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Cohort Profile: The Environmental Reproductive and Glucose Outcomes (ERGO) Study (Boston, MA) – a prospective pregnancy cohort study of the impacts of environmental exposures on parental cardiometabolic health

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ABSTRACT

Purpose: Pregnancy and the postpartum period are increasingly recognized as sensitive windows for cardiometabolic disease risk. Growing evidence suggests environmental exposures, including endocrine disrupting chemicals (EDCs), are associated with an increased risk of pregnancy complications that are associated with long-term cardiometabolic risk. However, the impact of perinatal EDC exposure on subsequent cardiometabolic risk post-pregnancy is less understood. The Environmental Reproductive and Glucose Outcomes (ERGO) study was established to investigate the associations of environmental exposures during the perinatal period with post-pregnancy parental cardiometabolic health.

Participants: Pregnant individuals aged ≥18 years without preexisting diabetes were recruited at <15 weeks of gestation from Boston, MA area hospitals. Participants completed ≤ 4 prenatal study visits (median: 12, 19, 26, 36 weeks of gestation) and 1 postpartum visit (median: 9 weeks), during which we collected biospecimens, health histories, demographic and behavioral data, and anthropometry. Participants completed a postpartum fasting 2-hr 75-g oral glucose tolerance test. Clinical data were abstracted from electronic medical records. Ongoing (as of 2023) extended post-pregnancy follow-up visits occur annually following similar data collection protocols.

Findings to date: We enrolled 653 unique pregnancies and retained 633 through delivery. Participants had a mean age of 33 years, 10% (n=61) developed gestational diabetes, and 8% (n=50) developed preeclampsia. Participant pregnancy and postpartum urinary phthalate metabolite concentrations and postpartum glycemic biomarkers were quantified. To date, studies within ERGO found higher exposure to phthalates and phthalate mixtures, and separately, higher exposure to radioactive ambient particulate matter, were associated with adverse gestational glycemic outcomes. Additionally, certain personal care products used in pregnancy, notably hair oils, were associated with higher urinary phthalate metabolite concentrations, earlier gestational age at delivery, and lower birthweight.

Future plans: Future work will leverage the longitudinal data on pregnancy and cardiometabolic outcomes, environmental exposures, biospecimens, questionnaire and pediatric data within the ERGO cohort.

Strengths and Limitations

- The ERGO study prospectively follows participants through pregnancy, postpartum, and into the critically understudied post-pregnancy period.
- Comprehensive data on clinical and biomarker outcomes, environmental exposures, and diverse questionnaire domains will allow for prospective study of the effects of exposures during the perinatal and post-pregnancy periods on parental cardiometabolic risk.
- Repeated measures of exposures, outcomes, and covariates over the pregnancy and postpartum periods will allow us to evaluate potential understudied sensitive and critical periods of exposure.
- Disruptions due to the COVID-19 pandemic impacted participant follow-up and retention, particularly for in-person postpartum visits.
- ERGO findings may not be generalizable across broader populations given the cohort's high educational attainment, majority non-Hispanic White study population, and English-speaking eligibility criteria at two of three study sites.

INTRODUCTION

The perinatal period is a sensitive window for long-term parental health due to the rapid and extensive changes across multiple organ systems, both during pregnancy and postpartum (1-6). Normal physiological changes in pregnancy pose a metabolic challenge to individuals due to adjustments the body makes for fetal growth and development, resulting in increased insulin resistance, inflammation, and alterations in body composition, lipid levels, and hemodynamic factors (7-10). As such, pregnancy often represents a stress test for longer-term cardiometabolic health (11), with individuals experiencing certain complications being at much higher risk for later-life cardiovascular disease (CVD). For instance, gestational diabetes mellitus (GDM) and preeclampsia are strong predictors of future type 2 diabetes mellitus and CVD risk (3, 12-19). Lifestyle and pharmaceutical intervention studies during the perinatal period have shown mixed success in reducing the risk of pregnancy complications (20-24) and/or chronic disease following complicated pregnancies (23, 25-29), emphasizing the importance of identifying modifiable risk factors to prevent long-term morbidity. Despite advances in understanding genetic and lifestyle risk factors, research on the contribution of environmental factors to cardiometabolic disease risk during and after pregnancy is underdeveloped (30).

Endocrine disrupting chemicals (EDCs), such as phthalates, are commonly used in industrial and consumer products, leading to widespread human exposure to complex mixtures of many EDCs (1, 31). Phthalates often are used as plasticizers, solvents, and lubricants in industrial applications and are found in many consumer products including personal care products, food and food packaging, and housing materials (32-36). As with other EDCs (1, 37-41), phthalate exposure has been associated with adverse cardiometabolic health outcomes (42-45). Specifically, in pregnant populations, phthalate exposure has been associated with increased risk of GDM (46-49), hypertensive disorders of pregnancy (50-52), preterm birth (53, 54), increased gestational weight gain (GWG) (55-60), and

subclinical effects such as altered blood lipid levels (60-62), and alterations in markers of glycemic regulation (46, 60, 63, 64).

Phthalates have been posited to alter metabolic regulation through multiple pathways, including effects on peroxisome proliferator-activated receptors (PPARs) α- and γ- (37, 65-67), which regulate glucose and lipid metabolism (37). Additionally, phthalates are linked to increased inflammation (68-72), oxidative stress (68, 72-74), and hormone-induced disruptions in insulin signaling (75, 76), as evidenced by toxicologic and epidemiologic data. During pregnancy, these phthalate-induced effects may exacerbate existing pregnancy-induced metabolic stress, leading to increased metabolic perturbations (e.g., increased insulin resistance). Pregnant individuals with underlying metabolic dysfunction may be less able to adapt to this additional stress, such that they may be more likely to cross the threshold from subclinical dysfunction to overt metabolic disease. However, even subclinical metabolic changes during pregnancy, such as elevated glucose levels (77-79), blood pressure (80, 81), and gestational weight gain (2, 20, 82) can increase risk of later-life cardiometabolic disease (83).

To date, studies of the impacts of perinatal EDC exposures on metabolic endpoints have focused almost exclusively on pregnancy outcomes, despite evidence that metabolic dysfunction during the post-pregnancy period also may impact subsequent cardiometabolic disease risk. For example, elevated postpartum blood glucose levels, elevated hemoglobin A1c (HbA1c), and greater postpartum weight retention have been associated with greater risk of type 2 diabetes (77, 78, 84-86). However, the extent to which exposure to EDCs impacts metabolic regulation after pregnancy remains unclear. Further data are needed to elucidate the effects of pregnancy and postpartum EDC exposures on cardiometabolic health of previously pregnant individuals. Additionally, longitudinal data may help identify sensitive periods (i.e., pregnancy, individual trimesters, postpartum) during which EDC exposures have a greater impact on postpartum cardiometabolic risk, which could help inform risk reduction strategies.

Therefore, the Environmental Reproductive and Glucose Outcomes (ERGO) study was designed to investigate the impacts of exposure to phthalates and phthalate mixtures on cardiometabolic health indicators during pregnancy and the postpartum period with funding support from the National Institutes of Health (NIH) (R01ES026166).

Primary Aims

The original primary aims of the ERGO study were to:

1. Characterize pregnancy phthalate exposure and its associations with gestational glucose dysregulation [i.e., GDM, gestational glucose intolerance(87), and continuous blood glucose levels] assessed during routine clinical screening.
2. Estimate associations of biomarkers of phthalate exposure in pregnancy with postpartum glucose dysregulation (i.e., HbA1c, fasting insulin and glucose, Homeostatic Model Assessment for Insulin Resistance [HOMA-IR], and 2-hr postprandial blood glucose) and adiposity (i.e., weight retention, skinfold thickness, waist- and hip- circumference, and body mass index) measured at 6-12 weeks postpartum.
3. Assess associations of postpartum biomarkers of phthalate exposure with postpartum glucose dysregulation (i.e., HbA1c, fasting insulin and glucose, HOMA-IR, and 2-hr postprandial blood glucose) and adiposity (i.e., weight retention, skinfold thickness, waist- and hip- circumference, and body mass index) measured at 6-12 weeks postpartum.

Through additional funding, the ongoing aims of the ERGO study have expanded to include an extended follow-up period, broader investigation of the impacts of other environmental exposures, as well as identification of the exposure sources of EDCs in pregnancy, postpartum, and the extended post-pregnancy period, on the cardiometabolic health of pregnant and previously pregnant individuals. Expanded ERGO study activities were/are supported by projects funded through the NIH (R01ES033185; P30ES000002) and the March of Dimes (MOD Research Grant #6-FY19-367).

COHORT DESCRIPTION

Study Setting and Recruitment

ERGO Participant Recruitment

The ERGO study recruited pregnant participants from obstetrics clinics during routine prenatal visits beginning in December 2016 at Brigham and Women's Hospital (BWH) and in April 2018 at Beth Israel Deaconess Medical Center (BIDMC), both located in Boston, MA; recruitment ended in November 2020. Research staff identified potential participants from patients scheduled for routine initial or early prenatal visits at BIDMC and BWH obstetrics and maternal-fetal medicine clinics and were prescreened for eligibility using electronic medical records. Eligibility criteria included: <15 weeks of gestation at recruitment, English speaking, ≥18 years of age, and plans to receive prenatal care and deliver at one of the recruiting hospital sites. Participants with triplet or higher order gestations, preexisting type 1 or type 2 diabetes, and those unable to tolerate a fasting oral glucose tolerance test (OGTT) were ineligible for the study. Participants were eligible to enroll during subsequent pregnancies that occurred during ERGO's recruitment period.

Trained research staff approached potentially eligible individuals in participating clinics and provided with study information; those wishing to enroll provided written informed consent. Participants had the option to additionally enroll their anticipated infant(s) in the study at any time during pregnancy or at the postpartum visit. At BWH, ERGO participants were recruited using the same eligibility criteria as participants co-enrolled in the LIFECODES pregnancy cohort (88). Enrolled ERGO participants were followed across pregnancy (data collection completed), postpartum (<2 years, data collection completed), and into the extended post-pregnancy follow-up period (≥2 years post-index pregnancy; data collection ongoing).

SPRING Cohort Participation & Contributions

In addition to directly enrolled participants described above, the ERGO cohort was augmented with data and biological samples collected from participants in the Study of Pregnancy Regulation of INsulin and Glucose (SPRING), a cohort based at Massachusetts General Hospital (MGH) with complementary data and sample collection protocols to ERGO (89, 90). SPRING recruitment and eligibility criteria have been previously described (90). Briefly, SPRING recruited pregnant individuals from the MGH obstetric practice and the broader Boston, MA area community through social media and community advertisements during March 2016–2021. Participants were eligible if they were between 4-14 weeks of gestation with preexisting GDM risk factors (89). SPRING participants completed three study visits in pregnancy and postpartum, with similar cadence to ERGO (Visits at: ≤15 weeks of gestation, 24-32 weeks of gestation, and 6-24 weeks postpartum). During study visits, SPRING collected similar covariate and clinical data, participant biospecimens, as well as data from supplemental ERGO product use questionnaires. Detailed descriptions of SPRING study activities and data collection protocols were included in previous publications (89-92) and are not covered in detail below. ERGO study activities described below refer to those completed by directly enrolled ERGO participants recruited from BWH and BIDMC, unless specifically noted.

ERGO Enrollment and Retention

We consented 515 eligible pregnant participants into the ERGO cohort, representing 521 unique pregnancies (n=328 from BWH and n=193 from BIDMC; n=6 participants enrolled in a second pregnancy) (Figure 1B). Of those, 33 pregnancies were removed for participants who withdrew (n=16), became ineligible after consent (n=16), or had duplicate enrollments for the same pregnancy (n=1, reenrolled when transferring care from BIDMC to BWH). Data from 165 SPRING participants were integrated into the cohort, resulting in a total ERGO study population of 647 participants, representing 653 unique pregnancies. Of those, we retained 633 (97%) pregnancies through delivery (n=17 transferred care, n=3 lost to follow up), 300 (46%) completed postpartum study visits, and 418 (64%)

had postpartum data collected from study visits, medical records, or remote questionnaires (Figure 1B). Of the 322 infants enrolled in ERGO, 140 (43%) completed the postpartum visit (n=136 singletons, n=4 twin infants).

Enrolled ERGO participants retained through delivery were invited to reconsent for an extended post-pregnancy follow-up period (≥2 years post-index pregnancy, ongoing as of 2023), regardless of whether they completed a postpartum study visit. Reconsented participants were invited to enroll their ERGO child(ren) to participate in supplemental pediatric data collection in parallel with parent follow-up activities, even if they did not consent their child during infancy. In-person data collection from Year 2 through Year 4 post-pregnancy is supported by an NIH-funded multi-cohort study (R01ES033185). This study leverages existing complementary pregnancy and postpartum data collected in both the ERGO and UPSIDE MOMS cohorts (R01NR017602) and new data collection at extended post-pregnancy follow-up visits to investigate the effects of phthalate exposure during pregnancy and postpartum on post-pregnancy cardiometabolic health indicators. SPRING participants are not currently included in extended follow-up activities.

Overview of ERGO Study Activities

Pregnancy & Postpartum Follow-up (completed)

Enrolled ERGO participants were initially followed from early pregnancy into the postpartum period (6-12 weeks) (Figure 1A). During pregnancy, participants completed up to 4 in-person study visits (V1-4), designed to occur during the following time periods: V1, <15 weeks of gestation (median: 12); V2, 16-24 weeks of gestation (median: 19); V3, 24-28 weeks of gestation (median: 26), and V4, 34-38 weeks of gestation (median: 36). During pregnancy study visits, data were collected using a combination of participant questionnaires, electronic medical records, and participant biospecimens, as described in detail below.

Delivery information was abstracted from electronic medical records. After delivery, participants were sent a congratulatory card and a small gift (i.e., infant socks) by mail or in-person on the postpartum floor, along with a reminder that an ERGO RA would follow up to assist with scheduling their postpartum study visit. ERGO staff members called participants at an average of 2-4 weeks postpartum to schedule their in-person postpartum visit. Additional contact was made through email and text messages as appropriate.

Postpartum visits took place in-person at the Center for Clinical Investigation (CCI) at Brigham and Women's Hospital between 6-12 weeks postpartum for both BWH and BIDMC participants. However, due to disruptions from the COVID-19 pandemic, we extended the follow-up window through up to 24 months postpartum. This allowed participants nearing the 12-week cutoff who would have otherwise been lost to follow-up during the initial COVID-19 shutdown to complete postpartum visits; the shutdown started in Massachusetts on March 16, 2020, and resulted in research shutdowns for in-person visits through June 22, 2020. In practice, the latest visit occurred at 41 weeks (~9.5 months) postpartum, and the median was 9 weeks. Participants fasted prior to their visit; completed a 2-hr 75-g OGTT; provided a urine and two blood samples (fasting and 2-hours postprandial); completed a postpartum questionnaire and 24-hour food recall, and study staff collected anthropometric and blood pressure measurements. After the OGTT, participants were provided a snack as well as vouchers to cover the cost of their lunch following the study visit and the valet parking at the CCI. Additionally, participants were provided with electronic gift cards or a check for their participation. During the postpartum visit, participants were given the option to provide additional consent for their infant(s) to participate in a parallel data collection. If parents consented, research staff collected infant anthropometric measurements and a urine sample during the postpartum visit, as described below.

SPRING participants provided data from up to three study visits, which aligned most closely with ERGO V1, V3, and the postpartum visit. Infants born to SPRING participants did not participate.

Extended Post-pregnancy Follow-up (ongoing as of 2023)

During the extended post-pregnancy ERGO follow-up period, participants complete up to three additional annual in-person (CCI at BWH) or remote study visits starting at ≥2 years post-index pregnancy (ongoing). These visits are defined as Year 2 (Y2: ≥24 to <36 months), Year 3 (Y3: ≥36 to <48 months), etc. These visits follow similar protocols to the postpartum visit and include a combination of participant questionnaires, staff-collected anthropometric and vitals data, and participant biospecimens, as discussed below. SPRING participants are not currently included in extended ERGO follow-up activities.

Data Collection

The primary domains and timing of participant data collected in ERGO can be found in Table 1.

Table 1. ERGO Study Data Collection Domains by Study Visit (P= participant, C= neonate/child)

		Completed Study Timepoints (median weeks)						Ongoing Follow-up Visits			
		Pregnancy						Post-Pregnancy			
Category	Measure/Domain	Visit 1 (12 weeks)	Visit 2 (19 weeks)	Visit 3 (26 weeks)	Visit 4 (36 weeks)	Delivery (39 weeks)	Postpartum (9 weeks)	Year 2	Year 3	Year 4	Year 5+
Biological Samples	Urine	P	P	P	P		P, C	P, C	P, C	P, C	P, C
	Blood	P		P			P	P	P	P	P
	Toenails			P			P	P	P	P	P
Biomarker data	Non-fasting 50-g GLT			P[a]							
	Fasting 3-hr 100-g OGTT			P[b]							
	Fasting 2-hr 75-g OGTT			P[c]			P	P	P	P	P
	Fasting insulin						P	P	P	P	P
	HbA1c						P	P	P	P	P
	HOMA-IR						P	P	P	P	P
	Lipid panel							P	P	P	P
	ApoB100							P	P	P	P
	Urinary phthalate & DINCH metabolites	P	P	P	P		P	P	P	P	P
	Urinary phenol metabolites				P						
Questionnaire domains	Demographics	P						P, C			
	Medical history	P						P, C	P, C	P, C	P, C
	Reproductive history	P						P	P	P	P
	Diet	P	P	P	P		P	P, C	P, C	P, C	P, C
	Physical activity	P	P	P	P		P	P, C	P, C	P, C	P, C
	Personal care product use	P	P	P	P		P	P, C	P, C	P, C	P, C
	Household environment	P	P	P	P		P	P, C	P, C	P, C	P, C

	Breastfeeding		P				P	P, C			
	Stress appraisal			P			P	P	P	P	P
	Social networks/ support			P			P				
	Adverse Childhood Experiences (93)							P			
	Sleep			P			P	P, C	P, C	P, C	P, C
	Emotional Well-being (EPDS) (94)			P			P	P	P	P	P
	Racism/ discrimination			P			P				
	COVID-19 impacts	P (June 2020)									
	Environmental health literacy						P (1+ years post-pregnancy)				
	Medication & supplement use	P					P	P, C	P, C	P, C	P, C
	Behavior & neurodevelopment							C	C	C	C
Clinical Data Abstraction	Medication use	P						C	C	C	C
	Blood pressure	P	P	P	P		P				
	Height	P	P	P	P	C					
	Weight	P	P	P	P	C	P				
	Pregnancy complications					P					
	Fetal ultrasound measures	C	C	C	C						
	Labor/delivery records					P, C					
	Growth charts						C[d]	C	C	C	C
Vitals & anthropometry	Blood pressure						P	P	P	P	
	Pulse wave velocity							P	P	P	
	Skin fold thickness measures						P, C	P	P	P	
	Waist & hip circumference						P	P	P	P	P
	Abdominal/waist circumference						C	C	C	C	C
	Height						P, C	P, C	C	C	C
	Weight						P, C	P, C	P, C	P, C	P, C

Abbreviations: GLT, glucose load test; OGTT, oral glucose tolerance test, HbA1c, hemoglobin A1c; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; ApoB100, apolipoprotein B-100; DINCH, 1,2-Cyclohexane dicarboxylic acid diisononyl ester.
[a]When available, non-fasting 1-hr 50-g GLT blood glucose levels from routine clinical screening were abstracted for all participants.
[b]When available, fasting 3-hr 100-g OGTT blood glucose levels from routine clinical screening were abstracted for all participants.
[c]SPRING participants completed fasting 75-g OGTTs at study visits during pregnancy.
[d]Historical growth records from pediatric visits will be abstracted for child participants enrolled in the follow-up study (ongoing).

Participant Questionnaires

Pregnancy & Postpartum (completed)

Participants completed questionnaires at all study visits. Specific domains included in questionnaires at each visit are shown in Table 1 and key domains and measures are described in

more detail below. Survey format and content varied slightly by recruitment hospital, but key domains were included by all. At V1-V4, BWH participants co-enrolled in ERGO and LIFECODES completed paper questionnaires deployed by LIFECODES study staff at clinic visits, from which data was recorded and then shared with ERGO investigators. To maximize data harmonization between recruitment sites, the ERGO questionnaires deployed at BIDMC (V1-V4) included questions from the LIFECODES questionnaires plus additional domains of interest (e.g., hair product use, stress appraisal, household characteristics, social support). The majority of BIDMC participants completed the V1 questionnaire electronically using a REDCap link that was sent via email by research staff. Subsequent questionnaires (V2-V4) were primarily completed on paper while in clinical spaces and then entered in REDCap by study staff. During the COVID-19 pandemic, we deployed all ERGO questionnaires remotely via REDCap email links sent directly to participants at both BIDMC and BWH, which allowed us to continue collecting participant data despite interruptions to clinic access. BWH participants remotely completed the longer ERGO questionnaires during this time.

Between 20 and 22 weeks of gestation, participants completed the Diet Health History Questionnaire (DHQ), a food frequency questionnaire developed by the National Cancer Institute (Bethesda, MD), from which we calculated caloric intake and nutrient levels (95). As a measure of overall diet quality, participants also completed an adapted PrimeScreen questionnaire at V1, V2, V4, and postpartum (96).

Self-reported data on use of hair products and personal care products were collected at each study visit using validated questionnaires (97, 98). The hair product survey was developed by data collected in the Greater New York Hair Products Study (99) and included the following product categories: hair oils, hair lotions, leave-in conditioners, non-lye perms or relaxers, lye perms or relaxers, prescription hair products, natural hair products, or other hair products (98). Participants were asked to report whether they had used each product category within the past month, and if yes, how frequently they used that product category. To collect data on a broader range of personal care product

categories, participants completed a separate questionnaire on their use of the following product categories within the previous 48-hours: deodorant, hair gel/spray, conditioner/crème rinse, shampoo, perfume, hand/body lotion, shaving cream, nail polish, suntan lotion, colored cosmetics, liquid soap, bar soap, and other hair products (97). Data on frequency of use of these products were not collected during pregnancy or postpartum.

In June 2020, pregnant participants and those within 1 year postpartum completed a supplemental COVID-19 impact questionnaire, querying pandemic-related stress; infection history and precautions; and the Edinburgh Postnatal Depression Scale (EPDS) (94, 100). Between May 2021 and August 2022, we deployed an Environmental Health Literacy (EHL) questionnaire to ERGO participants who were at least a year postpartum, as part of an NIEHS-center funded pilot study (P30ES000002). The EHL questionnaire included sections related to participants' views on the environment and reproductive health, comfort with medical communications, and personal health habits.

SPRING collected similar participant-reported data on sociodemographic factors, personal medical and pregnancy history, and family medical history (91), as well as supplemental data from ERGO personal care and hair product use questionnaires during the postpartum visit.

Extended Post-Pregnancy Follow-up (ongoing as of 2023)

Participants in the post-pregnancy follow-up visits complete an initial "catch-up" questionnaire at their first post-pregnancy follow-up visit, regardless of the year post-pregnancy. Data are collected on pubertal timing, menstruation history, updates to health history, and reproductive history, including additional pregnancies and their outcomes since their index pregnancy. Additional sections on breastfeeding, sleep, food introduction, health history, and household exposures during the first 2 years of their index child's life are also included. Participants also complete year-specific questionnaires (e.g., Y3, Y4, Y5, etc.) that include key domains repeated at each visit (e.g., health updates, diet, physical activity, parent and child product use, etc.) and others that are asked only at specific years (e.g.,

Parent: Adverse Childhood Experiences; Child: age-specific developmental checklists, daycare/school activities) with sections related to both the parent and child (see Table 1).

Anthropometrics & Blood Pressure

Pregnancy & Postpartum Visits (completed)

Participant height and weight measurements from their initial prenatal visit, and repeated weight and blood pressure measures at each prenatal visit were abstracted from electronic medical records. At in-person ERGO postpartum visits, study staff measured participant height, waist and hip circumferences, skinfold thickness (i.e., subscapular, triceps, and suprailiac), and blood pressure, using research quality calibrated instruments and standard measurement protocols (101, 102). Staff used a Tanita TBF-400 bioelectrical impedance analysis body composition analyzer (Tanita, Arlington Heights, IL), to measure weight, BMI, body fat percent, body fat mass, fat free mass, body water mass, body water percent, and basal metabolic rate. Additionally, infant length, weight, head and abdominal circumferences, and skinfold thickness (i.e., subscapular, triceps, suprailiac) were measured for enrolled infants during their parent's postpartum study visit. All measurements were taken twice and averaged for analyses.

Extended Post-pregnancy Visits (ongoing as of 2023)

Research staff collect the same measurements at in-person post-pregnancy visits as at the postpartum visit, described above. Pulse wave velocity is also measured using an ATCOR SphygmoCor Xcel (ATCOR, Naperville, IL) following standard techniques (103). Additionally, a Tanita MC-780U multifrequency segmental body composition analyzer (Tanita, Arlington Heights, IL) will be used to obtain segmental (i.e., trunk, left leg, right arm, etc.) body measurements including fat percent and muscle mass.

Biospecimen Collection & Analysis

Blood Samples

Pregnancy & Postpartum Visits (completed)

Blood samples were collected from BIDMC participants during pre-established routine prenatal clinical blood draws during pregnancy V1 and V3. At the postpartum visit, clinical staff collected fasting and 2-hour postprandial blood samples from BIDMC and BWH participants following a 2-hr 75-g OGTT. Designated blood sample tubes were immediately sent to LabCorp® (LabCorp Raritan, NJ), where they were analyzed for levels of fasting and 2-hour postprandial glucose, fasting insulin, and HbA1c, via enzymatic testing, electrochemiluminescence immunoassays (Roche Elecys/E170; Roche Diagnostics, Indianapolis, IN) and turbidimetric inhibition immunoassays (Tina-quant Hemoglobin A1c; Roche Diagnostics, Indianapolis, IN), respectively. Two additional sample tubes were processed, aliquoted, and stored at -80°C by research staff for future analyses. HOMA-IR was calculated from fasting glucose and insulin levels.

Details of glycemic biomarkers measured in SPRING, including sample collection and laboratory methods, can be found in Thaweethai et al. (90).

Extended Post-pregnancy Visits (ongoing as of 2023)

During in-person post-pregnancy visits, clinical staff collect fasting, 1-hour, and 2-hour postprandial blood samples following a 2-hr 75-g OGTT. Designated sample tubes are immediately sent to LabCorp® for measurement of fasting insulin, HbA1c, and fasting-, 1-, and 2-hour postprandial glucose levels, as described above, as well as a full lipid panel including ApoB100 using nuclear magnetic resonance spectroscopy (Vantera NMR Clinical Analyzer; LipoScience Inc., Raleigh, NC) (104). At each blood sample collection, two additional sample tubes are processed, aliquoted, and stored at -80°C by research staff for future analyses. Lab results are shared with ERGO participants approximately one week after their study visit.

Urine Samples

Pregnancy & Postpartum Visits (completed)

Spot urine samples were collected from participants at all in-person study visits in non-sterile polypropylene collection cups. SPRING participants contributed urine samples collected at visits corresponding to ERGO V1, V3, and the postpartum visit, using the same method. During the initial phases of the COVID-19 pandemic, we developed and implemented a remote urine collection protocol. Participants were provided with instructions and supplies to collect a spot urine sample in a polypropylene collection cup at home, freeze it, and mail it back to our lab at Harvard University using provided insulated mailers and prepaid shipping labels for overnight shipment.

During the postpartum visit, urine samples were collected from enrolled infants using a diaper collection protocol consisting of a cotton collection pad placed in a study-provided diaper, which was then drained into a polypropylene urine collection cup (105). Research staff measured the specific gravity of all urine samples using an Atago 4410 (PAL10S) Digital Urine Specific Gravity refractometer to account for urinary dilution in future analyses.

Urine samples from V1-V3 and postpartum were sent to the Centers for Disease Control and Prevention (CDC) Sample Logistics Laboratory (Atlanta, GA, USA) for analysis. Laboratory staff quantified urinary concentrations of 14 phthalate and 2 phthalate alternative [i.e., di(isononyl) cyclohexane-1,2-dicarboxylate (DINCH)] metabolites using previously published methods (106). In a pilot study, an additional 130 urine samples from the most proximal study visit to delivery (i.e., V3 or V4) were analyzed for the same phthalate and DINCH metabolites, as well as 12 phenolic compounds, by NSF International's Applied Research Center (Ann Arbor, MI, USA) using replicated methods to those used by the CDC (106, 107).

Extended Post-pregnancy Visits (ongoing as of 2023)

During post-pregnancy visits, spot urine samples are collected from participants at each annual visit, either in-person or remotely, following the protocols described above. Additionally, remote parent-

collected child urine samples are obtained using established protocols for both diaper collection (108) and toilet hat collection (109), depending on the child's toilet training status. All urine samples are processed and aliquoted by research staff upon receipt as described above and are stored at -80°C prior to being sent for analysis.

Toenail Samples

Pregnancy & Postpartum Visits (completed)

Toenail sample collection at V3 and postpartum was added to the study protocol in December 2019. Prior to their V3 and postpartum visits, participants were given collection instructions and supplies to collect their toenail samples at home (110). Participants were instructed to remove any nail polish and clean their toenails prior to collection, noting whether there had been polish on the nails within 48-hours of collection. Participants stored collected nails in provided labeled envelopes and either brought them to their next in-person study visit or mailed them to our lab. Samples were stored at room temperature for future analysis.

Extended Post-pregnancy Visits (ongoing as of 2023)

During the post-pregnancy follow up, parent toenail samples are collected and stored as described above at each visit.

Medical Record Data Abstraction

Pregnancy & Postpartum Records (completed)

Pregnancy data abstracted from medical records included participant height, date of last menstrual period, repeated vital measurements (e.g., blood pressure, weight, gestational week), medications, ultrasound data, clinical laboratory results, and pregnancy complications. As key outcome measures, we abstracted all data on clinical GDM diagnoses and results of routine clinical GDM screening, which generally occurs between 24-28 weeks of gestation. Recruiting hospitals most

commonly use a 2-step screening approach comprised of 1) a non-fasting 1-hr 50-g glucose load test (GLT) followed by a 2) fasting 3-hr 100-g OGTT for those with abnormal GLT results. GDM is then diagnosed in individuals with 2 or more abnormal OGTT values (111).

Delivery data abstraction included date and gestational age at delivery; delivery time; labor details; interventions; medications; indication and mode of delivery; and intrapartum complications and morbidity. Vitals data were abstracted through the postpartum visit. Missing participant questionnaire data on sociodemographic and health history variables (e.g., race and ethnicity, insurance status, parity, family history) were abstracted from medical records when available. If available, data were also abstracted from clinical postpartum visit records for participants who did not complete an in-person or remote postpartum study visit.

Of note, SPRING screened and diagnosed GDM in participants directly using the International Association of the Diabetes in Pregnancy Study Group's (IADPSG) 2010 criteria (112), rather than via medical record diagnosis; full details are included in Thaweethai et al. (90).

Neonatal Records (completed)

Measures of gestational age at delivery, fetal distress, infant sex, length, birth weight, and head circumference, Apgar scores, neonatal intensive care unit admission, and neonatal complications were abstracted from medical records. Additional fetal biometry data from prenatal ultrasounds were abstracted from electronic medical records during pregnancy for BIDMC participants only.

Pediatric Records (ongoing as of 2023)

If participants consent to provide access to their index child's pediatric medical records as part of the supplemental pediatric data collection during the extended ERGO follow-up, data on pediatric growth, routine well-visit assessments, infections, vaccinations, medications, health conditions (e.g., allergy, eczema, gastroesophageal reflux disease), clinical laboratory values, and other diagnoses will be abstracted.

Patient and Public Involvement Statement

Participants were not involved in designing, managing, or conducting ERGO study research activities, outside of their role as study participants providing biological samples and completing data collection activities.

FINDINGS TO DATE

Among the 653 eligible unique ERGO pregnancies (corresponding to 647 individual participants), 633 were retained through delivery; participation in data collection activities varied across study visits and by recruitment site. On average, participants were 33.0 (SD: 4.8) years of age at consent with a mean (SD) BMI at V1 of 27.8 (6.6) kg/m^2 (Table 2).

Table 2. ERGO participant characteristics (n=647 participants, n=653 unique pregnancies)

Characteristic	n	%[a]	Mean (SD)	Range
Age at consent (years)	653		32.9 (4.8)	19.3, 48.3
Visit 1 BMI (kg/m^2)	650		27.8 (6.6)	16.8, 56.5
Underweight (<18.5)	8	1%		
Normal weight (18.5–24.9)	261	40%		
Overweight (25–29.9)	187	29%		
Obese (≥30)	194	30%		
Self-reported race/ethnicity	651			
Non-Hispanic White	377	58%		
Hispanic	103	16%		
Non-Hispanic Black	76	12%		
Asian	56	9%		
More than one race	24	4%		
Another race/ethnicity	15	2%		
Parity	645			
Nulliparous	312	48%		
Educational attainment	629			
College degree or higher	497	79%		
Partnership status	624			
Married	484	78%		
Single, living with partner	108	17%		
Single, not living with partner	32	5%		
Employment status	615			
Employed (full- or part-time)	559	86%		
Insurance status	462			
Private insurance	271	59%		
Other (e.g., self-pay, Medicaid)	191	41%		

Smoking status	615	
Smoked during pregnancy	19	3%
Family history of diabetes	629	
Yes	221	35%
Family history of CVD/hypertension	462	
Yes	181	39%

Abbreviations: SD, standard deviation; BMI, body mass index; CVD, cardiovascular disease.
[a]Frequencies may not sum to 100 due to rounding.

Most participants held a college degree or higher (79%), were married or living with a partner (95%) and did not have a family history of diabetes (65%). Self-reported smoking during pregnancy was low (3%). Participant self-reported personal care product use varied slightly across study visits but substantially by product category (Figure 2).

GDM screening data from 1-hr 50-g GLTs were available in 481 pregnancies [mean (SD): 112.7 (27.8) mg/dL; 6.3 (1.5) mmol/L] and results of fasting 3-hr 100-g OGTTs were available in 85 pregnancies; in general, SPRING participants did not have data on 1-hr GLTs or 100-g OGTTs in pregnancy as they completed 75-g OGTTs at V1 and V3 per SPRING protocol (Table 3). During pregnancy, 10% of participants were diagnosed with GDM and 8% developed preeclampsia. The mean (SD) total gestational weight gain was 11.5 (6.0) kg, with 31% of pregnancies falling within the Institute of Medicine (IOM) recommended total GWG-for-pre-pregnancy BMI ranges (41% above range; 28% below range).(113) Of the 633 ERGO deliveries, 63% were vaginal, 10% were preterm (<37 weeks of gestation), and the mean (SD) gestational week at delivery was 38.6 (2.0) weeks. Due to twin gestations, the total number of delivered infants was 653 (n=613 singletons and n=40 twin infants) and the mean (SD) infant birth weight was 3,192 (571) g (Table 3).

Table 3. ERGO participant measures from pregnancy, delivery, and postpartum data collection

Adult Participant Measures	n	%	Mean (SD)	Range
Pregnancy	653[a]			
Clinical glucose screening levels (mg/dL)[b]				
Non-fasting 50-g GLT, 1-hr glucose	481		113 (27.8)	37, 213
Fasting 3-hr 100-g OGTT				
Fasting glucose	87		82 (9.5)	65, 107
1-hr glucose	85		160 (34.6)	85, 251

2-hr glucose	85		134 (34.1)	70, 228
3-hr glucose	85		100 (36.1)	34, 205
Total gestational weight gain (kg)	634		11.5 (6.0)	-21.5, 29.9
GWG-for-BMI, IOM guidelines (113)	633			
Insufficient	180	28%		
Recommended	193	31%		
Excessive	260	41%		
Pregnancy complications	647			
Gestational diabetes	61	10%		
Preeclampsia	50	8%		
Gestational hypertension	69	11%		
Delivery	633[c]			
Gestational weeks at delivery	633		38.6 (2.0)	24.0, 41.7
Preterm birth (<37 weeks)	66	10%		
Delivery mode				
Vaginal, spontaneous	231	36%		
Vaginal, induced	170	27%		
Cesarean, scheduled	113	18%		
Cesarean, emergent	119	19%		
Postpartum	418[d]			
Week postpartum at data collection	418		9.0 (4.1)	3.7, 41.0
BMI (kg/m^2)	408		28.3 (6.1)	18.1, 54.1
Weight retention (kg)	406		2.4 (4.9)	-14.6, 24.7
Adjusted weight retention (kg/weeks)	406		0.7 (1.5)	-2.2, 3.7
Anthropometrics				
Hip circumference (cm)	188		108.5 (13.2)	79.0, 171.8
Waist circumference (cm)	188		91.7 (14.4)	67.7, 145.5
Waist-to-hip ratio	188		0.8 (0.1)	0.5, 1.1
Skinfold thickness (mm)				
Suprailiac	176		15.5 (7.7)	2.8, 39.3
Subscapular	163		19.5 (8.2)	6.6, 39.0
Triceps	175		24.0 (6.2)	11.6, 39.1
Blood Pressure (mmHg)				
Systolic	221		115 (12.5)	87, 184
Diastolic	221		69 (9.8)	52, 119
Glycemic biomarkers				
Fasting insulin (µIU/mL)[e]	176		7.0 (8.0)	0.6, 73.8
HOMA-IR[e]	176		1.5 (1.9)	0.1, 18.7
HbA1c (%)	293		5.3 (0.3)	4.1, 6.1
Fasting glucose (mg/dL)	313		83 (8.6)	61, 124
Fasting 2-hr 75-g OGTT				
2-hr glucose (mg/dL)	291		94 (26.0)	29, 208
Infant Measures	**n**	**%**	**Mean (SD)**	**Range**
Birth	653[f]			
Gestational age at birth (weeks)	653		38.6 (2.0)	24.0, 41.7
Twin gestation	20	3%		

Birth weight (g)	651		3192 (571)	710, 5150
Birth length (cm)	478		48.8 (4.5)	18.5, 56.0
Head circumference (cm)	447		34.1 (1.8)	23.0, 39.0
Apgar score				
1-minute	641		7.9 (1.4)	1, 10
5-minute	639		8.9 (0.6)	3, 10
Infant sex	642			
Female	340	53%		
Neonatal intensive care unit admission	117	18%		
Postpartum	140[g]			
Gestational age at birth (weeks)[h]	140		39.0 (1.4)	34.4, 41.6
Age at visit (weeks)	140		8.1 (2.7)	4.0, 26.0
Weight (g)	140		5011 (818)	2760, 8020
Length (cm)	137		57.2 (4.3)	31.4, 69.5
Head circumference (cm)	131		38.7 (1.8)	32.1, 44.5
Abdominal circumference (cm)	129		38.8 (3.5)	24.0, 58.2
Skinfold thickness (mm)				
Suprailiac	119		5.4 (1.6)	2.7, 9.4
Subscapular	131		7.4 (1.6)	4.1, 12.0
Triceps	125		8.6 (1.7)	4.4, 13.1

Abbreviations: GLT, glucose load test; OGTT, oral glucose tolerance test; GWG, gestational weight gain; BMI, body mass index; IOM, Institute of Medicine; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; HbA1c, hemoglobin A1c.

[a]n=653 unique pregnancies, n=647 individual participants.

[b]Most SPRING participants did not complete clinical 50-g GLT or 100-g OGTT screenings as they completed 75-g OGTTs in early- and mid/late-pregnancy.

[c]n=633 unique pregnancies, n=627 individual participants.

[d]n=418 unique pregnancies, n=414 individual participants.

[e]SPRING will contribute participant fasting insulin data to ERGO when available.

[f]n=653 total ERGO infants delivered from n=633 unique ERGO pregnancies; n=613 singleton and n=20 twin gestations (n=40 infants).

[g]n=140 infants completing postpartum study visit (n=136 singleton infants, n=4 twin infants (2 sets of twins))

[h]Among infants completing postpartum visit data collection.

We collected postpartum data for 418 pregnancies (Table 3) and completed 300 full in-person (n=6 remote) postpartum study visits (n=186 ERGO visits; n=114 SPRING visits), during which we collected data from 140 infants (Table 3). Postpartum data were collected at a median of 9 weeks postpartum. Participant postpartum weight retention ranged from -14.6 to 24.7 kg (-2.2 to 3.7 kg/week) and mean (SD) HbA1c and HOMA-IR levels were 5.3% (0.3) and 1.5 (1.9), respectively. To date, a

subset of 1,053 participant urine samples collected in pregnancy (i.e., V1, V2, V3) and postpartum have been analyzed for concentrations of urinary phthalate and DINCH metabolites.

Initial studies in the ERGO cohort have focused on exposure and outcome data from pregnancy. To address the first aim of the ERGO Study, we investigated associations of prenatal exposure to phthalates and phthalate mixtures with glycemic outcomes during pregnancy within a subset of the LIFECODES pregnancy cohort, including participants concurrently enrolled in ERGO. We found that higher urinary metabolite concentrations of certain phthalates and phthalate mixtures during pregnancy were associated with higher odds of developing GDM and gestational glucose intolerance during pregnancy, with evidence of potential trimester-specific effects (114). This paper was among the first studies to investigate exposures to phthalate mixtures as they relate to glycemic outcomes in pregnancy. In a separate study, our team found an association between exposure to higher levels of ambient particulate matter (PM) gross beta-activity, a measure of exposure to environmental radiation via inhalation of radioactive PM components, and higher blood glucose levels during pregnancy within a subset of ERGO participants (115).

A pilot project supported by the March of Dimes Foundation (Research Grant #6-FY19-367) leveraged laboratory data and ERGO participant data to investigate personal care product use as it relates to EDC exposure and health in pregnancy in a series of recent publications (116-119). Using reporter gene assays, we found evidence of hormonal activity among commonly used hair products, including hair oils (118). Among ERGO participants, we found that self-reported use of certain hair and personal care product categories, particularly hair oils, was associated with urinary phthalate and DINCH metabolite concentrations (117) and that use of these products during pregnancy was associated with earlier gestational age at delivery (116, 119) and lower sex-specific birthweight-for-gestational age Z-scores (116).

FUTURE PLANS

Extended ERGO participant follow-up will continue via the ongoing annual post-pregnancy visits for both parent and child participants starting at ≥2 years post-index pregnancy with additional annual visits. Through the funded collaboration with the UPSIDE MOMS cohort (R01NR017602), urinary phthalate metabolite concentrations and blood markers of cardiometabolic health will be quantified in additional ERGO participant samples from postpartum through the Y4 post-pregnancy visit. New and existing data from pregnancy through Y4 will then be combined with parallel data from the UPSIDE MOMS cohort to study effects of phthalate exposures during pregnancy and postpartum on post-pregnancy cardiometabolic health in the combined cohort. Future research in the ERGO cohort will leverage the comprehensive longitudinal assessment of cardiometabolic health markers, environmental exposures, stored biospecimens, and pediatric data to study broader impacts of the environment on the health of pregnant, previously pregnant individuals, and their children.

STRENGTHS AND LIMITATIONS

The ERGO study has many notable strengths. Perhaps most important is the study's ability to longitudinally examine the relationships between repeated measures of environmental exposures and markers of cardiometabolic risk from the sensitive periods of pregnancy and postpartum through the extended post-pregnancy period, an understudied but potentially critical period for later-life cardiometabolic disease risk. Additionally, the ERGO study collected rich participant-reported data across key domains, including diet, the home environment, and behavioral factors associated with EDC exposures, such as personal care product use, as well as detailed data on additional health outcomes collected from medical record data, including pregnancy complications, adiposity measures, blood pressure and hypertensive disorders, fetal and neonatal measures, and ongoing postpartum health indicators. The ERGO study also collected data on sociodemographic indicators, personal and family

health history, stress, and social support. Not only will these data allow future researchers to account for the potential confounding role of these covariates, but they may help identify potentially modifiable factors, such as use of personal care products, which contribute to environmental exposures and their impacts on health.

Like many research cohorts, ERGO study activities were substantially impacted by the COVID-19 pandemic and its associated disruptions to research activities, facility access, and in-person study visits. These disruptions affected follow-up for multiple study visits, but most noticeably for the in-person postpartum visits. However, we were able to alter our visit protocols and developed a remote visit format, from which we were able to collect data, including remote glucose data, from participants who would otherwise have been lost to follow-up. Disruptions to participant follow-up resulted in a more modest sample size for certain study visits and activities, which may limit our ability to examine exposure-outcome relationships across subsets of the study population. Additionally, the ERGO cohort was English speaking, primarily non-Hispanic White, highly educated, and located in the Boston, MA metro-area, which may limit the generalizability of our findings to broader and more socio-demographically diverse populations. That said, ERGO has already identified novel risk factors of EDC exposure and adverse health outcomes, such as preterm birth and hair oil use, which are more common in diverse population groups, including non-Hispanic Black women. Thus, even with limited diversity, ERGO may provide key information on how environmental factors and their sources can impact parent and child health across the life course, while identifying modifiable and intervenable risk factors to improve health.

Collaborations

The authors encourage collaboration with interested investigators. Those interested should contact our research team to discuss possible collaborations and/or obtain additional information about the ERGO study. Specific data collection forms, questionnaires, and protocol documents are available

upon request. Additional information can be found on the For Researchers tab on the ERGO website: https://ergo.sph.harvard.edu/.

FURTHER DETAILS

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Author contributions

EVP participated in data management and analysis, abstraction of medical records, study design of ongoing ERGO efforts, and the writing of this manuscript. MRQ participated in data collection, sample processing, data management and analysis, abstraction of medical records, study implementation, and the preparation, review and editing of this manuscript. PLW participated in study design, data management and analysis, interpretation of results, and review and editing of the current manuscript. TFM participated in study design and implementation, resources for recruitment, sample collection and processing, and review and editing of the current manuscript. DEC participated in study design and implementation, supervision of recruitment, sample collection and processing, data management, and review and editing of current manuscript. EWS participated in the study design and implementation, data collection methodologies, review and editing of the current manuscript. BJW participated in interpretation of study results, review and editing of the current manuscript, MRH participated in study design and implementation, recruitment, data and sample collection, data management, interpretation

of study results, and review and editing of the current manuscript. KO participated in study implementation, interpretation of study results, and review and editing of the current manuscript. FMB participated in study design, data collection methodologies, review and editing of the current manuscript. CEP contributed SPRING study resources, including access to and harmonization of data and samples with ERGO, data management, and review and editing of the current manuscript. AB participated in study design, data management and analysis, interpretation of results, and review and editing of the current manuscript. ZW participated in data management and analysis, and review and editing of the current manuscript. KST participated in study design and implementation for expanded ongoing ERGO efforts, data analysis, and review and editing of the current manuscript. RH participated in study design and implementation, data management and interpretation of results, review and editing of current manuscript. TJT led in the design of the research questions and ERGO study, she oversaw human subjects and IRB approval, data collection and study implementation, including recruitment and retention efforts, as well as data management, analysis, interpretation of study results, and review and editing of the current manuscript.

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Competing interests

CEP is an Associate Editor of Diabetes Care, receives payments from Wolters Klumer for UpToDate chapters on diabetes in pregnancy, and has received payments for consulting and speaking from Mediflix, Inc. All other authors declare no additional actual or perceived competing interests.

Ethics approval

This study was approved by the Harvard Longwood Campus Institutional Review Board (HLC IRB) (ERGO BIDMC: #IRB17-1917) and the Partners (now Mass General Brigham) Human Research Institutional Review Board (ERGO BWH: #2016P000847; LIFECODES: #2009P000810; SPRING: #2015P002447).

Data availability statement

Data will be made available to interested collaborators pending submission and approval of a data interest form, analysis plan, and necessary IRB and institutional approvals.

FIGURE LEGENDS

Figure 1. Overview of (A) planned ERGO participant visits during pregnancy, early postpartum, and the extended post-pregnancy period and (B) ERGO participant enrollment in early pregnancy and retention through delivery and early postpartum data collection.

Abbreviations: ERGO, Environmental Reproductive and Glucose Outcomes Study; BWH, Brigham & Women's Hospital; BIDMC, Beth Israel Deaconess Medical Center; SPRING, Study of Pregnancy Regulation of Insulin and Glucose; MGH, Massachusetts General Hospital.

Figure 2. Self-reported personal care product use (% using) across pregnancy (V1-4) and postpartum (PP) study visits. Participants self-reported use of products during the 48-hours or 1-month prior to each visit depending on the survey instrument.

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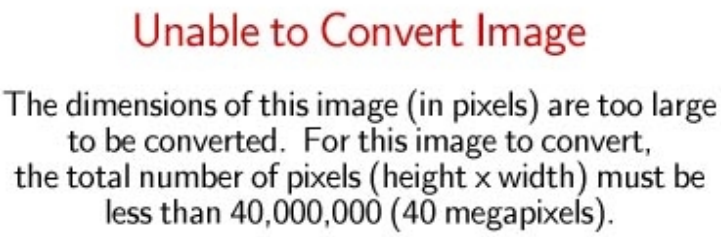

Figure 1. Overview of (A) planned ERGO participant visits during pregnancy, early postpartum, and the extended post-pregnancy period and (B) ERGO participant enrollment in early pregnancy and retention through delivery and early postpartum data collection.
Abbreviations: ERGO, Environmental Reproductive and Glucose Outcomes Study; BWH, Brigham & Women's Hospital; BIDMC, Beth Israel Deaconess Medical Center; SPRING, Study of Pregnancy Regulation of Insulin and Glucose; MGH, Massachusetts General Hospital.

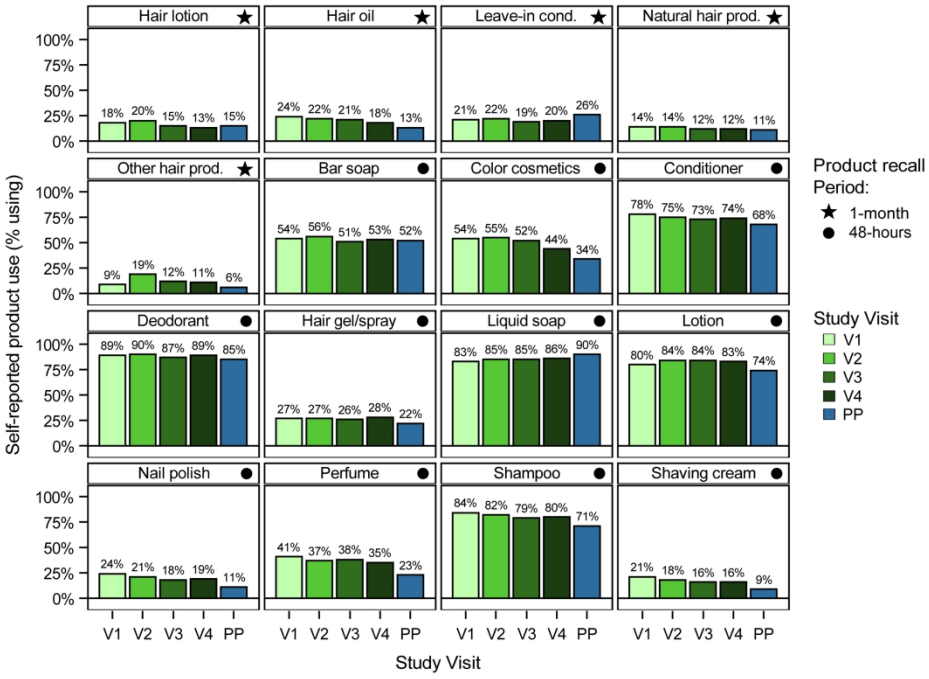

Figure 2. Self-reported personal care product use (% using) across pregnancy (V1-4) and postpartum (PP) study visits. Participants self-reported use of products during the 48-hours or 1-month prior to each visit depending on the survey instrument.

106x80mm (600 x 600 DPI)

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Cohort Profile: The Environmental Reproductive and Glucose Outcomes (ERGO) Study (Boston, MA) – a prospective pregnancy cohort study of the impacts of environmental exposures on parental cardiometabolic health

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Cohort Profile: The Environmental Reproductive and Glucose Outcomes (ERGO) Study (Boston, MA) – a prospective pregnancy cohort study of the impacts of environmental exposures on parental cardiometabolic health

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ABSTRACT

Purpose: Pregnancy and the postpartum period are increasingly recognized as sensitive windows for cardiometabolic disease risk. Growing evidence suggests environmental exposures, including endocrine disrupting chemicals (EDCs), are associated with an increased risk of pregnancy complications that are associated with long-term cardiometabolic risk. However, the impact of perinatal EDC exposure on subsequent cardiometabolic risk post-pregnancy is less understood. The Environmental Reproductive and Glucose Outcomes (ERGO) study was established to investigate the associations of environmental exposures during the perinatal period with post-pregnancy parental cardiometabolic health.

Participants: Pregnant individuals aged ≥18 years without preexisting diabetes were recruited at <15 weeks of gestation from Boston, MA area hospitals. Participants completed ≤ 4 prenatal study visits (median: 12, 19, 26, 36 weeks of gestation) and 1 postpartum visit (median: 9 weeks), during which we collected biospecimens, health histories, demographic and behavioral data, and anthropometry. Participants completed a postpartum fasting 2-hr 75-g oral glucose tolerance test. Clinical data were abstracted from electronic medical records. Ongoing (as of 2024) extended post-pregnancy follow-up visits occur annually following similar data collection protocols.

Findings to date: We enrolled 653 unique pregnancies and retained 633 through delivery. Participants had a mean age of 33 years, 10% (n=61) developed gestational diabetes, and 8% (n=50) developed preeclampsia. Participant pregnancy and postpartum urinary phthalate metabolite concentrations and postpartum glycemic biomarkers were quantified. To date, studies within ERGO found higher exposure to phthalates and phthalate mixtures, and separately, higher exposure to radioactive ambient particulate matter, were associated with adverse gestational glycemic outcomes. Additionally, certain personal care products used in pregnancy, notably hair oils, were associated with higher urinary phthalate metabolite concentrations, earlier gestational age at delivery, and lower birthweight.

Future plans: Future work will leverage the longitudinal data on pregnancy and cardiometabolic outcomes, environmental exposures, biospecimens, questionnaire and pediatric data within the ERGO cohort.

Strengths and Limitations

- The ERGO study prospectively follows participants through pregnancy, postpartum, and into the critically understudied post-pregnancy period.
- Comprehensive data on clinical and biomarker outcomes, environmental exposures, and diverse questionnaire domains will allow for prospective study of the effects of exposures during the perinatal and post-pregnancy periods on parental cardiometabolic risk.
- Repeated measures of exposures, outcomes, and covariates over the pregnancy and postpartum periods will allow us to evaluate potential understudied sensitive and critical periods of exposure.
- Disruptions due to the COVID-19 pandemic impacted participant follow-up and retention, particularly for in-person postpartum visits.
- ERGO findings may not be generalizable across broader populations given the cohort's high educational attainment, majority non-Hispanic White study population, and English-speaking eligibility criteria at two of three study sites.

INTRODUCTION

The perinatal period is a sensitive window for long-term parental health due to the rapid and extensive changes across multiple organ systems, both during pregnancy and postpartum.[1-6] Normal physiological changes in pregnancy pose a metabolic challenge to individuals due to adjustments the body makes for fetal growth and development, resulting in increased insulin resistance, inflammation, and alterations in body composition, lipid levels, and hemodynamic factors.[7-10] As such, pregnancy often represents a stress test for longer-term cardiometabolic health,[11] with individuals experiencing certain complications being at much higher risk for later-life cardiovascular disease (CVD). For instance, gestational diabetes mellitus (GDM) and preeclampsia are strong predictors of future type 2 diabetes mellitus and CVD risk.[3, 12-19] Lifestyle and pharmaceutical intervention studies during the perinatal period have shown mixed success in reducing the risk of pregnancy complications [20-24] and/or chronic disease following complicated pregnancies,[23, 25-29] emphasizing the importance of identifying modifiable risk factors to prevent long-term morbidity. Despite advances in understanding genetic and lifestyle risk factors, research on the contribution of environmental factors to cardiometabolic disease risk during and after pregnancy is underdeveloped.[30]

Endocrine disrupting chemicals (EDCs), such as phthalates, are commonly used in industrial and consumer products, leading to widespread human exposure to complex mixtures of many EDCs.[1, 31] Phthalates often are used as plasticizers, solvents, and lubricants in industrial applications and are found in many consumer products including personal care products, food and food packaging, and housing materials.[32-36] As with other EDCs,[1, 37-41] phthalate exposure has been associated with adverse cardiometabolic health outcomes.[42-45] Specifically, in pregnant populations, phthalate exposure has been associated with increased risk of GDM,[46-49] hypertensive disorders of pregnancy,[50-52] preterm birth,[53, 54]

increased gestational weight gain (GWG),[55-60] and subclinical effects such as altered blood lipid levels,[60-62] and alterations in markers of glycemic regulation.[46, 60, 63, 64]

Phthalates have been posited to alter metabolic regulation through multiple pathways, including effects on peroxisome proliferator-activated receptors (PPARs) α- and γ-,[37, 65-67] which regulate glucose and lipid metabolism.[37] Additionally, phthalates are linked to increased inflammation,[68-72] oxidative stress,[68, 72-74] and hormone-induced disruptions in insulin signaling,[75, 76] as evidenced by toxicologic and epidemiologic data. During pregnancy, these phthalate-induced effects may exacerbate existing pregnancy-induced metabolic stress, leading to increased metabolic perturbations (e.g., increased insulin resistance). Pregnant individuals with underlying metabolic dysfunction may be less able to adapt to this additional stress, such that they may be more likely to cross the threshold from subclinical dysfunction to overt metabolic disease. However, even subclinical metabolic changes during pregnancy, such as elevated glucose levels,[77-79] blood pressure,[80, 81] and gestational weight gain [2, 20, 82] can increase risk of later-life cardiometabolic disease.[83]

To date, studies of the impacts of perinatal EDC exposures on metabolic endpoints have focused almost exclusively on pregnancy outcomes, despite evidence that metabolic dysfunction during the post-pregnancy period also may impact subsequent cardiometabolic disease risk. For example, elevated postpartum blood glucose levels, elevated hemoglobin A1c (HbA1c), and greater postpartum weight retention have been associated with greater risk of type 2 diabetes.[77, 78, 84-86] However, the extent to which exposure to EDCs impacts metabolic regulation after pregnancy remains unclear. Further data are needed to elucidate the effects of pregnancy and postpartum EDC exposures on cardiometabolic health of previously pregnant individuals. Additionally, longitudinal data may help identify sensitive periods (i.e., pregnancy, individual trimesters, postpartum) during which EDC exposures have a greater impact on postpartum cardiometabolic risk, which could help inform risk reduction strategies.

Therefore, the Environmental Reproductive and Glucose Outcomes (ERGO) study was designed to investigate the impacts of exposure to phthalates and phthalate mixtures on cardiometabolic health indicators during pregnancy and the postpartum period with funding support from the National Institutes of Health (NIH) (R01ES026166).

Primary Aims

The original primary aims of the ERGO study were to:

1. Characterize pregnancy phthalate exposure and its associations with gestational glucose dysregulation (i.e., GDM, gestational glucose intolerance, and continuous blood glucose levels) assessed during routine clinical screening.
2. Estimate associations of biomarkers of phthalate exposure in pregnancy with postpartum glucose dysregulation (i.e., HbA1c, fasting insulin and glucose,[79] Homeostatic Model Assessment for Insulin Resistance [HOMA-IR], and 2-hr postprandial blood glucose) and adiposity (i.e., weight retention, skinfold thickness, waist- and hip- circumference, and body mass index) measured at 6-12 weeks postpartum.
3. Assess associations of postpartum biomarkers of phthalate exposure with postpartum glucose dysregulation (i.e., HbA1c, fasting insulin and glucose, HOMA-IR, and 2-hr postprandial blood glucose) and adiposity (i.e., weight retention, skinfold thickness, waist- and hip- circumference, and body mass index) measured at 6-12 weeks postpartum.

Through additional funding, the ongoing aims of the ERGO study have expanded to include an extended follow-up period, broader investigation of the impacts of other environmental exposures, as well as identification of the exposure sources of EDCs in pregnancy, postpartum, and the extended post-pregnancy period, on the cardiometabolic health of pregnant and previously pregnant individuals. Expanded ERGO study activities were/are supported by

projects funded through the NIH (R01ES033185; P30ES000002) and the March of Dimes (MOD Research Grant #6-FY19-367).

COHORT DESCRIPTION

Study Setting and Recruitment

ERGO Participant Recruitment

The ERGO study recruited pregnant participants from obstetrics clinics during routine prenatal visits beginning in December 2016 at Brigham and Women's Hospital (BWH) and in April 2018 at Beth Israel Deaconess Medical Center (BIDMC), both located in Boston, MA; recruitment ended in November 2020. Eligibility criteria included: <15 weeks of gestation at recruitment, English speaking, ≥18 years of age, and plans to receive prenatal care and deliver at one of the recruiting hospital sites. Participants with triplet or higher order gestations, preexisting diagnosis of type 1 or type 2 diabetes, and those with a preexisting condition making them unable to tolerate a fasting oral glucose tolerance test (OGTT) (e.g., prior bariatric surgery) were ineligible for the study. Individuals with preexisting prediabetes or glucose intolerance were eligible to participate. Participants were eligible to enroll during subsequent pregnancies that occurred during ERGO's recruitment period.

Trained research staff identified potential participants from patients scheduled for routine initial or early prenatal visits at BIDMC and BWH general obstetrics and maternal-fetal medicine clinics. Staff reviewed electronic medical records to perform an initial screening of patient eligibility based on patient age, estimated week of gestation, and documented diagnosis of type 1 or type 2 diabetes, if available. Staff approached potentially eligible individuals in participating clinics and provided them with study information and confirmed their eligibility; those eligible and wishing to enroll provided written informed consent. If an enrolled participant was determined to

no longer meet eligibility criteria during the study period (e.g., missed type 1 or type 2 diabetes diagnosis; a condition making them unable to tolerate OGTT; pregnancy loss) they were deemed ineligible after consent and excluded from analyses. Participants had the option to additionally enroll their anticipated infant(s) in the study at any time during pregnancy or at the postpartum visit. At BWH, ERGO participants were recruited using the same eligibility criteria as participants co-enrolled in the LIFECODES pregnancy cohort.[87] Enrolled ERGO participants were followed across pregnancy (data collection completed), postpartum (<2 years, data collection completed), and into the extended post-pregnancy follow-up period (≥2 years post-index pregnancy; data collection ongoing) (Figure 1A).

SPRING Cohort Participation & Contributions

In addition to directly enrolled participants described above, the ERGO cohort was augmented with data and biological samples collected from participants in the Study of Pregnancy Regulation of INsulin and Glucose (SPRING), a cohort based at Massachusetts General Hospital (MGH) with complementary data and sample collection protocols to ERGO.[88, 89] SPRING recruitment and eligibility criteria have been previously described.[89] Briefly, SPRING recruited pregnant individuals from the MGH obstetric practice and the broader Boston, MA area community through social media and community advertisements during March 2016–2021. Participants were eligible if they were between 4-14 weeks of gestation with preexisting GDM risk factors.[88] SPRING participants completed three study visits in pregnancy and postpartum, with similar cadence to ERGO (Visits at: ≤15 weeks of gestation, 24-32 weeks of gestation, and 6-24 weeks postpartum). During study visits, SPRING collected similar covariate and clinical data, participant biospecimens, as well as data from supplemental ERGO product use questionnaires. Detailed descriptions of SPRING study activities and data collection protocols were included in previous publications [88-91] and are not covered in detail

below. ERGO study activities described below refer to those completed by directly enrolled ERGO participants recruited from BWH and BIDMC, unless specifically noted.

ERGO Enrollment and Retention

We consented 515 eligible pregnant participants into the ERGO cohort, representing 521 unique pregnancies (n=328 from BWH and n=193 from BIDMC; n=6 participants enrolled in a second pregnancy) (Figure 1B). Of those, 33 pregnancies were removed for participants who withdrew (n=16), became ineligible after consent (n=9 nonviable pregnancy or loss; n=3 identified type 1 or 2 diabetic; n=3 unable to tolerate OGTT due to prior bariatric surgery; n=1 genetic disease affecting glucose metabolism), or had duplicate enrollments for the same pregnancy (n=1 reenrolled when transferring care from BIDMC to BWH). Data from 165 SPRING participants were integrated into the cohort, resulting in a total ERGO study population of 647 participants, representing 653 unique pregnancies. Of those, we retained 633 (97%) pregnancies through delivery (n=17 transferred care, n=3 lost to follow up), 304 (47%) completed postpartum study visits, and 465 (71%) had postpartum data collected from study visits, medical records, or remote questionnaires (Figure 1B). Of the 322 infants enrolled in ERGO, 140 (43%) completed the postpartum visit (n=136 singletons, n=4 twin infants).

Enrolled ERGO participants retained through delivery were invited to reconsent for an extended post-pregnancy follow-up period (≥2 years post-index pregnancy, ongoing as of 2024), regardless of whether they completed a postpartum study visit. Reconsented participants were invited to enroll their ERGO child(ren) to participate in supplemental pediatric data collection in parallel with parent follow-up activities, even if they did not consent their child during infancy. In-person data collection from Year 2 through Year 4 post-pregnancy is supported by an NIH-funded multi-cohort study (R01ES033185). This study leverages existing complementary pregnancy and postpartum data collected in both the ERGO and UPSIDE MOMS cohorts (R01NR017602) and new data collection at extended post-pregnancy follow-up

visits to investigate the effects of phthalate exposure during pregnancy and postpartum on post-pregnancy cardiometabolic health indicators. SPRING participants are not currently included in extended follow-up activities.

Overview of ERGO Study Activities

Pregnancy & Postpartum Follow-up (completed)

Enrolled ERGO participants were initially followed from early pregnancy into the postpartum period (6-12 weeks) (Figure 1A). During pregnancy, participants completed up to 4 in-person study visits (V1-4), designed to occur during the following time periods: V1, <15 weeks of gestation (median: 12); V2, 16-24 weeks of gestation (median: 19); V3, 24-28 weeks of gestation (median: 26), and V4, 34-38 weeks of gestation (median: 36). During pregnancy study visits, data were collected using a combination of participant questionnaires, electronic medical records, and participant biospecimens, as described in detail below.

Delivery information was abstracted from electronic medical records. After delivery, participants were sent a congratulatory card and a small gift (i.e., infant socks) by mail or in-person on the postpartum floor, along with a reminder that an ERGO RA would follow up to assist with scheduling their postpartum study visit. ERGO staff members called participants at an average of 2-4 weeks postpartum to schedule their in-person postpartum visit. Additional contact was made through email and text messages as appropriate.

Postpartum visits took place in-person at the Center for Clinical Investigation (CCI) at Brigham and Women's Hospital between 6-12 weeks postpartum for both BWH and BIDMC participants. However, due to disruptions from the COVID-19 pandemic, we extended the follow-up window through up to 24 months postpartum. This allowed participants nearing the 12-week cutoff who would have otherwise been lost to follow-up during the initial COVID-19 shutdown to complete postpartum visits; the shutdown started in Massachusetts on March 16,

2020, and resulted in research shutdowns for in-person visits through June 22, 2020. In practice, the latest visit occurred at 41 weeks (~9.5 months) postpartum, and the median was 9 weeks. Participants fasted prior to their visit; completed a 2-hr 75-g OGTT; provided a urine and two blood samples (fasting and 2-hours postprandial); completed a postpartum questionnaire and 24-hour food recall, and study staff collected anthropometric and blood pressure measurements. After the OGTT, participants were provided a snack as well as vouchers to cover the cost of their lunch following the study visit and the valet parking at the CCI. Additionally, participants were provided with electronic gift cards or a check for their participation. During the postpartum visit, participants were given the option to provide additional consent for their infant(s) to participate in a parallel data collection. If parents consented, research staff collected infant anthropometric measurements and a urine sample during the postpartum visit, as described below.

SPRING participants provided data from up to three study visits, which aligned most closely with ERGO V1, V3, and the postpartum visit. Infants born to SPRING participants did not participate.

Extended Post-pregnancy Follow-up (ongoing as of 2024)

During the extended post-pregnancy ERGO follow-up period, participants complete up to three additional annual in-person (CCI at BWH) or remote study visits starting at ≥2 years post-index pregnancy (ongoing). These visits are defined as Year 2 (Y2: ≥24 to <36 months), Year 3 (Y3: ≥36 to <48 months), etc. These visits follow similar protocols to the postpartum visit and include a combination of participant questionnaires, staff-collected anthropometric and vitals data, and participant biospecimens, as discussed below. SPRING participants are not currently included in extended ERGO follow-up activities.

Data Collection

The primary domains and timing of participant data collected in ERGO can be found in Table 1.

Table 1. ERGO Study Data Collection Domains by Study Visit (P= participant, C= neonate/child)

		Completed Study Timepoints (median weeks)						Ongoing Follow-up Visits			
		Pregnancy						Post-Pregnancy			
Category	Measure/Domain	Visit 1 (12 weeks)	Visit 2 (19 weeks)	Visit 3 (26 weeks)	Visit 4 (36 weeks)	Delivery (39 weeks)	Postpartum (9 weeks)	Year 2	Year 3	Year 4	Year 5+
Biological Samples	Urine	P	P	P	P		P, C	P, C	P, C	P, C	P, C
	Blood	P		P			P	P	P	P	P
	Toenails			P			P	P	P	P	P
Biomarker data	Non-fasting 50-g GLT			P[a]							
	Fasting 3-hr 100-g OGTT			P[b]							
	Fasting 2-hr 75-g OGTT			P[c]			P	P	P	P	P
	Fasting insulin						P	P	P	P	P
	HbA1c						P	P	P	P	P
	HOMA2-IR, -%S, -%B						P	P	P	P	P
	Lipid panel							P	P	P	P
	ApoB100							P	P	P	P
	Urinary phthalate & DINCH metabolites	P	P	P	P		P	P	P	P	P
	Urinary phenol metabolites				P						
Questionnaire domains	Demographics	P						P, C			
	Medical history	P						P, C	P, C	P, C	P, C
	Reproductive history	P						P	P	P	P
	Diet	P	P	P	P		P	P, C	P, C	P, C	P, C
	Physical activity	P	P	P	P		P	P, C	P, C	P, C	P, C
	Personal care product use	P	P	P	P		P	P, C	P, C	P, C	P, C
	Household environment	P	P	P	P		P	P, C	P, C	P, C	P, C
	Breastfeeding		P				P	P, C			
	Stress appraisal			P			P	P	P	P	P
	Social networks/ support			P			P				
	Adverse Childhood Experiences [92]							P			
	Sleep			P			P	P, C	P, C	P, C	P, C
	Emotional Well-being (EPDS) [93]			P			P	P	P	P	P
	Racism/ discrimination			P			P				
	COVID-19 impacts	P (June 2020)									
	Environmental health literacy						P (1+ years post-pregnancy)				
	Medication & supplement use	P					P	P, C	P, C	P, C	P, C

	Behavior & neurodevelopment							C	C	C	C
Clinical Data Abstraction	Medication use	P						C	C	C	C
	Blood pressure	P	P	P	P		P				
	Height	P	P	P	P	C					
	Weight	P	P	P	P	C	P				
	Pregnancy complications					P					
	Fetal ultrasound measures	C	C	C	C						
	Labor/delivery records					P, C					
	Growth charts						C[d]	C	C	C	C
Vitals & anthropometry	Blood pressure						P	P	P	P	
	Pulse wave velocity							P	P	P	
	Skin fold thickness measures						P, C	P	P	P	
	Waist & hip circumference						P	P	P	P	P
	Abdominal/waist circumference						C	C	C	C	C
	Height						P, C	P, C	C	C	C
	Weight						P, C	P, C	P, C	P, C	P, C

Abbreviations: GLT, glucose load test; OGTT, oral glucose tolerance test, HbA1c, hemoglobin A1c; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; -%S, for insulin sensitivity; -%B, for beta-cell function; ApoB100, apolipoprotein B-100; DINCH, 1,2-Cyclohexane dicarboxylic acid diisononyl ester.

[a]When available, non-fasting 1-hr 50-g GLT blood glucose levels from routine clinical screening were abstracted for all participants.

[b]When available, fasting 3-hr 100-g OGTT blood glucose levels from routine clinical screening were abstracted for all participants.

[c]SPRING participants completed fasting 75-g OGTTs at study visits during pregnancy.

[d]Historical growth records from pediatric visits will be abstracted for child participants enrolled in the follow-up study (ongoing).

Participant Questionnaires

Pregnancy & Postpartum (completed)

Participants completed questionnaires at all study visits. Specific domains included in questionnaires at each visit are shown in Table 1 and key domains and measures are described in more detail below. Survey format and content varied slightly by recruitment hospital, but key domains were included by all. At V1-V4, BWH participants co-enrolled in ERGO and LIFECODES completed paper questionnaires deployed by LIFECODES study staff at clinic visits, from which data was recorded and then shared with ERGO investigators. To maximize data harmonization between recruitment sites, the ERGO questionnaires deployed at BIDMC

(V1-V4) included questions from the LIFECODES questionnaires plus additional domains of interest (e.g., hair product use, stress appraisal, household characteristics, social support). The majority of BIDMC participants completed the V1 questionnaire electronically using a REDCap link that was sent via email by research staff. Subsequent questionnaires (V2-V4) were primarily completed on paper while in clinical spaces and then entered in REDCap by study staff. During the COVID-19 pandemic, we deployed all ERGO questionnaires remotely via REDCap email links sent directly to participants at both BIDMC and BWH, which allowed us to continue collecting participant data despite interruptions to clinic access. BWH participants remotely completed the longer ERGO questionnaires during this time.

Between 20 and 22 weeks of gestation, participants completed the Diet Health History Questionnaire (DHQ), a food frequency questionnaire developed by the National Cancer Institute (Bethesda, MD), from which we calculated caloric intake and nutrient levels.[94] As a measure of overall diet quality, participants also completed an adapted PrimeScreen questionnaire at V1, V2, V4, and postpartum.[95]

Self-reported data on use of hair products and personal care products were collected at each study visit using validated questionnaires.[96, 97] The hair product survey was developed by data collected in the Greater New York Hair Products Study [98] and included the following product categories: hair oils, hair lotions, leave-in conditioners, non-lye perms or relaxers, lye perms or relaxers, prescription hair products, natural hair products, or other hair products.[97] Participants were asked to report whether they had used each product category within the past month, and if yes, how frequently they used that product category. To collect data on a broader range of personal care product categories, participants completed a separate questionnaire on their use of the following product categories within the previous 48-hours: deodorant, hair gel/spray, conditioner/crème rinse, shampoo, perfume, hand/body lotion, shaving cream, nail

polish, suntan lotion, colored cosmetics, liquid soap, bar soap, and other hair products.[96] Data on frequency of use of these products were not collected during pregnancy or postpartum.

In June 2020, pregnant participants and those within 1 year postpartum completed a supplemental COVID-19 impact questionnaire, querying pandemic-related stress; infection history and precautions; and the Edinburgh Postnatal Depression Scale (EPDS).[93, 99] Between May 2021 and August 2022, we deployed an Environmental Health Literacy (EHL) questionnaire to ERGO participants who were at least a year postpartum, as part of an NIEHS-center funded pilot study (P30ES000002). The EHL questionnaire included sections related to participants' views on the environment and reproductive health, comfort with medical communications, and personal health habits.

SPRING collected similar participant-reported data on sociodemographic factors, personal medical and pregnancy history, and family medical history,[90] as well as supplemental data from ERGO personal care and hair product use questionnaires during the postpartum visit.

Extended Post-Pregnancy Follow-up (ongoing as of 2024)

Participants in the post-pregnancy follow-up visits complete an initial "catch-up" questionnaire at their first post-pregnancy follow-up visit, regardless of the year post-pregnancy. Data are collected on pubertal timing, menstruation history, updates to health history, and reproductive history, including additional pregnancies and their outcomes since their index pregnancy. Additional sections on breastfeeding, sleep, food introduction, health history, and household exposures during the first 2 years of their index child's life are also included. Participants also complete year-specific questionnaires (e.g., Y3, Y4, Y5, etc.) that include key domains repeated at each visit (e.g., health updates, diet, physical activity, parent and child product use, etc.) and others that are asked only at specific years (e.g., Parent: Adverse

Childhood Experiences; Child: age-specific developmental checklists, daycare/school activities) with sections related to both the parent and child (see Table 1).

Anthropometrics & Blood Pressure

Pregnancy & Postpartum Visits (completed)

Participant height and weight measurements from their initial prenatal visit, and repeated weight and blood pressure measures at each prenatal visit were abstracted from electronic medical records. At in-person ERGO postpartum visits, study staff measured participant height, waist and hip circumferences, skinfold thickness (i.e., subscapular, triceps, and suprailiac), and blood pressure, using research quality calibrated instruments and standard measurement protocols.[100, 101] Staff used a Tanita TBF-400 bioelectrical impedance analysis body composition analyzer (Tanita, Arlington Heights, IL), to measure weight, BMI, body fat percent, body fat mass, fat free mass, body water mass, body water percent, and basal metabolic rate. Additionally, infant length, weight, head and abdominal circumferences, and skinfold thickness (i.e., subscapular, triceps, suprailiac) were measured for enrolled infants during their parent's postpartum study visit. All measurements were taken twice and averaged for analyses.

Extended Post-pregnancy Visits (ongoing as of 2024)

Research staff collect the same measurements at in-person post-pregnancy visits as at the postpartum visit, described above. Pulse wave velocity is also measured using an ATCOR SphygmoCor Xcel (ATCOR, Naperville, IL) following standard techniques.[102] Additionally, a Tanita MC-780U multifrequency segmental body composition analyzer (Tanita, Arlington Heights, IL) will be used to obtain segmental (i.e., trunk, left leg, right arm, etc.) body measurements including fat percent and muscle mass.

Biospecimen Collection & Analysis

Blood Samples

Pregnancy & Postpartum Visits (completed)

Blood samples were collected from BIDMC participants during pre-established routine prenatal clinical blood draws during pregnancy V1 and V3. At the postpartum visit, clinical staff collected fasting and 2-hour postprandial blood samples from BIDMC and BWH participants following a 2-hr 75-g OGTT. Plasma samples in sodium fluoride/potassium oxalate tubes were immediately sent to LabCorp® (LabCorp Raritan, NJ), where they were analyzed for levels of fasting and 2-hour postprandial glucose, fasting insulin, and HbA1c, via enzymatic testing, electrochemiluminescence immunoassays (Roche Elecys/E170; Roche Diagnostics, Indianapolis, IN) and turbidimetric inhibition immunoassays (Tina-quant Hemoglobin A1c; Roche Diagnostics, Indianapolis, IN), respectively. Two additional sample tubes were processed, aliquoted, and stored at -80°C by research staff for future analyses.

Details of glycemic biomarkers measured in SPRING, including sample collection and laboratory methods, can be found in Thaweethai et al.[89]

Estimates of insulin resistance (HOMA2-IR), insulin sensitivity (HOMA2-%S), and beta-cell function (HOMA2-%B) were calculated from fasting insulin and glucose levels [103, 104] using the HOMA2 Calculator (University of Oxford, UK; Version 2.2.3) in Microsoft Excel.[105]

Extended Post-pregnancy Visits (ongoing as of 2024)

During in-person post-pregnancy visits, clinical staff collect fasting, 1-hour, and 2-hour postprandial blood samples following a 2-hr 75-g OGTT. Designated sample tubes are immediately sent to LabCorp® for measurement of fasting insulin, HbA1c, and fasting-, 1-, and 2-hour postprandial glucose levels, as described above, as well as a full lipid panel including ApoB100 using nuclear magnetic resonance spectroscopy (Vantera NMR Clinical Analyzer; LipoScience Inc., Raleigh, NC).[106] At each blood sample collection, two additional sample

tubes are processed, aliquoted, and stored at -80°C by research staff for future analyses. Lab results are shared with ERGO participants approximately one week after their study visit.

Urine Samples

Pregnancy & Postpartum Visits (completed)

Spot urine samples were collected from participants at all in-person study visits in non-sterile polypropylene collection cups. SPRING participants contributed urine samples collected at visits corresponding to ERGO V1, V3, and the postpartum visit, using the same method. During the initial phases of the COVID-19 pandemic, we developed and implemented a remote urine collection protocol. Participants were provided with instructions and supplies to collect a spot urine sample in a polypropylene collection cup at home, freeze it, and mail it back to our lab at Harvard University using provided insulated mailers and prepaid shipping labels for overnight shipment.

During the postpartum visit, urine samples were collected from enrolled infants using a diaper collection protocol consisting of a cotton collection pad placed in a study-provided diaper, which was then drained into a polypropylene urine collection cup.[107] Research staff measured the specific gravity of all urine samples using an Atago 4410 (PAL10S) Digital Urine Specific Gravity refractometer to account for urinary dilution in future analyses.

Urine samples from V1-V3 and postpartum were sent to the Centers for Disease Control and Prevention (CDC) Sample Logistics Laboratory (Atlanta, GA, USA) for analysis. Laboratory staff quantified urinary concentrations of 14 phthalate and 2 phthalate alternative [i.e., di(isononyl) cyclohexane-1,2-dicarboxylate (DINCH)] metabolites using previously published methods.[108] In a pilot study, an additional 130 urine samples from the most proximal study visit to delivery (i.e., V3 or V4) were analyzed for the same phthalate and DINCH metabolites,

as well as 12 phenolic compounds, by NSF International's Applied Research Center (Ann Arbor, MI, USA) using replicated methods to those used by the CDC.[108, 109]

Extended Post-pregnancy Visits (ongoing as of 2024)

During post-pregnancy visits, spot urine samples are collected from participants at each annual visit, either in-person or remotely, following the protocols described above. Additionally, remote parent-collected child urine samples are obtained using established protocols for both diaper collection [110] and toilet hat collection,[111] depending on the child's toilet training status. All urine samples are processed and aliquoted by research staff upon receipt as described above and are stored at -80°C prior to being sent for analysis.

Toenail Samples

Pregnancy & Postpartum Visits (completed)

Toenail sample collection at V3 and postpartum was added to the study protocol in December 2019. Prior to their V3 and postpartum visits, participants were given collection instructions and supplies to collect their toenail samples at home.[112] Participants were instructed to remove any nail polish and clean their toenails prior to collection, noting whether there had been polish on the nails within 48-hours of collection. Participants stored collected nails in provided labeled envelopes and either brought them to their next in-person study visit or mailed them to our lab. Samples were stored at room temperature for future analysis.

Extended Post-pregnancy Visits (ongoing as of 2024)

During the post-pregnancy follow up, parent toenail samples are collected and stored as described above at each visit.

Medical Record Data Abstraction

Pregnancy & Postpartum Records (completed)

Pregnancy data abstracted from medical records included participant height, date of last menstrual period, repeated vital measurements (e.g., blood pressure, weight, gestational week), medications, ultrasound data, clinical laboratory results, and pregnancy complications. As key outcome measures, we abstracted all data on clinical GDM diagnoses and results of routine clinical GDM screening, which generally occurs between 24-28 weeks of gestation. Recruiting hospitals most commonly use a 2-step screening approach comprised of 1) a non-fasting 1-hr 50-g glucose load test (GLT) followed by a 2) fasting 3-hr 100-g OGTT for those with abnormal GLT results. GDM is then diagnosed in individuals with 2 or more abnormal OGTT values.[113]

Delivery data abstraction included date and gestational age at delivery; delivery time; labor details; interventions; medications; indication and mode of delivery; and intrapartum complications and morbidity. Vitals data were abstracted through the postpartum visit. Missing participant questionnaire data on sociodemographic and health history variables (e.g., race and ethnicity, insurance status, parity, family history) were abstracted from medical records when available. If available, data were also abstracted from clinical postpartum visit records for participants who did not complete an in-person or remote postpartum study visit.

Of note, SPRING screened and diagnosed GDM in participants directly using the International Association of the Diabetes in Pregnancy Study Group's (IADPSG) 2010 criteria,[114] rather than via medical record diagnosis; full details are included in Thaweethai et al.[89]

Neonatal Records (completed)

Measures of gestational age at delivery, fetal distress, infant sex, length, birth weight, and head circumference, Apgar scores, neonatal intensive care unit admission, and neonatal complications were abstracted from medical records. Additional fetal biometry data from

prenatal ultrasounds were abstracted from electronic medical records during pregnancy for BIDMC participants only.

Pediatric Records (ongoing as of 2024)

If participants consent to provide access to their index child's pediatric medical records as part of the supplemental pediatric data collection during the extended ERGO follow-up, data on pediatric growth, routine well-visit assessments, infections, vaccinations, medications, health conditions (e.g., allergy, eczema, gastroesophageal reflux disease), clinical laboratory values, and other diagnoses will be abstracted.

Patient and Public Involvement Statement

Participants were not involved in designing, managing, or conducting ERGO study research activities, outside of their role as study participants providing biological samples and completing data collection activities.

FINDINGS TO DATE

Among the 653 eligible unique ERGO pregnancies (corresponding to 647 individual participants), 633 were retained through delivery; participation in data collection activities varied across study visits and by recruitment site. On average, participants were 33 (SD: 4.8) years of age at consent with a mean (SD) BMI at Visit 1 of 27.8 (6.6) kg/m^2 (Table 2).

Table 2. ERGO participant characteristics (n=647 participants, n=653 unique pregnancies)

Characteristic	n	%[a]	Mean (SD)	Range
Age at consent (years)	653		32.9 (4.8)	19.3, 48.3
Visit 1 BMI (kg/m^2)	650		27.8 (6.6)	16.8, 56.5
Underweight (<18.5)	8	1%		
Normal weight (18.5–24.9)	261	40%		
Overweight (25–29.9)	187	29%		
Obese (≥30)	194	30%		
Self-reported race and ethnicity	651			
Non-Hispanic White	377	58%		
Hispanic	103	16%		

Non-Hispanic Black	76	12%
Asian	56	9%
More than one race	24	4%
Some other race	15	2%
Parity	646	
Nulliparous	312	48%
Educational attainment	635	
College degree or higher	498	78%
Partnership status	624	
Married	484	78%
Single, living with partner	108	17%
Single, not living with partner	32	5%
Employment status	615	
Employed (full- or part-time)	559	91%
Insurance status[b]	472	
Private insurance	278	59%
Other (Self-pay, Medicaid/SSI/ Mass Health, Unsure)	194	41%
Smoking status	615	
Smoked during pregnancy	19	3%
Family history of diabetes	629	
Yes	221	35%
Family history of CVD/hypertension[b]	462	
Yes	181	39%

Abbreviations: SD, standard deviation; BMI, body mass index; CVD, cardiovascular disease; SSI, Supplemental Security Income.
[a]Frequencies may not sum to 100 due to rounding.
[b]Data not collected for SPRING participants.

Most participants held a college degree or higher (78%), were married or living with a partner (95%) and did not have a family history of diabetes (65%). Self-reported smoking during pregnancy was low (3%). Participant self-reported personal care product use varied slightly across study visits but substantially by product category (Figure 2). Participants who were lost to follow up prior to delivery (n=20) were less likely to identify as non-Hispanic White (35% vs. 59%), younger (mean: 30.3 vs. 33.0 years), and had higher mean Visit 1 BMI (29.9 vs. 27.7 kg/m^2) (Supplemental Table S1). Among the full ERGO study population, the distribution of participants across self-reported race and ethnicity categories was similar to that of U.S. females aged 15-50 years, except for a slightly lower percentage of ERGO participants identifying as Hispanic (16% vs. 21%) (Supplemental Table S2). ERGO participants were more

racially diverse than the population of females aged 15-50 years in the Boston metro area (non-Hispanic White: 58% vs. 64%) and in Massachusetts (65%). The proportion of ERGO participants holding a college degree or higher was substantially higher than among females aged 25-44 in the U.S. (40%), Boston metro area (61%), and Massachusetts (55%). Conversely, ERGO participants were less likely to report having private health insurance compared to the comparison populations (Supplemental Table S2).

GDM screening data from 1-hr 50-g GLTs were available in 481 pregnancies [mean (SD): 112.7 (27.8) mg/dL; 6.3 (1.5) mmol/L] and results of fasting 3-hr 100-g OGTTs were available in 85 pregnancies; in general, SPRING participants did not have data on 1-hr GLTs or 100-g OGTTs in pregnancy as they completed 75-g OGTTs at V1 and V3 per SPRING protocol (Table 3). During pregnancy, 10% of participants were diagnosed with GDM and 8% developed preeclampsia. The mean (SD) total gestational weight gain was 11.5 (6.0) kg, with 31% of pregnancies falling within the Institute of Medicine (IOM) recommended total GWG-for-pre-pregnancy BMI ranges (41% above range; 28% below range).[115] Of the 633 ERGO deliveries, 63% were vaginal, 10% were preterm (<37 weeks of gestation), and the mean (SD) gestational week at delivery was 38.6 (2.0) weeks. Due to twin gestations, the total number of delivered infants was 653 (n=613 singletons and n=40 twin infants) and the mean (SD) infant birth weight was 3,192 (571) g (Table 3).

Table 3. ERGO participant measures from pregnancy, delivery, and postpartum data collection

Adult Participant Measures	n	%	Mean (SD)	Range
Pregnancy	653[a]			
Clinical glucose screening levels (mg/dL)[b]				
Non-fasting 50-g GLT, 1-hr glucose	481		113 (27.8)	37, 213
Fasting 3-hr 100-g OGTT				
Fasting glucose	87		82 (9.5)	65, 107
1-hr glucose	85		160 (34.6)	85, 251
2-hr glucose	85		134 (34.1)	70, 228
3-hr glucose	85		100 (36.1)	34, 205
Total gestational weight gain (kg)	634		11.5 (6.0)	-21.5, 29.9

GWG-for-BMI, IOM guidelines [115]	633			
Insufficient	180	28%		
Recommended	193	31%		
Excessive	260	41%		
Pregnancy complications	647[c]			
Gestational diabetes	61	10%		
Preeclampsia	50	8%		
Gestational hypertension	69	11%		
Delivery	633[d]			
Gestational weeks at delivery	633		38.6 (2.0)	24.0, 41.7
Preterm birth (<37 weeks)	66	10%		
Delivery mode				
Vaginal, spontaneous	231	36%		
Vaginal, induced	170	27%		
Cesarean, scheduled	113	18%		
Cesarean, emergent	119	19%		
Postpartum	465[e]			
Week postpartum at data collection	465		9.0 (4.3)	2.3, 41.0
BMI (kg/m^2)	409		28.3 (6.1)	18.1, 54.1
Weight retention (kg)	407		2.4 (4.9)	-14.6, 24.7
Adjusted weight retention (kg/weeks)	407		0.7 (1.5)	-2.2, 3.7
Anthropometrics				
Hip circumference (cm)	189		108.5 (13.2)	79.0, 171.8
Waist circumference (cm)	189		91.6 (14.4)	67.7, 145.5
Waist-to-hip ratio	189		0.8 (0.1)	0.5, 1.1
Skinfold thickness (mm)				
Suprailiac	176		15.5 (7.7)	2.8, 39.3
Subscapular	163		19.5 (8.2)	6.6, 39.0
Triceps	175		24.0 (6.2)	11.6, 39.1
Blood Pressure (mmHg)				
Systolic	315		115 (13.2)	87, 223
Diastolic	315		70 (9.5)	52, 119
Glycemic biomarkers				
HbA1c (%)	293		5.3 (0.3)	4.1, 6.1
Fasting 2-hr 75-g OGTT				
Fasting insulin (µIU/mL)	289		6.5 (6.6)	0.6, 73.8
Fasting glucose (mg/dL)	313		83 (8.6)	61, 124
2-hr glucose (mg/dL)	291		94 (26.0)	29, 208
HOMA2-IR	289		0.72 (0.70)	0.06, 7.46
HOMA2-B (%)[f]	289		85.6 (38.0)	30.5, 425.9
HOMA2-S (%)[f]	289		220.1 (171.9)	13.4, 1641.5
Infant Measures	**n**	**%**	**Mean (SD)**	**Range**
Birth	653[g]			
Gestational age at birth (weeks)	653		38.6 (2.0)	24.0, 41.7
Twin gestation	20	3%		
Birth weight (g)	651		3192 (571)	710, 5150

Birth length (cm)	478		48.8 (4.5)	18.5, 56.0
Head circumference (cm)	447		34.1 (1.8)	23.0, 39.0
Apgar score				
1-minute	641		7.9 (1.4)	1, 10
5-minute	639		8.9 (0.6)	3, 10
Infant sex	642			
Female	340	53%		
Neonatal intensive care unit admission	117	18%		
Postpartum	140[h]			
Gestational age at birth (weeks)[i]	140		39.0 (1.4)	34.4, 41.6
Age at visit (weeks)	140		8.1 (2.7)	4.0, 26.0
Weight (g)	140		5011 (818)	2760, 8020
Length (cm)	137		57.2 (4.3)	31.4, 69.5
Head circumference (cm)	131		38.7 (1.8)	32.1, 44.5
Abdominal circumference (cm)	129		38.8 (3.5)	24.0, 58.2
Skinfold thickness (mm)				
Suprailiac	119		5.4 (1.6)	2.7, 9.4
Subscapular	131		7.4 (1.6)	4.1, 12.0
Triceps	125		8.6 (1.7)	4.4, 13.1

Abbreviations: SD, standard deviation; GLT, glucose load test; OGTT, oral glucose tolerance test; GWG, gestational weight gain; BMI, body mass index; IOM, Institute of Medicine; HOMA2, Homeostatic Model Assessment; HOMA2-IR, HOMA2 for Insulin Resistance; HOMA2-B, HOMA2 for beta-cell function; HOMA2-S, HOMA2 for insulin sensitivity; HbA1c, hemoglobin A1c.

[a]n=653 unique pregnancies, n=647 individual participants.

[b]Most SPRING participants did not complete clinical 50-g GLT or 100-g OGTT screenings as they completed 75-g OGTTs in early- and mid/late-pregnancy.

[c]Sample sizes with available data: n=637, gestational diabetes; n=647, preeclampsia; n=634, gestational hypertension.

[d]n=633 unique pregnancies, n=627 individual participants.

[e]n=465 unique pregnancies, n=461 individual participants.

[f]Expressed as %, where 100% is normal.

[g]n=653 total ERGO infants delivered from n=633 unique ERGO pregnancies; n=613 singleton and n=20 twin gestations (n=40 infants).

[h]n=140 infants completing postpartum study visit (n=136 singleton infants, n=4 twin infants (2 sets of twins))

[i]Among infants completing postpartum visit data collection.

We collected postpartum data for 465 pregnancies (Table 3) and completed 304 full postpartum study visits (n=298 in-person and n=6 remote visits; n=190 ERGO visits and n=114 SPRING visits), during which we collected data from 140 infants (Table 3). Postpartum data were collected at a median of 9 weeks postpartum. Participant postpartum weight retention ranged from -14.6 to 24.7 kg (-2.2 to 3.7 kg/week) and mean (SD) HbA1c and HOMA2-IR levels

were 5.3% (0.3) and 0.72 (0.7), respectively. Participants who completed a postpartum visit were more likely to report being non-Hispanic White (61% vs. 50%), parous (56% vs. 46%), to have private insurance (72% vs. 38%), a college degree (87% vs. 74%), and to have had gestational diabetes (13% vs. 8%) compared to those with no postpartum data, but were more similar to participants with postpartum questionnaire or abstracted medical record data (Supplemental Table S3).To date, a subset of 1,053 participant urine samples collected in pregnancy (i.e., V1, V2, V3) and postpartum have been analyzed for concentrations of urinary phthalate and DINCH metabolites.

Initial studies in the ERGO cohort have focused on exposure and outcome data from pregnancy. To address the first aim of the ERGO Study, we investigated associations of prenatal exposure to phthalates and phthalate mixtures with glycemic outcomes during pregnancy within a subset of the LIFECODES pregnancy cohort, including participants concurrently enrolled in ERGO. We found that higher urinary metabolite concentrations of certain phthalates and phthalate mixtures during pregnancy were associated with higher odds of developing GDM and gestational glucose intolerance during pregnancy, with evidence of potential trimester-specific effects.[116] This paper was among the first studies to investigate exposures to phthalate mixtures as they relate to glycemic outcomes in pregnancy. In a separate study, our team found an association between exposure to higher levels of ambient particulate matter (PM) gross beta-activity, a measure of exposure to environmental radiation via inhalation of radioactive PM components, and higher blood glucose levels during pregnancy within a subset of ERGO participants.[117]

A pilot project supported by the March of Dimes Foundation (Research Grant #6-FY19-367) leveraged laboratory data and ERGO participant data to investigate personal care product use as it relates to EDC exposure and health in pregnancy in a series of recent publications.[118-121] Using reporter gene assays, we found evidence of hormonal activity

among commonly used hair products, including hair oils.[120] Among ERGO participants, we found that self-reported use of certain hair and personal care product categories, particularly hair oils, was associated with urinary phthalate and DINCH metabolite concentrations [119] and that use of these products during pregnancy was associated with earlier gestational age at delivery [118, 121] and lower sex-specific birthweight-for-gestational age Z-scores.[118]

FUTURE PLANS

Extended ERGO participant follow-up will continue via the ongoing annual post-pregnancy visits for both parent and child participants starting at ≥2 years post-index pregnancy with additional annual visits. Through the funded collaboration with the UPSIDE MOMS cohort (R01NR017602), urinary phthalate metabolite concentrations and blood markers of cardiometabolic health will be quantified in additional ERGO participant samples from postpartum through the Y4 post-pregnancy visit. New and existing data from pregnancy through Y4 will then be combined with parallel data from the UPSIDE MOMS cohort to study effects of phthalate exposures during pregnancy and postpartum on post-pregnancy cardiometabolic health in the combined cohort. Future research in the ERGO cohort will leverage the comprehensive longitudinal assessment of cardiometabolic health markers, environmental exposures, stored biospecimens, and pediatric data to study broader impacts of the environment on the health of pregnant, previously pregnant individuals, and their children.

STRENGTHS AND LIMITATIONS

The ERGO study has many notable strengths. Perhaps most important is the study's ability to longitudinally examine the relationships between repeated measures of environmental exposures and markers of cardiometabolic risk from the sensitive periods of pregnancy and

postpartum through the extended post-pregnancy period, an understudied but potentially critical period for later-life cardiometabolic disease risk. Additionally, the ERGO study collected rich participant-reported data across key domains, including diet, the home environment, and behavioral factors associated with EDC exposures, such as personal care product use, as well as detailed data on additional health outcomes collected from medical record data, including pregnancy complications, adiposity measures, blood pressure and hypertensive disorders, fetal and neonatal measures, and ongoing postpartum health indicators. The ERGO study also collected data on sociodemographic indicators, personal and family health history, stress, and social support. Not only will these data allow future researchers to account for the potential confounding role of these covariates, but they may help identify potentially modifiable factors, such as use of personal care products, which contribute to environmental exposures and their impacts on health.

Like many research cohorts, ERGO study activities were substantially impacted by the COVID-19 pandemic and its associated disruptions to research activities, facility access, and in-person study visits. These disruptions affected follow-up for multiple study visits, but most noticeably for the in-person postpartum visits. However, we were able to alter our visit protocols and developed a remote visit format, from which we were able to collect data, including remote glucose data, from participants who would otherwise have been lost to follow-up. Disruptions to participant follow-up resulted in a more modest sample size for certain study visits and activities, which may limit our ability to examine exposure-outcome relationships across subsets of the study population. Additionally, the ERGO cohort was English speaking, primarily non-Hispanic White, highly educated, and located in the Boston, MA metro-area. ERGO participants' high educational attainment but lower rate of private health insurance may reflect the high density of universities, professional schools, and training hospitals in the Boston metro-area, resulting in a relatively large population of graduate students and postgraduate trainees who may be eligible

for public or subsidized insurance programs, particularly given Massachusetts' longstanding public insurance programs and broader coverage for pregnant individuals. These factors may limit the generalizability of our findings to populations with greater diversity in education and related socio-demographic factors. That said, the ERGO has already identified novel risk factors of EDC exposure and adverse health outcomes, such as preterm birth and hair oil use, which are more common in diverse population groups, including non-Hispanic Black women. Thus, ERGO may provide key information on how environmental factors and their sources can impact parent and child health across the life course, while identifying modifiable and intervenable risk factors to improve health.

Collaborations

The authors encourage collaboration with interested investigators. Those interested should contact our research team to discuss possible collaborations and/or obtain additional information about the ERGO study. Specific data collection forms, questionnaires, and protocol documents are available upon request. Additional information can be found on the For Researchers tab on the ERGO website: https://ergo.sph.harvard.edu/.

FURTHER DETAILS

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Author contributions

EVP participated in data management and analysis, abstraction of medical records, study design of ongoing ERGO efforts, and lead the writing and editing of this manuscript. MRQ participated in data collection, sample processing, data management and analysis, abstraction of medical records, study implementation, and the preparation, review and editing of the current manuscript. PLW participated in study design, data management and analysis, interpretation of results, and review and editing of the current manuscript. TFM participated in study design and implementation, resources for recruitment, sample collection and processing, and review and editing of the current manuscript. DEC participated in study design and implementation, supervision of recruitment, sample collection and processing, data management, and review and editing of current manuscript. EWS participated in the study design and implementation, data collection methodologies, review and editing of the current manuscript. BJW participated in interpretation of study results, review and editing of the current manuscript, MRH participated in study design and implementation, recruitment, data and sample collection, data management, interpretation of study results, and review and editing of the current manuscript. KO participated in study implementation, interpretation of study results, and review and editing of the current manuscript. FMB participated in study design, data collection methodologies, review and editing of the current manuscript. CEP contributed SPRING study resources, including access to and harmonization of data and samples with ERGO, data management, and review and editing of the current manuscript. AB participated in study design, data management and analysis, interpretation of results, and review and editing of the current manuscript. ZW participated in data management and analysis, and review and editing of the current manuscript. KST participated in study design and implementation for expanded ongoing ERGO efforts, data analysis, and review and editing of the current manuscript. RH participated in study design and implementation, data management and interpretation of results, review and editing of current

manuscript. TJT led in the design of the research questions and ERGO study, she oversaw human subjects and IRB approval, data collection and study implementation, including recruitment and retention efforts, as well as data management, analysis, interpretation of study results, and review and editing of the current manuscript.

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Competing interests

CEP is an Associate Editor of Diabetes Care, receives payments from Wolters Klumer for UpToDate chapters on diabetes in pregnancy, and has received payments for consulting and speaking from Mediflix, Inc. All other authors declare no additional actual or perceived competing interests.

Data availability statement

Data will be made available to interested collaborators pending submission and approval of a data interest form, analysis plan, and necessary IRB and institutional approvals.

FIGURE LEGENDS

Figure 1. Overview of (A) planned ERGO participant visits during pregnancy, early postpartum, and the extended post-pregnancy period and (B) ERGO participant enrollment in early pregnancy and retention through delivery and early postpartum data collection.

Abbreviations: ERGO, Environmental Reproductive and Glucose Outcomes Study; BWH, Brigham & Women's Hospital; BIDMC, Beth Israel Deaconess Medical Center; SPRING, Study of Pregnancy Regulation of Insulin and Glucose; MGH, Massachusetts General Hospital.

Figure 2. Self-reported personal care product use (% using) across pregnancy (V1-4) and postpartum (PP) study visits. Participants self-reported use of products during the 48-hours or 1-month prior to each visit depending on the survey instrument.

Ethical approval statement

This study was approved by the Harvard Longwood Campus Institutional Review Board (HLC IRB) (ERGO BIDMC: #IRB17-1917) and the Partners (now Mass General Brigham) Human Research Institutional Review Board (ERGO BWH: #2016P000847; LIFECODES: #2009P000810; SPRING: #2015P002447).

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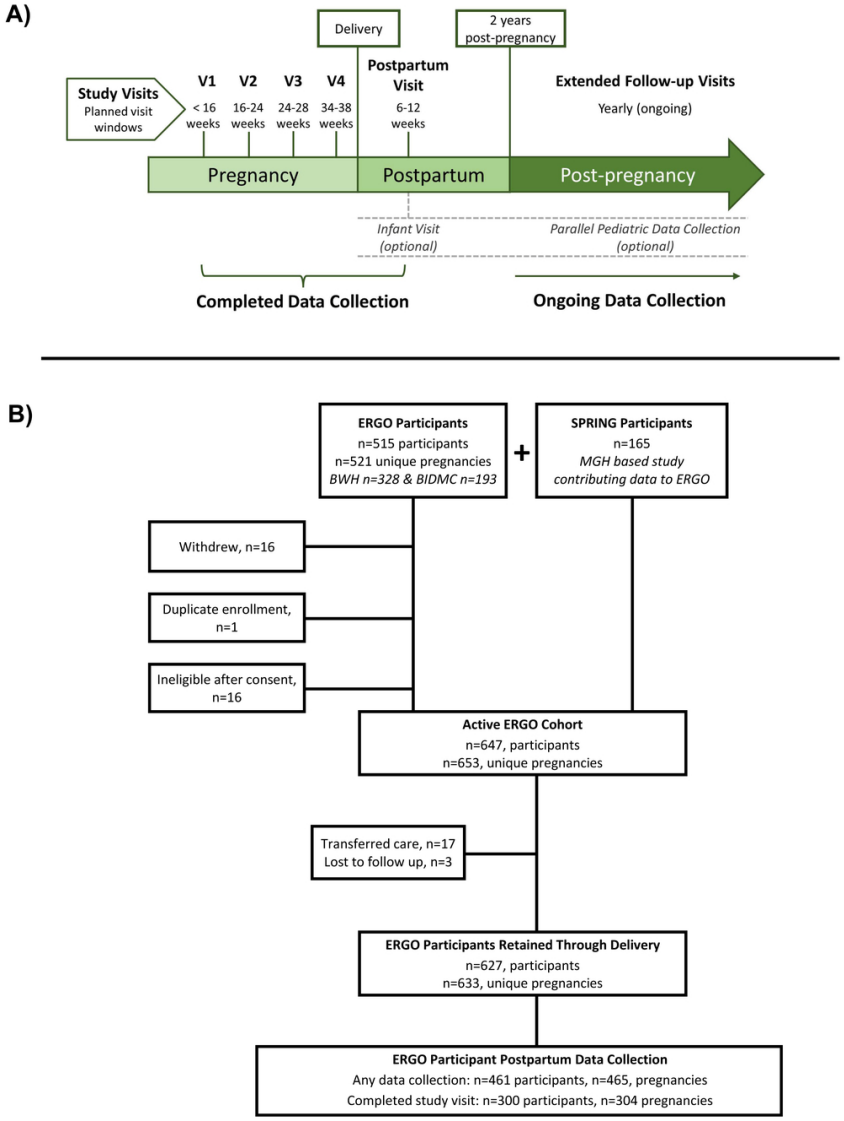

Figure 1. Overview of (A) planned ERGO participant visits during pregnancy, early postpartum, and the extended post-pregnancy period and (B) ERGO participant enrollment in early pregnancy and retention through delivery and early postpartum data collection.
Abbreviations: ERGO, Environmental Reproductive and Glucose Outcomes Study; BWH, Brigham & Women's Hospital; BIDMC, Beth Israel Deaconess Medical Center; SPRING, Study of Pregnancy Regulation of Insulin and Glucose; MGH, Massachusetts General Hospital.

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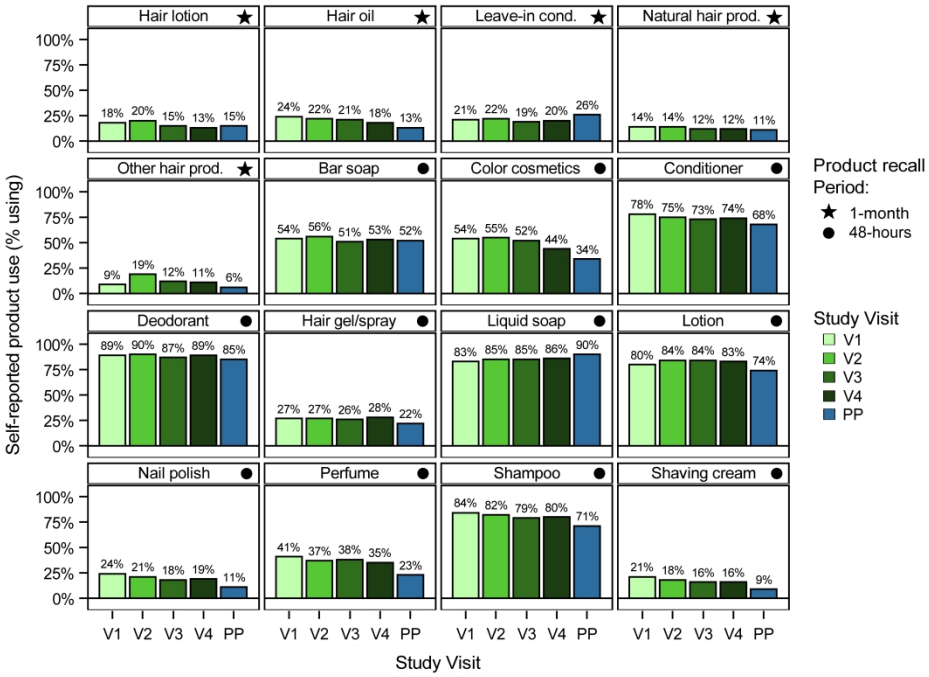

Figure 2. Self-reported personal care product use (% using) across pregnancy (V1-4) and postpartum (PP) study visits. Participants self-reported use of products during the 48-hours or 1-month prior to each visit depending on the survey instrument.

106x80mm (1200 x 1200 DPI)

Supplemental Materials

Cohort Profile: The Environmental Reproductive and Glucose Outcomes (ERGO) Study (Boston, MA) – a prospective pregnancy cohort study of the impacts of environmental exposures on parental cardiometabolic health

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Table S1. Characteristics of ERGO pregnancies retained through delivery (n=633 unique pregnancies) compared to those lost to follow-up during pregnancy (n=20 unique pregnancies)

	Retained to delivery (n=633)		Lost to follow-up (n=20)[a]	
Characteristic	**n**	**Mean (SD) or %**	**n**	**Mean (SD) or %**
Age (years)	633	33.0 (4.8)	20	30.3 (5.8)
Visit 1 BMI (kg/m^2)	631	27.7 (6.5)	19	29.8 (8.4)
Self-reported race and ethnicity	631		20	
Non-Hispanic White	370	59%	7	35%
Hispanic	99	16%	4	20%
Non-Hispanic Black	71	11%	5	25%
Asian	53	8%	3	15%
More than one race	24	4%	0	0%
Some other race	14	2%	1	5%
Parity	630		16	
Nulliparous	303	48%	9	56%
Type of insurance	463		9	
Private insurance/HMO	270	58%	8	89%
Other (Self pay, Medicaid/SSI/MassHealth, Unsure)	193	42%	1	11%
Educational attainment	623		12	
College degree or higher	488	78%	10	83%

Abbreviations: BMI, body mass index; ERGO, the Environmental Reproductive and Glucose Outcomes Study; HMO, health maintenance organization; SD, standard deviation; SSI, Supplemental Security Income.

[a]n=17 participants transferred care; n=3 unknown lost to follow-up.

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Table S2. Demographic characteristics among ERGO participants compared to Female population subgroups in the Boston metro area, Massachusetts, and the United States based on 2019 U.S. Census Data[1]

Characteristic	ERGO	Boston Metro Area	Massachusetts	United States
College degree (Female, 25-44 years)	78%	61%	55%	40%
Race and ethnicity (Female, 15-50 years)				
Non-Hispanic White	58%	64%	65%	55%
Hispanic	16%	13%	14%	21%
Non-Hispanic Black	12%	8%	8%	14%
Asian	9%	11%	9%	7%
More than 1 race	4%	2%	3%	3%
Some other race	2%	1%	1%	1%
Type of Insurance (Female, 19-44 years)[a]				
Private Insurance/HMO	59%	77%	73%	68%
Public[b]	40%	19%	23%	19%
Uninsured	0%	4%	4%	13%

Abbreviations: ERGO, the Environmental Reproductive and Glucose Outcomes Study; HMO, health maintenance organization; SSI, Supplemental Security Income.
[a]Private insurance includes coverage provided by an employer or union or coverage purchased directly; Public insurance includes Medicaid, Medicare, CHAMPVA (Civilian Health and Medical program of the Dept. of Veterans Affairs), and care provided by the Dept. of Veterans Affairs and the military.
[b]ERGO participants selecting: "self pay" or "Medicaid/SSI/Mass Health"; n=4 (1%) ERGO participants selected "Unsure" for insurance (not shown).
[1]Source: U.S. Census Bureau. 2019 American Community Survey. Accessed 9 April 2024. https://data.census.gov/

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Table S3. Characteristics among ERGO participants with postpartum visit data (n=304), other postpartum data (n=161), and no postpartum data (n=188) as of April 2024

	Postpartum Visit Data (n=304)		Other Postpartum Data[a] (n=161)		No Postpartum Data[b] (n=188)	
Characteristic	**n**	**Mean (SD) or %**	**n**	**Mean (SD) or %**	**n**	**Mean (SD) or %**
Age (years)	304	32.9 (4.6)	161	33.2 (4.7)	188	32.5 (5.1)
Visit 1 BMI (kg/m^2)	302	27.5 (6.2)	161	27.0 (6.5)	187	28.9 (7.1)
Gestational weeks at delivery	304	38.9 (1.8)	160	38.5 (2.2)	169	38.4 (2.2)
Self-reported race and ethnicity	304		161		186	
Non-Hispanic White	186	61%	99	61%	92	50%
Hispanic	46	14%	24	15%	33	18%
Non-Hispanic Black	32	11%	14	9%	30	16%
Asian	27	9%	14	9%	15	8%
More than one race	8	3%	8	5%	8	4%
Some other race	5	2%	2	1%	8	4%
Parity	304		160		182	
Nulliparous	135	44%	79	49%	98	54%
Type of insurance	186		157		129	
Private insurance/HMO	133	72%	98	62%	47	38%
Other (Self pay, Medicaid/SSI/MassHealth, Unsure)	53	28%	59	38%	82	62%
Educational attainment	301		160		174	
College degree or higher	263	87%	122	76%	128	74%
Pregnancy complications[c]	303		161		183	
Gestational diabetes[d]	39	13%	8	5%	14	8%
Preeclampsia	20	7%	12	7%	18	10%
Delivery mode	304		160		169	
Vaginal, spontaneous	135	44%	56	35%	40	24%
Vaginal, induced	60	20%	50	31%	60	35%
Cesarean, scheduled	57	19%	27	17%	29	17%
Cesarean, emergent	52	17%	7	17%	40	24%
Infant NICU admission	304		160		169	
Yes	54	18%	27	17%	36	21%

Abbreviations: BMI, body mass index; ERGO, the Environmental Reproductive and Glucose Outcomes Study; HMO, health maintenance organization; SD, standard deviation; SSI, Supplemental Security Income; NICU, neonatal intensive care unit.

[a]Participants did not complete the postpartum study visit but have postpartum data from electronic medical record abstraction and/or remote questionnaires.

[b]No postpartum data as of April 2024 – additional postpartum data may be abstracted from participant electronic medical records in the future.

[c]Gestational diabetes data sample size by column: n=334, postpartum visit; n=159, other postpartum data; n=175, no postpartum data.

[d]Reflects the high proportion of SPRING participants (high GDM risk) that completed in-person study visits (n=114, 69%) as part of the SPRING study protocol compared to directly enrolled ERGO participants (n=190, 39%) (mixed GDM risk).