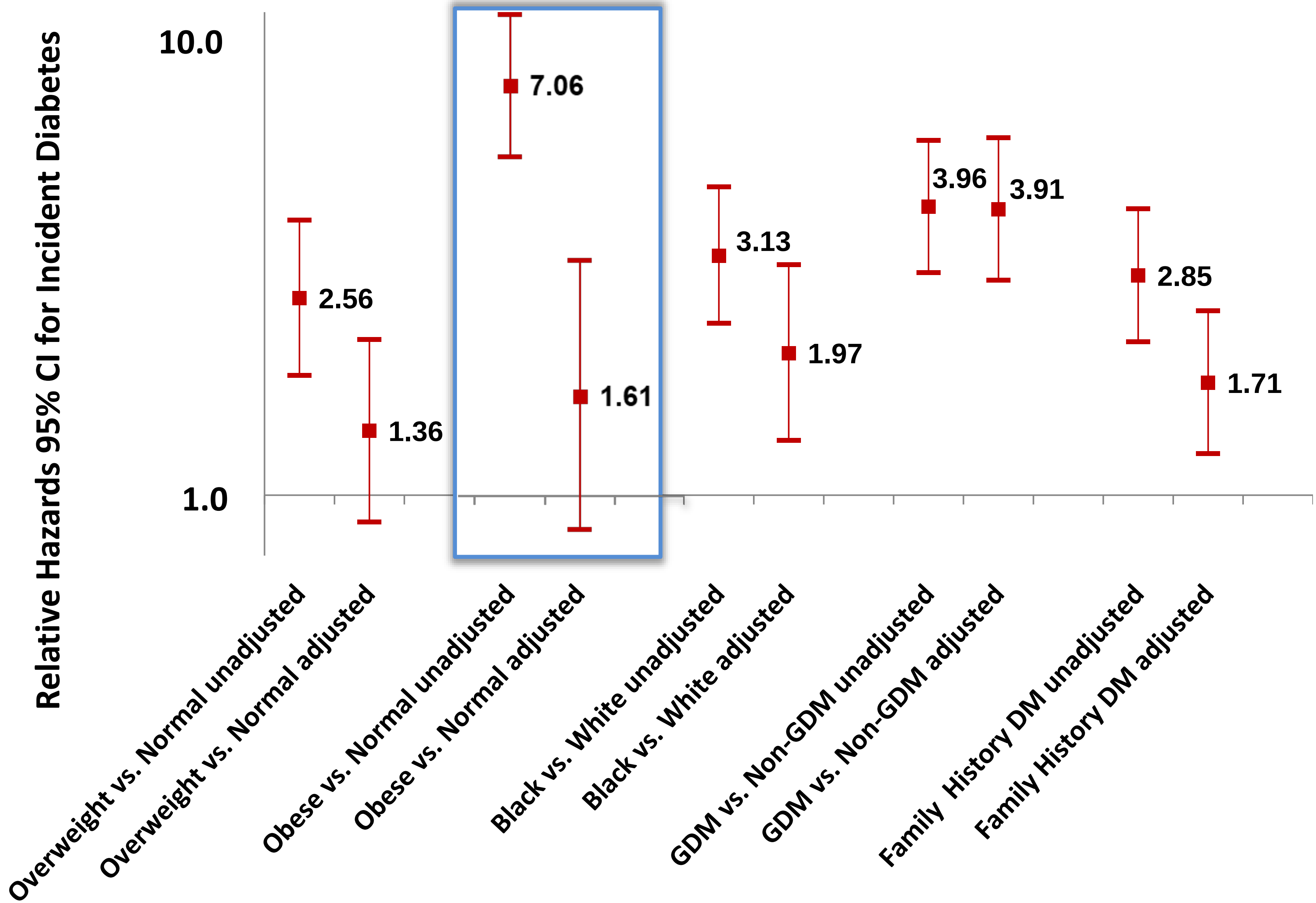
Low SES
25% enrolled in WIC

Infant Feeding Intensity and Glucose Tolerance (2-hr 75 g OGTT) at 6-9 weeks Postpartum After GDM



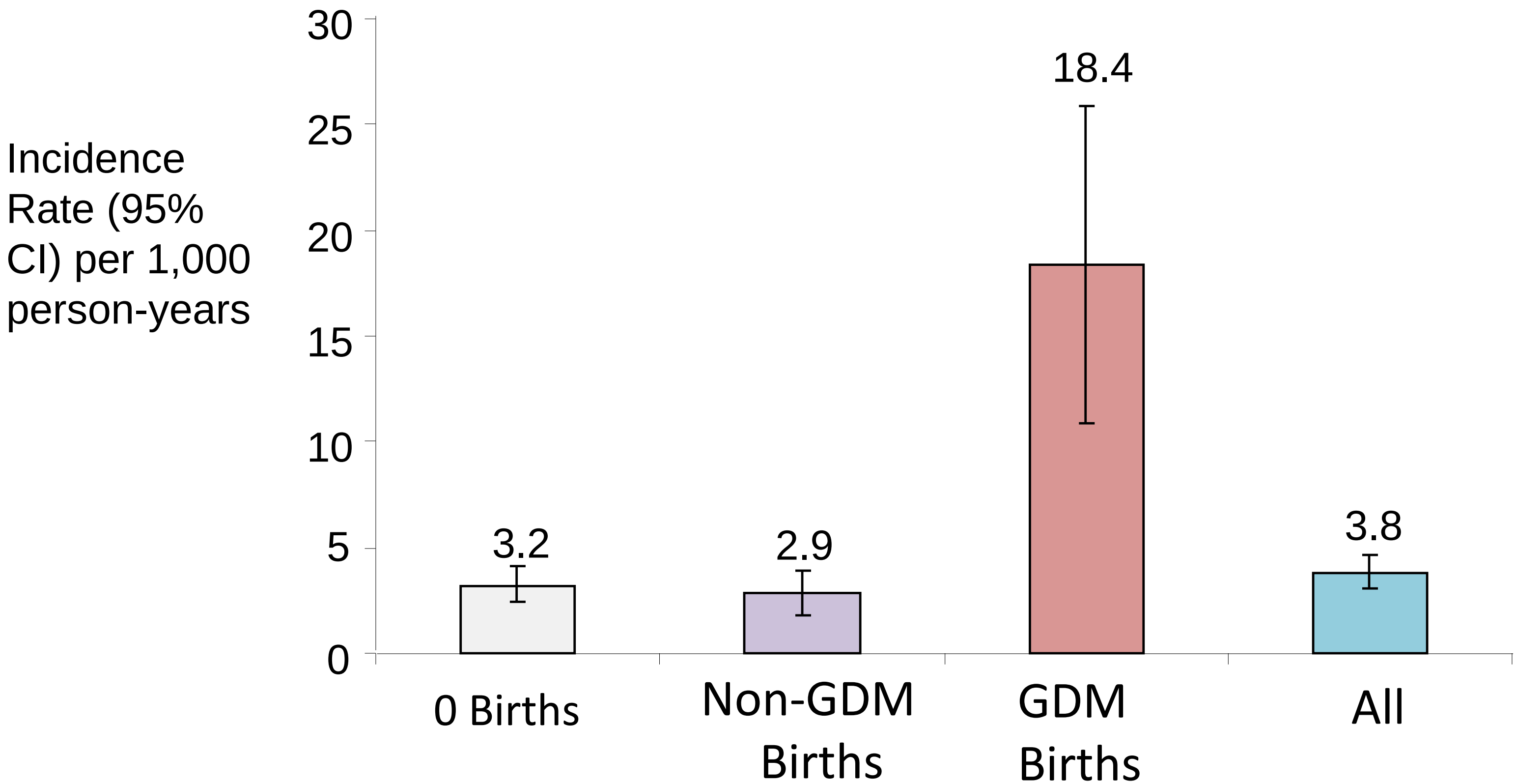
Gunderson et al. Diabetes Care, 2012, The SWIFT Study

Relative Hazards of Incident Diabetes by Covariates



Incidence Rates of Diabetes per 1,000 person-years, 95%CIs In CARDIA Women across the childbearing Years

(Gunderson et al. Diabetes 2007)



DM Cases, n	53	29	23	105
Person-years	16,502	10,129	1,253	27,884
Incident Rate (% per y)	0.3	0.3	1.84	0.4