Supplemental Appendix

Study Protocol and Methods

SWIFT Study Recruitment and Eligibility Criteria

Study exams occurred at 7 medical centers and 6 medical offices throughout the 5,000 square-mile Kaiser Permanente Northern California Region. SWIFT Study activities were carried out in three areas: 1) North: Sacramento, South Sacramento, Roseville, Rancho Cordova, Elk Grove, Point West, and Folsom Medical facilities; 2) East: Division of Research (DOR) Research Clinic (Oakland), Hayward and Richmond Medical Center; and 3) South: Fremont, Santa Clara, and San Jose Medical Centers.

All study participants received prenatal care, and delivered at a Kaiser Permanente hospitals and met study eligibility criteria as follows: 1) Age 20 to 45 years at delivery, 2) Availability of clinical medical record and delivery record from the KPNC Health Connect electronic medical record, 3) GDM pregnancy diagnosed by Carpenter and Coustan's criteria, 4) Delivered a singleton, live birth ≥ 35 weeks gestation, 5) No pre-existing diabetes or other serious medical conditions prior to index GDM pregnancy, 6) No diabetes diagnosis at 6 to 9 weeks postpartum for the index GDM pregnancy, 7) No use of steroids, or other medications significantly affecting glucose tolerance, 8) Not planning to move from the northern California area within the subsequent two years, 9) Not planning another pregnancy within the next two years, and 10) English or Spanish speaking.

We also selected women for the study based on their infant feeding practices, intentions and status from delivery through 6-9 weeks postpartum to classify them into one of two groups: 1) *Intensive formula (Exclusive or Mostly Formula)*: Breastfed <3 weeks and fed

>17 oz. of formula per day; also includes inconsistent feeding pattern, or 2) *Intensive lactation* (Exclusive or Mostly Breast milk) defined as only breast milk only since birth, or >0 to 6 oz. of formula per day at 6-9 weeks postpartum with the intention to continue breastfeeding at this intensity for at least 4 months.

Infant Feeding Intensity Groups – Formula Intake by Infant Age:

The lactation intensity groups represented average formula intake for infants that is <25% (mostly breastfeeding) or >70% (exclusive or mostly formula feeding) of the energy requirements for infants by age. The cut points for classification at 6-9 weeks postpartum assessments reflect 70% of average daily formula intake (>17 oz per day at 2 months, and >14 oz at 1 month of age) and no more than 25% (≤6 oz per day) at age 2 months.

Physical Activity Assessment

The Pregnancy Physical Activity Questionnaire (PPAQ), a 32-item semi-quantitative and validated questionnaire (reproducibility measures of 0.78 to 0.93 based on intraclass correlation coefficients estimating the proportion of the total variance explained by between-subject variance) was used to assess physical activity during the postpartum period.(20)

Statistical Methods and Analyses

Weibull Regression.

The study is characterized by heavy interval censoring, with unequal intervals (though, the vast majority of assessments are near 12 months, and near 24 months postpartum), and with one of the primary covariates of interest being time-dependent (lactation duration). Semi-parametric methods for regression analysis under these circumstances have been proposed, but are

difficult to implement computationally and/or very high dimension with many nuisance parameters (Sparling, Younes, and Lachin, 2006). As an alternative, parametric models are robust for heavily interval censored data, and more informative than non-parametric approaches (Lindsey and Ryan, 1998). The Weibull regression is a commonly used parametric regression model, and allows for a wide range in distributional shapes (Lindsey and Ryan, 1998). It is an accelerated failure time model, and the only such model with regression parameters that can be interpreted as hazard ratios. (Hosmer, Lemeshow and May, 2008). In summary, we have chosen the Weibull regression approach due flexibility in capturing a wide range in hazard functions, and for practical reasons including the ability to accommodate right and interval censoring and time-dependent covariates and ease in interpretation of regression coefficients as hazard ratios. Estimation is via standard maximum likelihood. The only assumption regarding failure/censoring times is the standard assumption that censoring is non-informative. Our assumed Weibull model is a special case in a very broad 3-parameter family of regression models, with the Weibull model specified via one of the hazard function parameters fixed at 0 ("kappa"). Departures from the Weibull model, including non-proportionality is assessed by a Wald test of kappa = 0, (Sparling, Younes, and Lachin, 2006). We found no evidence of departure from model assumptions.

References:

Hosmer D, Lemeshow S, and May S. (2008). Applied Survival Analysis (2nd Edn.). Hoboken: Wiley Series in Probability and Statistics.

Lindsey JC, Ryan LM. Tutorial in biostatistics methods for interval-censored data. Stat Med. 1998 Jan 30;17(2):219-38. PMID:9483730

Sparling YH, Younes N, Lachin JM, Bautista OM. Parametric survival models for interval censored data with time-dependent covariates. Biostatistics 2006; 7(4):599-614.

Estimates of the Cumulative Incidence Proportion of Incident Diabetes

To estimate the 2 year cumulative incidence proportion of incident diabetes for levels of lactation intensity at study baseline, we selected the following fixed values for the model covariables: maternal age = 35 years, race = Hispanic, Education <= high school, BMI = 30 kg/m^2, GDM treatment = diet only, prenatal 3-hr 100 gram OGTT Z-score sum = 0.5, gestational age at GDM diagnosis = 25 weeks, and no subsequent births.

Adjusted 2 year cumulative incidence proportion of incident diabetes for levels of lactation intensity at study baseline:

Exclusive Formula feeding	25.4%,
Mostly Formula/Inconsistent or mixed	17.5%,
Mostly Lactation	14.8%,
Exclusive Lactation	12.8%.

Analysis of time dependent current lactation status

We examined current lactation status as a time-dependent covariate to determine whether prolonged lactation and reduction in diabetes risk was related to active lactation (current) or cumulative lactation duration. We found that current lactation status was not associated with diabetes incidence (all p-values > 0.58). This finding makes sense given that the vast majority of diabetes events (95%) in our study occurred at or beyond 11 months post-baseline, and the majority of women (79%) were not lactating by 11 months post-baseline. We therefore observed very few incident diabetes cases in the time varying current lactation category.

Supplemental Tables:

Table S1: Newborn Characteristics of Infants Born to Women with GDM by Incident Diabetes Mellitus Status during the Two Years of Study Follow-up.

Table S2**:** Prenatal and Baseline Characteristics of Women with GDM by Lactation Intensity Groups at 6-9 weeks postpartum (Study baseline).

Table S3*:* Newborn Characteristics of Infants Born to Women with GDM by Lactation Intensity Groups at 6-9 weeks Postpartum (Study baseline).

Table S4*:* Distribution of 959 SWIFT Participants (n, %) among Lactation Intensity Groups at 6-9 weeks Postpartum and Lactation Duration Groups at the End of Follow-up, (P<0.001).

Table S1: Newborn Characteristics of Infants Born to Women with GDM by Incident Diabetes Mellitus Status during the Two Years of Study Follow-up.

Newborn Characteristics	Incident DM n=113	No DM n=846	P value
Mean (SD), Birth weight (g)	3546 (576.9)	3390 (484.8)	0.002
Mean (SD), Length (cm)	51.0 (2.5)	50.5 (2.4)	0.026
Mean (SD), Weight for length z-score	-0.2 (1.5)	-0.3 (1.4)	0.52
Median (IQR), Weight for length z-score	-0.3 (1.8)	-0.3 (1.8)	0.47
Sex, N (%)			0.145
Female	46 (40.7)	406 (48.0)	
Male	67 (59.3)	440 (52.0)	
Gestational age, N (%)			0.38
34 to <37 weeks (preterm)	7 (6.2)	37 (4.4)	
≥ 37 weeks (term)	106 (93.8)	809 (95.6)	
Birth Weight, N (%) ǂ			0.21
1,500 – 2,499 g	3 (2.7)	23 (2.7)	
2,500 – 2,999 g	17 (15.0)	159 (18.8)	
3,000 – 3,999 g	74 (65.5)	577 (68.2)	
4,000 g or more	19 (16.8)	87 (10.3)	
Size for gestational age, N (%) ǂ			0.013
Small (SGA)	1 (0.9)	18 (2.1)	
Appropriate (AGA)	75 (66.4)	655 (77.4)	
Large (LGA)	37 (32.7)	173 (20.5)	
Apgar score at 5 min, N (%) ǂ			0.26
6 or lower	0 (0.0)	9 (1.1)	
7 or higher	110 (97.3)	826 (97.6)	
Missing	3 (2.7)	11 (1.3)	
Newborn Nursery, N (%)			0.47
NICU	6 (5.3)	39 (4.6)	
Brief/Intermediate level	10 (8.9)	51 (6.0)	
Well care	97 (85.8)	756 (89.4)	
Hospital stay, N (%)			0.149
≥ 3 days	28 (24.8)	161 (19.0)	
< 3 days	85 (75.2)	685 (81.0)	

Chi-squared test for categorical variables; T-test or ANOVA for continuous variables. Kruskal-Wallis Test to compare medians. ǂ Fisher exact test for cell sizes <5. Two-sided P values.

***Table S2*:** Prenatal and Baseline Characteristics of Women with GDM by Lactation Intensity Groups at 6-9 weeks postpartum (Study baseline).

Characteristics	Exclusive Formula n=153	Mostly Formula n=214	Mostly Lactation n=387	Exclusive Lactation n=205
Socio-demographics				
Mean (SD), Age at baseline (year)	33.0 (4.9)	33.4 (5.0)	33.4 (4.8)	33.5 (4.4)
Education, N (%) ***				
High school or less	60 (39.2)	56 (26.2)	79 (20.4)	35 (17.1)
Some College	55 (36.0)	55 (25.7)	106 (27.4)	54 (26.3)
College Graduate	38 (24.8)	103 (48.1)	202 (52.2)	116 (56.6)
Race/ethnicity, N (%)‡ ***				
Non-Hispanic White	34 (22.2)	43 (20.1)	79 (20.4)	69 (33.6)
Non-Hispanic Black	22 (14.4)	19 (8.9)	20 (5.2)	11 (5.4)
Hispanic	48 (31.4)	68 (31.8)	118 (30.5)	58 (28.3)
Asian	43 (28.1)	80 (37.3)	166 (42.9)	63 (30.7)
Other	6 (3.9)	4 (1.9)	4 (1.0)	4 (2.0)
Parity, N (%)				
Primiparous	49 (32.0)	93 (43.5)	132 (34.1)	72 (35.1)
Multiparous	104 (68.0)	121 (56.5)	255 (65.9)	133 (64.9)
Polycystic Ovarian Syndrome (PCOS)	10 (6.5)	11 (5.1)	31 (8.0)	10 (4.9)
WIC recipient, N (%)***	59 (38.6)	55 (25.7)	87 (22.5)	45 (22.0)
Family History of Diabetes, N (%)	70 (45.8)	103 (48.1)	204 (52.7)	96 (46.8)
Prenatal characteristics				
Mean (SD), Pre-pregnancy BMI (kg/m^2)***	31.2 (8.3)	30.0 (7.8)	29.3 (6.7)	28.3 (6.1)
Pre-pregnancy weight status, N (%)*				
BMI <25 kg/m^2	38 (24.8)	66 (30.8)	114 (29.5)	73 (35.6)
25 kg/m^2 ≤ BMI < 30 kg/m^2	37 (24.2)	60 (28.0)	125 (32.3)	65 (31.7)
BMI ≥ 30 kg/m^2	78 (51.0)	88 (41.2)	148 (38.2)	67 (32.7)
Mean (SD), Gestational weight gain (kg)	10.8 (7.9)	10.2 (6.5)	10.2 (6.5)	10.3 (6.9)
Mean (SD), 3-hr 100 g OGTT (mg/dL)				
Fasting glucose	92.2 (11.4)	93.4 (11.1)	92.0 (12.6)	90.4 (12.8)
1 hour glucose	199.0 (22.1)	201.3 (23.0)	198.6 (23.2)	199.1 (23.1)
2 hour glucose	177.1 (25.0)	176.3 (28.8)	176.0 (29.2)	176.7 (24.7)
3 hour glucose	126.3 (34.7)	128.5 (31.1)	127.8 (33.3)	122.7 (33.7)
Mean (SD), Sum 3-hr OGTT z-scores	0.0 (2.3)	0.3 (2.6)	0.0 (2.8)	- 0.2 (2.6)
Median (IQR), Sum 3-hr OGTT z-scores	- 0.3 (2.9)	- 0.3 (2.9)	- 0.6 (3.0)	- 0.7 (2.6)

Table S2 *(Continued)*: Prenatal and Baseline Characteristics of Women with GDM by Lactation Intensity Groups at 6-9 weeks postpartum (Study baseline).

Characteristics	Exclusive Formula n=153	Mostly Formula n=214	Mostly Lactation n=387	Exclusive Lactation n=205
Prenatal characteristics				
Mean (SD), Gestational age at GDM diagnosis (weeks)	24.9 (7.8)	24.9 (7.2)	25.4 (6.9)	26.4 (6.5)
Treatment of GDM, N (%) ǂ				
Diet modification only	108 (70.6)	141 (65.9)	263 (68.0)	143 (69.8)
Oral hypoglycemic agents	43 (28.1)	65 (30.4)	105 (27.1)	57 (27.8)
Insulin	2 (1.3)	8 (3.7)	19 (4.9)	5 (2.4)
Hospital Labor and delivery				
Mean (SD), Length of gestation (weeks)**	39.0 (1.1)	39.3 (1.1)	38.9 (1.2)	39.2 (1.0)
Mean (SD), Length of stay (days)***	2.6 (1.1)	2.8 (1.3)	2.5 (1.0)	2.3 (0.9)
Cesarean section, N (%)*	61 (39.9)	74 (34.6)	113 (29.2)	57 (27.8)

Chi-squared test for categorical variables; T-test or ANOVA for continuous variables. Kruskal-Wallis Test to compare medians. ǂ Fisher exact test for cell sizes <5. Two-sided P values.

Table S2 *(Continued):* Prenatal and Baseline Characteristics of Women with GDM by Lactation Intensity Groups at 6-9 weeks Postpartum (Study baseline).

Characteristics	Exclusive Formula n=153	Mostly Formula n=214	Mostly Lactation n=387	Exclusive Lactation n=205
6-9 weeks Postpartum (baseline)				
Mean (SD), BMI (kg/m^2)***	32.0 (7.7)	30.6 (7.1)	29.8 (6.4)	28.5 (5.2)
Mean (SD), Waist Circumference (cm)***	93.6 (14.9)	91.5 (15.8)	89.1 (13.1)	86.9 (11.0)
Mean (SD), Weight change post-delivery (kg)	-8.9 (4.0)	-8.7 (3.7)	-9.1 (3.6)	-9.5 (3.4)
Mean (SD), HOMA-IR***	7.0 (4.1)	6.5 (5.1)	4.9 (3.2)	4.3 (2.8)
Median (IQR), HOMA-IR***	5.9 (4.7)	5.1 (5.4)	4.1 (3.5)	3.5 (2.5)
Mean (SD), 2-hr 75 g OGTT Results				
Fasting glucose (mg/dL) ***	97.8 (9.1)	97.3 (10.2)	93.2 (8.0)	92.2 (7.9)
2-hr post-load glucose (mg/dL) ***	110.6 (25.8)	117.4 (27.6)	113.0 (28.5)	106.9 (28.4)
Mean (SD), 2-hr 75 g OGTT Results				
Fasting glucose (mmol/L)***	5.4 (0.5)	5.4 (0.6)	5.1 (0.4)	5.1 (0.4)
2-hr post-load glucose (mmol/L)***	6.1 (1.4)	6.5 (1.5)	6.2 (1.6)	5.9 (1.6)
Glucose Tolerance, N (%) ***				
Normal	89 (58.2)	119 (55.6)	265 (68.5)	155 (75.6)
IFG only	43 (28.1)	53 (24.8)	53 (13.7)	27 (13.2)
IGT only	9 (5.9)	20 (9.3)	50 (12.9)	16 (7.8)
IFG and IGT	12 (7.8)	22 (10.3)	19 (4.9)	7 (3.4)
Depression, N (%)				
None	126 (86.3)	174 (84.5)	325 (86.0)	176 (88.9)
Moderate or Severe	20 (13.7)	32 (15.5)	53 (14.0)	22 (11.1)
Median, (IQR) Lifestyle Behaviors				
Total Physical Activity (PA)*	46.5 (25.7)	41.8 (27.3)	42.8 (24.2)	42.9 (22.8)
Moderate to Vigorous PA	24.3 (19.4)	22.0 (19.2)	21.5 (16.6)	20.5 (16.2)
Glycemic Index ***	186.5 (133.4)	223.6 (113.8)	232.5 (135.4)	248.9 (151.1)
Dietary fiber (g/100 Kcal)***	0.9 (0.4)	1.0 (0.4)	1.0 (0.5)	1.1 (0.5)
Dietary Animal fat (% Kcal)***	28.4 (11.0)	25.8 (11.9)	24.4 (11.4)	24.2 (9.9)
Contraception Methods, N (%) ǂ				
Progesterone only	8 (5.2)	4 (1.9)	10 (2.6)	4 (2.0)
Combination Oral Pills	24 (15.7)	20 (9.4)	46 (11.9)	28 (13.7)
Intrauterine Device	17 (11.1)	18 (8.3)	41 (10.6)	15 (7.3)
None/Barrier	104 (68.0)	172 (80.4)	290 (74.9)	158 (77.0)
Subsequent Birth (1), N (%)	16 (10.5)	32 (15.0)	44 (11.4)	22 (10.7)

***Table S3**:* Newborn Characteristics of Infants Born to Women with GDM by Lactation Intensity Groups at 6-9 weeks Postpartum (Study baseline).

Newborn Characteristics	Exclusive Formula n=153	Mostly Formula n=214	Mostly Lactation n=387	Exclusive Lactation n=205
Mean (SD), Birth weight (g)*	3435 (478.9)	3426 (495.7)	3355 (523.5)	3470 (460.6)
Mean (SD), Length (cm)*	50.5 (2.5)	51.0 (2.4)	50.3 (2.5)	50.7 (2.4)
Mean (SD), Weight for length z-score*	-0.2 (1.5)	-0.5 (1.3)	-0.3 (1.4)	-0.2 (1.3)
Median (IQR), Weight for length z-score*	-0.2 (1.8)	-0.5 (1.6)	-0.4 (1.8)	-0.2 (1.9)
Sex, N (%)*				
Female	76 (49.7)	81 (37.8)	192 (49.6)	103 (50.2)
Male	77 (50.3)	133 (62.2)	195 (50.4)	102 (49.8)
Gestational age, N (%)‡ **				
34 to <37 weeks (preterm)	6 (3.9)	5 (2.3)	29 (7.5)	4 (2.0)
≥37 weeks (term)	147 (96.1)	209 (97.7)	358 (92.5)	201 (98.0)
Birth Weight, N (%)‡ *				
1,500 – 2,499 g	3 (2.0)	2 (0.9)	18 (4.7)	3 (1.5)
2,500 – 2,999 g	26 (17.0)	38 (17.8)	85 (22.0)	27 (13.2)
3,000 – 3,999 g	108 (70.5)	150 (70.1)	241 (62.2)	152 (74.1)
4,000 g or more	16 (10.5)	24 (11.2)	43 (11.1)	23 (11.2)
Birth Size for gestational age, N (%)‡				
Small (SGA)	0 (0.0)	7 (3.3)	9 (2.3)	3 (1.5)
Appropriate (AGA)	119 (77.8)	161 (75.2)	293 (75.7)	157 (76.6)
Large (LGA)	34 (22.2)	46 (21.5)	85 (22.0)	45 (22.0)
Apgar score at 5 min, N (%)‡				
6 or lower	1 (0.7)	4 (1.9)	4 (1.0)	0 (0.0)
7 or higher	149 (97.3)	209 (97.6)	377 (97.4)	201 (98.0)
Missing	3 (2.0)	1 (0.5)	6 (1.6)	4 (2.0)
Newborn Nursery, N (%)‡ **				
NICU	10 (6.5)	11 (5.1)	22 (5.7)	2 (1.0)
Brief/Intermediate level	10 (6.5)	21 (9.8)	26 (6.7)	4 (2.0)
Well care	133 (86.9)	182 (85.1)	339 (87.6)	199 (97.1)
Hospital stay, N (%)*				
≥ 3 days	37 (24.2)	48 (22.4)	77 (19.9)	27 (13.2)
< 3 days	116 (75.8)	166 (77.6)	310 (80.1)	178 (86.8)

Footnote: Chi-square test was used for categorical variables; F test was used for continuous variables. Kruskal-Wallis test for comparison of medians.

ǂ Fisher's exact test for cell sizes < 5.

Two-sided P-values. Statistical significance: *P <0.05; ** P<0.01; *** P<0.001

***Table S4**:* Distribution of 959 SWIFT Participants (n, %) among Lactation Intensity Groups at 6-9 weeks Postpartum and Lactation Duration Groups at the End of Follow-up, (P-value <0.001).

Lactation Intensity Groups at 6-9 weeks postpartum (baseline)	**Lactation Duration Groups**				
	0 to 2 months	**>2 to 5 months**	**>5 to 10 months**	**>10 months**	**Total, n (%)**
Exclusive Lactation	2	20	45	138	205
	0.2	2.1	4.7	14.4	21.4
Mostly Lactation (≤6 oz formula Per day)	5	73	116	193	387
	0.5	7.6	12.1	20.1	40.3
Mostly Formula Feeding (>17 oz of formula Per day) or Inconsistent/mixed	29	97	47	41	214
	3.0	10.1	4.9	4.3	22.3
Exclusive Formula Feeding	153	0	0	0	153
	16.0	0	0	0	16.0
Overall Total, N (%)	189	190	208	372	959
	19.7	19.8	21.7	38.8	100

Table Abbreviations:

HOMA-IR = Homeostatic Metabolic Assessment of Insulin Resistance Index

IGT = impaired glucose tolerance

IFG = impaired fasting glucose

IQR = Interquartile range

NICU = Newborn Intensive Care Unit

OGTT = oral glucose tolerance test

PA = physical activity in met-hours per week

SD = standard deviation

Sum of 3-hr OGTT z-scores = sum of four z-scores for the prenatal 100 g OGTT glucose values (fasting, 1 hour, 2 hour and 3 hour)

AGA = Appropriate for gestational age

SGA = Small for gestational age

LGA = Large for gestational age

WIC = Special Supplemental Nutrition Program for Women, Infants and Children (eligibility based on income <185% of the federal poverty level).