Project Viva Women's Health Data Collection Protocol:

A longitudinal study of women's health

07.13.22

Table of Contents

I. Introduction

Project Viva is a prospective cohort study of maternal and child health. In 1999-2002 we recruited 2,670 pregnant women during their first trimester of pregnancy from eight obstetric (OB) offices of a multi-site group practice in eastern Massachusetts, Harvard Vanguard Medical Associates. There were 2128 live singleton births to 2,100 women (28 women enrolled with successive pregnancies) and approximately 1,500 mothers are still involved in the study. We collect data repeatedly from multiple sources, including questionnaires, interviews, medical records, examinations, and biospecimen samples.

Project Viva intends to follow participants as long as there is grant funding and interest from the participants. Some of the most beneficial health findings come from long-term follow-up. Project Viva's general study objectives for our maternal cohort are outlined in this protocol. Project Viva data is used in several studies (separate protocols), as well as ancillary studies that fall under our regular data repository, genetic data repository, or epigenetic data repository. This protocol addresses the primary data collection for mothers enrolled in Project Viva and the main focus areas of research among these women.

II. Project Viva Investigators

Project Viva is reviewed by Harvard Pilgrim Health Care's Institutional Review Board and is led by investigators at the Division of Chronic Disease Research Across the Lifecourse (CoRAL), Department of Population Medicine, Harvard Pilgrim Health Care Institute (HPHCI) and Harvard Medical School (HMS). All Project Viva staff are employees of HPHCI.

A Viva Co-Investigator (Co-I) is anyone listed as a PI or Co-I on the NIH grants that support the majority of Project Viva operations, or the PI of one of the other grants that support Viva science. In addition to being a PI or Co-I, one must also be actively involved with the Co-I meetings and operations. Most co-Investigators are approved under other IRB-approved protocols that contain specific scientific aims but may not support operations.

III. Project Viva Historic Recruitment

This section outlines how and when Project Viva recruited women and the eligibility criteria.

Project Viva Research Assistants approached pregnant women immediately following their initial obstetric (IOB) prenatal visit at one of eight HVMA obstetric offices to determine eligibility. The 8 HVMA locations included Kenmore, Copley, Cambridge, Post Office Square, Quincy, Wellesley, Medford, and West Roxbury. Project Viva recruited women from 1999 to 2002.

Women were eligible if they met the following criteria:

- Less than 22 weeks pregnant at the time of enrollment, as defined by due date or last menstrual period (LMP), if due date was not available. Gestational age for the inclusion criteria was based on a patient's reported due date. The Research Assistant calculated gestational age from the

expected due date using a pregnancy wheel. If the due date was not known, the Research Assistant calculated gestational age based on LMP. The women had to know either her due date or LMP to be eligible to participate.
- Received prenatal care at one of the selected HVMA practices.
- Planned on delivering at Brigham and Women's Hospital (BWH) or Beth Israel Deaconess Medical Center (BIDMC).
- Were able to answer questionnaires in English.

Women were ineligible if they met any of the following criteria:
- Planned to terminate the pregnancy.
- Planned to move from the local area before the end of the initial follow-up period, 6 months after delivery.
- Had multiple gestation (twins, triplets, etc.) since they are likely not be comparable to other women, and the limited number would preclude separate analyses.

If a woman was eligible, we asked her to enroll in the study by providing written informed consent and completing the early pregnancy visit (V1).

IV. Study Objectives

This section outlines the study objectives. This includes outcome focus areas of interest, exposures, and other variables that may be used in analyses.

The primary objectives of Project Viva's Maternal and Women's Health research fall into four main focus areas as detailed below. Any study that does not fall under a focus area will be submitted to the Harvard Pilgrim Health Care Institutional Review Board (IRB) as a separate protocol. The Project Viva women's health research main focus areas are listed below.

Focus Area 1: Maternal Pregnancy and Post-partum Outcomes

Project Viva is interested in studying the health of mothers during and after pregnancy. Outcomes of specific interest include: gestational weight gain, length of pregnancy, pregnancy-related health conditions (such as gestational diabetes and preeclampsia). This area also includes fertility measures and treatments before and after the Viva index pregnancy.

Focus Area 2: Neurocognitive and behavioral outcomes (includes mood/affective disorders, menopausal symptoms, and sleep).

Project Viva is interested in studying neurological, cognitive, and behavioral health measures, assessed using questionnaire measures, actigraphic measures of sleep duration and quality, and cognitive tests.

Focus Area 3: Obesity and Cardio-Metabolic Outcomes (includes physical activity, diet)

Project Viva is interested in studying cardiometabolic outcomes and risk factors, including obesity, blood pressure, cardiovascular fitness, non-invasive measures of atherosclerosis, biomarkers of cardiometabolic risk, and physical activity.

Focus Area 4: Bone Health and Body Composition.

Project Viva is interested in studying body composition, which is assessed in multiple ways and at multiple time points, including height, weight, circumferences, skinfolds, bioelectrical impedance, and DXA scans.

Exposures

In relation to the above outcomes, Project Viva studies a number of individual, family, household, and environmental exposures from the pre-pregnancy period onwards, that include but are not limited to: body mass index (BMI) and other anthropometric measures; sedentary behaviors, sleep and physical activity; genetics; gestational weight gain and post-partum weight loss; post-partum depression; time to pregnancy as measure of fertility; experiences of stress, racism and violence; sociodemographic variables; lactation; results of blood, urine and hair assays; diet and eating behaviors; geographic information system (GIS) variables, including distance to roadways and highways and census variables; asthma and allergies; and cognition and behavior. Most of these variables can be exposures, outcomes, or covariates depending on the specific analysis. The lead investigator for each analysis specifies exposures, outcomes, and covariates in an analysis plan.

V. Historic Consent Forms

This section describes all historic Project Viva consent forms used with our women's health cohort, including consent forms for main visits, sub-studies, visit addendums, and waivers of consent approvals.

A. Consent forms for enrollment through 6 months post-partum

This section describes all consent forms dealing with data collected between enrollment and 6 months postpartum.

i. Original Maternal Consent Covering Visit 1 (1st Trimester) to Visit 4 (~6 months postpartum)

Project Viva's original consent form for mothers covers maternal data collection for the first four visits. There are several versions of the consent form, which reflect changes occurring in the study and from discussions with the IRB. These include adding language about what the blood would be used for, adding the Certificate of Confidentiality, combining data with medical records, and adding visit components to the delivery and 6-month visits. The consent provisions are as follows.

I. Purpose: To examine the roles of diet and other factors in maintaining the health of pregnant women and their babies.
II. Early Pregnancy In-person Visit Components (<22 weeks gestation)
    a. Questionnaires
    b. In-Person Interview
    c. Blood draw at the lab (extra tube drawn at the lab, not a separate draw)
III. Mid-Pregnancy In-person Visit Components (26-28 weeks gestation)
    a. In-person interview
    b. Questionnaires
    c. Blood draw at the lab (extra tube drawn at the lab, not a separate draw)
IV. Delivery In-person Visit
    a. In-person interview one to three days post-partum
    b. For women delivering at Brigham and Women's, hospital staff to measure the weight of the placenta and collect a sample of umbilical cord blood immediately following delivery in the delivery suite
V. Six-month In-person Visit
    a. Questionnaire
VI. HVMA and delivery hospital medical records regarding pregnancy and delivery, including items such as results of laboratory tests, medical procedures, prescription dispensing, medical & reproductive history, and labor & delivery details
VII. Addenda for maternal blood pressure and weight measurements

ii. Corticotropin-releasing Hormone (CRH) Measurement Substudy

I. Purpose: To compare three processing techniques for measuring levels of corticotropin-releasing hormone.
II. Participants provided written informed consent to have a blood sample drawn at the lab (extra tube drawn at the same time as the routine blood draw, not a separate draw)

iii. Dental Substudy

I. Purpose: Women's oral health may be linked to the health of her pregnancy.
II. Participant provided written informed consent for Project Viva to contact her dentist to:
    a. Request a copy of dental x-rays taken during or closest to the index pregnancy
    b. Ask the dentist to complete a one-page questionnaire regarding the participant's oral health
III. Case: control ratio was 1:3, based on preterm vs. normal delivery, among women with dental x-rays within the past 5 years

iv. Waiver of Consent: Pharmacy Database

Project Viva participants provided written informed consent for medical record review, although we did not specifically list the pharmacy database on the consent form. The

waiver allows for Project Viva to review pharmacy records for women who gave permission for medical record review.

B. Consent forms for data collection at the "Early Childhood" visit (~3 years post-partum)

This section describes all consent forms dealing with data collected at 3 years post-partum.

i. Maternal In-Person Consent Form at 3 years post-partum
   I. Purpose: To examine the effects of diet and other factors during pregnancy and the period after birth on long-term health.
   II. Visit Components:
      a. Anthropometric measures and blood pressure
      b. Peabody Picture Vocabulary Test
      c. HVMA and hospital medical record data regarding pregnancy and delivery

ii. Maternal Consent for Maternal Blood Draw at 3 years post-partum
   I. Purpose: To examine the effects of diet and other factors during pregnancy and infancy on child development and health.
   II. Participant provided written informed consent for a blood draw.

C. Consent forms for data collection at the "Mid-Childhood" visit (~7 years post-partum)

This section describes all consent forms dealing with data collected at 7 years post-partum.

i. Maternal In-Person Consent Form at 7 years post-partum
   I. Purpose: The purpose of Project Viva is to examine the effects of diet and other factors during pregnancy and infancy on child development and health.
   II. Visit Components:
      a. Anthropometric measures
      b. Intelligence test
      c. Outpatient and hospital medical records and insurance claims from the first date of involvement in the study through the visit date

D. Consent and authorization forms for data collection for the "Early Teen" visit

This section describes all consent forms dealing with data collected at the "Early Teen" visit (AG12).

i. Maternal In-Person Consent and Authorization Form at "Early Teen" Visit (AG12)
   I. Purpose: The purpose of Project Viva is to examine the effects of factors during pregnancy, infancy on childhood on maternal and child health.

II. Visit Components:
    a. Anthropometric measures
    b. Outpatient and hospital medical records and insurance claims from 3 months prior to the pregnancy of your Project Viva child through the end of the study

E. Consent and authorization forms for data collection for the "Mid-Teen" visit

This section describes all consent forms dealing with data collected at the "Mid-Teen" visit.

i. Maternal Consent and Authorization Form at "Mid-Teen" Visit (AG17)

I. Purpose: The purpose of Project Viva is to examine the associations of factors during pregnancy, infancy, childhood, and adolescence with maternal, child and adolescent health.

II. Visit Components:
    a. Blood collection by trained phlebotomist, including 2-hour oral glucose tolerance test
    b. Biospecimen collection of urine
    c. Anthropometric measures and blood pressure
    d. Handgrip strength measurement
    e. Dual-energy x-ray absorptiometry (DXA) – total body, lumbar spine, and hip
    f. Family medical history interview
    g. Mid-Teen Questionnaire
    h. Internet-based, self-administered dietary recall: 1 completed during the in-person visit; 2 completed at home in the 1-week following the in-person visit
    i. Outpatient and hospital medical records and insurance claims from 3 months prior to the pregnancy of Project Viva teen through the end of the study
    j. Genetic and epigenetic analysis of biospecimen samples collected at Mid-Teen Visit and previous in-person visits

III. Additional consent opportunity presented:
    a. Data sharing with the ECHO Program: sharing participant data (including genetic and epigenetic data) with the ECHO program, managed by the US National Institutes of Health (NIH).

F. Consent form for data collection for the Age 19 survey

This section describes the consent form presented to mother participants dealing with data collected through the Age 19 survey.

i. Maternal Consent and Authorization Form at Age 19

I. Purpose: The purpose of Project Viva and ECHO is to examine the associations of factors during pregnancy, infancy, childhood, and adolescence with maternal, child and adolescent health.

II. Visit Components:
    a. Age 19 Questionnaire

b. Genetic and epigenetic analysis of biospecimen samples collected at Mid-Teen Visit and previous in-person visits for the ECHO program
c. Data and biospecimen sharing with the ECHO Program

G. Genetics Study Consent for Mothers

This section describes when genetics consent forms were presented to participants, the different versions of the consent form, and what is included in the consent forms. **Genetic analyses will be conducted ONLY on participants who specifically provide this consent.**

Project Viva approached mothers for genetics consent at the initial Early Pregnancy visit (V1), the Early Childhood Visit (V7), and the Mid-Childhood Visit (~7 years postpartum). The consent forms were only presented at Early and Mid-Childhood visits if a participant choose an undecided option, or no consent form was on file. At the Mid-Teen visit, genetic and epigenetic consent were included on the main consent form, which was presented to all participants who attended an in-person or remote visit.

If participants refused to participate in genetic and/or epigenetic analyses, no future genetic or epigenetic analyses will be run using those participants' samples.

a. Original Genetics Consent Form

Project Viva's original genetics consent form was presented only to women delivering at Brigham and Women's Hospital. This consent form covers both maternal blood and child blood on a single consent form.

Consent form options:

I. Project Viva can use Genetic material from mother for future studies. The mother chooses yes or no for each of the following domains:
    a. High blood pressure
    b. Asthma
    c. Growth
    d. Length (duration) of pregnancy (for mothers only)
    e. Other medical conditions identified in the future
II. Project Viva may store, but not use, genetic material from mother and can contact the participant in the future as projects arise.
III. Project Viva may not use or store genetic material from mother

b. Maternal Genetics Consent Form

If the original genetics consent form was not completed or option 2 (undecided) was selected, Project Viva Research Assistants administered the maternal genetics consent form at the Early Childhood or Mid-Childhood in-person visits.

Consent form options:

I. Project Viva can use Genetic material from mother for future studies. The mother chooses yes or no for each of the following domains:
    a. High blood pressure
    b. Asthma
    c. Growth
    d. Length (duration) of pregnancy (for mothers only)
    e. Other medical conditions identified in the future
II. Project Viva may store, but not use, genetic material from mother and can contact the participant in the future as projects arise.
III. Project Viva may not use or store genetic material from mother

c. Maternal Genetics & Epigenetics Ancillary Study Consent Form

Project Viva Research Assistants administered the maternal genetics & epigenetics consent form at the Early Teen in-person visit.

Consent form options:

I. Epigenetic Study
    a. Biosamples may be used by Project Viva for epigenetic analysis.
    b. Please do not use biosamples for epigenetic analysis at this time.
II. Genetic Study
    a. Project Viva can use Genetic material from mother for future studies. The mother chooses yes or no for each of the following domains:
        i. High blood pressure
        ii. Asthma
        iii. Growth
        iv. Length (duration) of pregnancy (for mothers only)
        v. Other medical conditions identified in the future

d. Mid-Teen Maternal Consent Form

At the Mid-Teen Visit, the option to participate in genetic and epigenetic analyses was presented on the main visit consent form. All participants who completed a Mid-Teen In-Person or Remote Visit were presented with the main consent form. As with all parts of the Visit, participants could choose not to participate in the genetic/epigenetic analysis portion of the Mid-Teen Visit. There was a section in these forms for participants to initial to separately and explicitly provide or refuse consent to the genetic and/or epigenetic components of the study.

Consent form options:

Epigenetic Research

_____ YES, you may use biospecimen samples that you have collected and stored from this and other Project Viva visits to perform **epigenetic analyses** to be used for research

_____ NO, you may not use biospecimen samples that you have collected and stored from this and other Project Viva visits to perform **epigenetic analyses** to be used for research

Genetic Research

_____ YES, you may use biospecimen samples that you have collected and stored from this and other Project Viva visits to perform **genetic analyses** to be used for research

_____ NO, you may not use biospecimen samples that you have collected and stored from this and other Project Viva visits to perform **genetic analyses** to be used for research

VI. Data Collection

A. Primary Data Collection

This section outlines Project Viva's primary data collection, and provides a description of each visit performed with our maternal cohort members. In addition to the primary data detailed below, we update contact information at every visit, including alternate contacts and name changes. Appendix B includes a visit flow-sheet that offers a graphical depiction of Project Viva's visits.

A1: Completed Visits

Project Viva has completed data collection on all visits through the Mid Teen visit. Each visit is described in detail below. The only foreseeable human subjects risk for completed visits is the risk of a privacy or confidentiality breach.

a. Early Pregnancy (V1), in-person

This visit took place in the OB department at one of eight HVMA offices. Viva staff approached potential participants at their first OB appointment. If they agreed to participate in Project Viva the visit was conducted. Study visits generally lasted about 20 minutes. Women ranged from 4.8 to 23.7 weeks pregnant at the time of the visit, with a mean of 10.5 weeks. Some women were greater than 22 weeks at this visit once LMP was cleaned and verified using other sources. We enrolled 2,622 women and 2,670 of their pregnancies (48 women enrolled two of their pregnancies).

The visit components included:

1. Interview: demographics, medical history, current pregnancy, and vitamin/supplement use
2. Supplement (self-administered): pre-pregnancy weight, menstrual periods, pregnancy intent, concerns and feelings
3. General questionnaire (self-administered): mother's childhood, household demographics, life experiences, feelings, and social and physical activities
4. Food Frequency Questionnaire (FFQ) or interviewer administered PrimeScreen (if FFQ not returned)
5. Blood collection at the HVMA lab
    a. Project Viva collected 2,089 blood samples at this visit.
    b. Assays completed to date with blood from this visit include CRP,thyroid hormones, LINE1, Creatinine, PFAS, Albumin, mtDNA, and Blood Metals.

b. Mid-Pregnancy (V2), in-person

This visit took place in the OB department at the same HVMA location as V1. Ideally, staff met each participant between her 26th and 28th week of pregnancy during her scheduled glucose challenge test. If this was not possible, we met her at the time of another appointment between the early pregnancy visit and before delivery. Women ranged from 16.4 to 37.4 weeks pregnant at the time of the visit, with a mean of 28.0 weeks. Visits generally lasted about 20 minutes, and we completed 2,081 visits.

The visit components included:

1. Interview for pregnancy updates: due date and hospital, cravings/aversions, and OTC medications
2. Supplement (self-administered): pre-pregnancy weight, menstrual periods, and pregnancy intent, concerns and feelings
3. Personal Safety Questionnaire (self- or interviewer administered based on participant preference)
4. General questionnaire (self-administered): social and physical activities, child feeding intentions and concerns, feelings, and dental care
5. Food Frequency Questionnaire (FFQ)
6. Abbreviated versions of Early Pregnancy interview, questionnaire and supplement (if not completed at Early Pregnancy Visit)
7. Blood collection
    a. Project Viva collected 1648 blood samples at this visit.
    b. Assays completed to date from blood at this visit include: hsCRP, cytokines, cortisol sulfate, estriol, CRH, leptin, fructosamine, LINE1, tocopherol isoforms (Vitamin E), adiponectin, mercury, selenium, lead, manganese, vitamin D RIA manual and automated, RBC fatty acids and plasma fatty acids, and antioxidants.

c. Delivery (V3), in-person

There were 2128 births to 2,100 unique women, of the initial 2,670 pregnancies. We conducted post-delivery follow-up at two hospitals: Beth Israel Deaconess Medical Center and Brigham and Women's Hospital, the receiving hospitals for all deliveries from the HVMA recruitment practices. Each HVMA practice delivered all of their patients at one of the two hospitals. Quincy, Wellesley, Kenmore, West Roxbury and Post Office Square patients delivered at the Brigham and Women's Hospital; Copley, Medford and Cambridge patients delivered at the Beth Israel Deaconess Medical Center. Visits took place 1-3 days after delivery on the post-partum maternity floor, ideally before visiting hours started, and lasted about 30 minutes. Cord blood collection took place in the delivery suite at the time of delivery. We completed 2072 visits.

The maternal visit components included:

1. Interview: delivery, child feeding, maternal diet and smoking
2. Personal Safety Questionnaire (self- or interviewer administered based on participant preference)
3. Hair sample collection (substudy)
    a. Project Viva collected maternal hair samples and analyzed them for mercury.

d. Infancy Visit (~Six-Month post-partum (V4)), in-person

Staff completed the Infancy visit in the pediatric office at one of the HVMA sites. Ideally visits took place between 5.5 and 8 months after delivery. The timing of the actual visit ranged from 4.9 to 10.6 months post-partum, with a mean of 6.4 months. The visit length was approximately one hour, and we completed 1697 visits with 1670 women.

The visit components for the mother included:

1. Interview: home environment and post-partum health
2. Supplement (self-administered): breastfeeding and formula feeding, and employment status
3. Personal Safety Questionnaire (self- or interviewer administered based on participant preference)
4. General questionnaire (self-administered): post-partum health, child feeding, social and physical activities, home environment, feelings, and maternal diet
5. Maternal weight and blood pressure measurements

e. 1 and 2 year (V5, V6), mail

Visit Description – For the Ages 1 and 2 mailed visits, Project Viva mailed participating mothers an annual questionnaire. If the participant was unwilling to complete the questionnaire via mail, Project Viva attempted administer the questionnaire over the phone.

1. For the 1 year visit, Project Viva received 1,280 questionnaires completed by mail or by phone.
2. For the 2 year visit, Project Viva received 1,392 questionnaires completed by mail or by phone.

f. Early Childhood (~3 years postpartum (V7)), in-person

This visit ideally took place at the Kenmore HVMA offices, or if that was not feasible, at the participant's home or other convenient location. Participants were eligible for this visit if the mother had completed at least one FFQ during pregnancy and had not disenrolled the child from follow-up. The visit length was approximately 1.5 hours. At this visit, women ranged from 2.8 years (2 years, 9 months) to 6.3 years (6 years, 4 months) postpartum after the index pregnancy, with a mean of 3.5 years. Participants living too far away, and those unable or unwilling to meet with us in person had the option to complete a "mailed only" visit, which included the same self-administered questionnaires plus an RA-administered family health interview over the phone. We completed 1296 in-person visits and an additional 157 by mail.

The visit components for the mother included:

1. Maternal anthropometry measurements, including standing height, weight, waist circumference, mid-upper arm circumference, triceps and subscapular skinfolds
2. Maternal blood pressure
3. Maternal Cognition: Peabody Picture Vocabulary Test
4. Interviewer-administered family health interview and supplement
5. General questionnaire
6. Blood collection
    a. Project Viva collected 1022 maternal blood samples. 289 samples were fasting (>8 hours).
    b. Maternal blood assays completed to date at this visit include: leptin, adiponectin, ghrelin, IgE, CRP, hemoglobin A1c, HOMA-IR, hsIL-6, lipids, SHBG, PYY, lipids, AMH, free testosterone, and total testosterone.

g. 4, 5 and 6 year (V8 – V10), mail

Visit Description— For the Ages 4, 5 and 6 mailed visits Project Viva mailed participating mothers an annual questionnaire.

1. For the 4 year visit, Project Viva received 1,226 completed mailed questionnaires.
2. For the 5 year visit, Project Viva received 859 completed mailed questionnaires.
3. For the 6 year visit, Project Viva received 955 completed mailed questionnaires.

h. Mid-Childhood (~7 years postpartum (Age7)), in-person

This visit ideally took place at the Kenmore HVMA offices, or if not feasible at the participant's home or other convenient location. All participants still enrolled in Project Viva were eligible for this visit. The visit length was approximately 3 hours. Participants living too far away, and those unable or unwilling to meet with us in person had the option to complete a "mail–only" visit which included the same self-administered questionnaires and an RA-administered family health interview over the phone. We completed 1,116 in-person visits and an additional 163 by mail.

The visit components for the mother included:

1. Interviewer administered family health interview

2. General questionnaire completed by the mother about her health and behavior, and the home environment
3. Maternal anthropometry measurements, including height, weight, bioimpedance and waist circumference
4. Mother intelligence: Kaufman Brief Intelligence Test (KBIT-2)

i. 8, 9, 10 and 11 year (Age8, Age9, Age10, Age11), mail

For the age 8, 9, 10 and 11 year visits, Project Viva mailed or emailed the participating mothers an annual questionnaire. Project Viva implemented online questionnaire completion at Age 9. Participants completed online questionnaires through a participant-specific site (protected by entering the child's date of birth) maintained by New England Research Institute (NERI), our database administrator at the time. Data participants entered into the online version was housed and saved in the same manner as RA entered data. Online questionnaires were temporarily discontinued while Project Viva transitioned from NERI to its current database administrator, REDCap. A portion of Age 11 participants had the option to complete an Age 11 online survey through REDCap.

a. For the 8 year visit, Project Viva received 707 completed mailed questionnaires.
b. For the 9 year visit, Project Viva received 918 completed mailed questionnaires.
c. For the 10 year visit, Project Viva received 789 completed mailed questionnaires.
d. For the 11 year visit, Project Viva received 699 completed mailed questionnaires.

j. Early Teen (AG12) Visit, in-person

This visit ideally took place at the Kenmore HVMA/Fenway offices, but may have also been conducted at the participant's home or other convenient location if travel to Boston was prohibitive. All participants still enrolled in Project Viva at the start of the Early Teen in-person visit were eligible to participate. The visit length was approximately 2½ hours. Participants had the option of completing a "mailed visit" if they lived too far away, or were unable or unwilling to meet with us in person. The "mailed visit" consisted of the same self-administered questionnaire and an RA-administered family medical history interview. Participants had the option to complete the questionnaires electronically using the REDCap survey option. A unique URL was sent to study participants who wished to complete their questionnaires electronically using the HPHC domain. We completed 1,038 in-person visits and 139 additional participants completed the visit questionnaire only. Our Early Teen Operations Manual served as an up-to-date data collection protocol for the Early Teen Visit.

The visit components for the mother included:

1. General questionnaire completed by the mother about her health and behavior, and the home environment
2. Interviewer administered family health interview
3. Maternal anthropometry measurements, including height, weight, bioimpedance and waist circumference

k. 14 and 15 year (Age 14, Age 15), mail

For the age 14 and age 15 year visits, Project Viva mailed or emailed the participating mothers an annual questionnaire. Participants had the option to complete electronic versions of the questionnaires through REDCap. A unique URL was sent to study participants who wished to complete their questionnaires electronically using the HPHC domain.

e. For the 14 year visit, Project Viva received 595 completed mailed questionnaires.
f. For the 15 year visit, Project Viva received 671 completed mailed questionnaires.

l. 16 year (Age 16), mail

For the age 16 year visits, Project Viva mailed or emailed the participating mothers an annual questionnaire. Participants also had the option to complete electronic versions of the questionnaires through REDCap. A unique URL was sent to study participants who wished to complete their questionnaires electronically using the HPHC domain.

g. For the 16 year visit, Project Viva received 805 completed mailed questionnaires.

m. Mid-Teen (AG17 Visit, in-person)

This visit ideally took place at the HPHCI Fenway office, but may have also been conducted at the participant's home or other convenient location if travel to Boston was prohibitive. All participants still enrolled in Project Viva at the start of the Mid-Teen visit were eligible to participate. The visit length was approximately 3 hours. Participants had the option of completing a "remote visit" if they lived too far away, or were unable or unwilling to meet with us in person. The "remote visit" consisted of the same self-administered questionnaires, an RA-administered family medical history interview, and a dietary recall. Participants had the option to complete the questionnaires electronically using the REDCap survey option. A unique URL was sent to study participants who wished to complete their questionnaires electronically using the HPHC domain. We completed 703 in-person visits, 132 remote visits, and 561 blood draws. Our Mid-Teen Operations Manual served as an up-to-date data collection protocol for the Mid-Teen Visit.

The visit components for the mother included:

1. General questionnaire completed by the mother about her health and behavior, and the home environment
2. Interviewer-administered family medical history interview
3. Maternal anthropometry measurements, including: height, weight, bioimpedance, waist and hip circumferences, middle-upper arm circumference, and tricep and subscapular skinfolds
4. Maternal blood pressure
5. Maternal handgrip strength

6. Maternal body composition and bone density: Dual-energy X-ray absorptiometry (DXA) – whole body, lumbar spine, and hip
7. Maternal blood collection, including 2-hour oral glucose tolerance test
8. Maternal urine collection
9. Internet-based, self-administered dietary recall: 1 completed during the in-person visit, 2 completed at home in the 1-week following the in-person visit

n. COVID-19 questionnaires, email only

To supplement the data collected during the Mid-Teen visit and the Age 19 questionnaire, Project Viva emailed the participating mothers questionnaires specific to their experiences during the global coronavirus pandemic. The COVID 1.0 Questionnaire was fielded from May 2020 – September 2020, and the COVID 2.0 Questionnaire was fielded from February 2021 – September 2021. Participants completed these electronic questionnaires through REDCap, using a unique URL sent to their email. We did not send these via mail given the work from home order during the pandemic, which did not allow for mailings to be sent

o. 19 year (Age 19), email/mail

For the age 19 visits, Project Viva mailed or emailed the participating mothers a questionnaire. Participants had the option to complete electronic versions of the questionnaires through REDCap. A unique URL was sent to study participants who wished to complete their questionnaires electronically using the HPHC domain.

A2: Ongoing Visits

a. Women's Health Visit 1

This visit will ideally take place at the HPHCI Fenway office, but may also be conducted at the participant's home or remotely if travel to Boston was prohibitive or the participant was not comfortable with an in-person study visit. All originally-enrolled mothers still enrolled in Project Viva at the start of the Women's Health Visit 1 are eligible to participate. Participants have the option to complete the consent and questionnaire electronically using REDCap. A unique URL is sent to study participants who wish to complete them electronically. Our Women's Health Visit 1 Operations Manual serves as an up-to-date data collection protocol for this visit.

The visit components include:

1. General questionnaire about health, behavior, and environment
2. Anthropometry measurements, including height, weight, bioimpedance, waist and hip circumferences, and middle-upper arm circumference
3. Blood pressure
4. Cognitive Tests

5. Short physical performance assessment
6. 7-day Actigraph watch data collection
7. 7-day twice-daily Sleep Diary data collection
8. After-visit summary collection for remote visit participants
9. For those who did not participate in these components during the Mid-Teen Visit:
    a. Body composition and bone density: Dual-energy X-ray absorptiometry (DXA) – whole body, lumbar spine, and hip
    b. Blood collection
    c. Urine collection

b. Annual Surveys, email/mail

Beginning in 2022, Project Viva stopped sending age-based questionnaires and began the practice of sending annual questionnaires. Participants have the option to complete electronic versions of the questionnaires through REDCap. A unique URL is sent to study participants who wish to complete their questionnaires electronically using the HPHC domain.

B. Secondary Data Collection – Medical Records

Project Viva has obtained medical record data from several sources, including HVMA medical records, hospital birth logs, dental records, and non-HVMA medical records. These arrived in a variety of forms, including electronic and paper. We have derived data from the records and these variables are now part of the existing Project Viva dataset. There is the potential that we could extract additional information from the records for research purpose related to this protocol, or to Project Viva's substudies or ancillary studies. Project Viva will seek additional IRB approval before deriving any variables that may be considered sensitive in nature.

a. Hospital delivery logs

Project Viva received hospital birth delivery logs from Beth Israel Deaconess Medical Center and Brigham and Women's Hospital. Data abstracted from these records include gravidity, medical risk factors, anesthesia, delivery method, complications during labor and delivery, obstetric procedures, birthweight, Apgar score, umbilical cord pH, congenital anomalies, abnormal conditions, and delivery location. The paper birth logs are currently archived at Iron Mountain, the Department of Population Medicine's document storage contractor.

b. HVMA/Atrius Medical Records & Insurance Claims

Project Viva collects information from HVMA medical records and insurance claims periodically. The data pulls related to our maternal cohort are outlined in detail below. These records and datasets are electronic. Project Viva has derived some very important exposure and outcome variables from this information including pre-pregnancy weight and BMI, gestational weight gain, preeclampsia, and gestational diabetes diagnosis.

i. Peri-Pregnancy Period Pull

Project Viva obtained full-text medical records from HVMA on all participants starting 3 months prior to LMP up to 6-months postpartum. From these we abstracted the following information onto our Medical Record Abstraction (MRA) form, and entered it into our database. These variables are currently part of Project Viva's data set. The full text medical records still exist in electronic form and remain on HPHC's server. The Medical Record Abstraction forms are archived at Iron Mountain.

1. Participant information: Medical Record Number, Date of Birth, Initial obstetric appointment date (IOB), occupation, domestic abuse history (y/n/missing), pregnancy planned/welcomes, Diethylstilbestrol (DES) exposure
2. Gravidity and information on previous pregnancies such as outcome, gestational age, infant sex and birth weight
3. Number of living children
4. Date of last menstrual period (LMP)
5. IOB pelvic exam, including pH, Wet Prep, Whiff test
6. Alpha-fetal protein and amniocentesis results
7. Ultrasound history and fetal measurements
8. Length and diameter of cervix

ii. Early Childhood

Project Viva obtained HVMA medical records and HPHC insurance claims data on 2,665 mother participants from RSDC during our Early Childhood visit. This pull included data through December 2004. The data from this pull includes full text medical records, and datasets on growth, prescriptions, immunizations, vital signs and diagnosis codes.

iii. Mid-Childhood

Project Viva obtained medical record data from HVMA on 1166 mother participants after the Mid-Childhood visit. We were unable to collect insurance claims data at that time because of contract agreements between the insurance carriers and HVMA.

We requested medical records only for the participants we saw in person at the Mid-Childhood visit, and who provided written informed consent for medical record review. For mothers this pull included data from enrollment date through the Mid-Childhoodvisit date. The medical record data from this pull included full-text medical records, and datasets on growth, prescriptions, immunizations, vital signs and diagnosis codes.

iv. Early Teen

For the "Early Teen" visit, we requested medical records and insurance claims for mom participants who provided written informed consent and authorization for medical record review from 3 months prior to their pregnancy with their Project Viva child through the end of the study. The data from this medical record pull included full-text medical records, data

sets on growth, prescriptions, immunizations, vital signs and diagnosis codes. Claims data included inpatient, outpatient, and emergency room data (including ICD codes, prescriptions, and billing information). Project Viva obtained this information for 886 mother participants.

c. Dental Records

Project Viva collected dental records from participants who agreed to participate in the dental substudy between enrollment and 6 months post-partum. As part of this substudy we received a copy of the last dental x-rays taken before giving birth. These x-rays were read by former Project Viva Co-Investigator Dr. Pitiphat and then returned to the dentist's office. Paperwork associated with this substudy is archived at Iron Mountain. Data extracted from these records include dentist-reported periodontal bone loss and treatments, and measurements from the radiographs.

For the analysis, we restricted the sample to mothers who had dental x-rays within 5 years before the index delivery. Cases were mothers who gave birth to a preterm or growth-restricted infant from September 1999 to February 2002. Controls were mothers who had term and normal-growth infants. The case to control ratio was 1:3, frequency matched by race, age and smoking status. This study has ended, but the data remain in Project Viva's data set and may be used in future analyses.

VII. Data Management

This section outlines how Project Viva stores data, both in electronic and paper form. It also outlines Project Viva's data access and transmission practices, and Project Viva's Certificate of Confidentiality.

A. Data Storage

a. Electronic Records – REDCap

REDCap is a secure, web-based research database and survey system developed by a multi-institutional consortium and initiated at Vanderbilt University. The system is fully HIPAA compliant provided that security features are utilized, and all study personnel will be trained on use of these features. REDCap may only be accessed by authorized users who must log in to the system and can only view databases that they have been given access to by the project administrator. Additionally, users can be given varying levels of data access (for example, the ability to view de-identified data only, or rights to view but not edit data). REDCap also uses Secure Sockets Layer (SSL) encryption of data, and provides complete audit reports documenting details of all changes that are made to forms and individual fields. HPHCI IT has reviewed and approved the software for use in our department.

Use of REDCap will allow us to increase the security of the data that we are collecting for Project Viva. We will no longer have to rely on an outside institution to house and maintain our database. The database will be hosted on the HPHCI server and users must be logged in to the

HPHCI network before they are able to access the HPHCI REDCap system. Authorized Project Viva users will have the ability to export data directly to statistical software programs for analysis, and we can restrict data export by other users. Additionally, REDCap can export completely de-identified datasets, which will allow us to eliminate the possibility of unauthorized individuals inadvertently receiving PHI.

b. Electronic Records – Harvard Pilgrim Health Care Institute (HPHCI) Servers

Project Viva electronic data is also stored on an access restricted HPHCI server. Project Viva data on this server can be accessed only by approved Project Viva study staff and investigators. HPHC machines are password protected, and passwords must be changed at least every 90 days. Access to HPHC's computer systems and file folders are managed by HPHCI, and Project Viva's Project Manager and Data Manager.

c. Electronic Records – Box

A cloud-based file storage system, Box is approved by HPHC's Office of Information Security for use by HPHCI staff for storing non-sensitive *and* sensitive data and PHI. Box and HPHC have a BAA for Box to provide a secure, approved, storage solution for HPHC, and the platform has been vetted by OIS for staff to utilize. Access to Box is controlled via HPHC's account and access validation system, AIM.

d. Electronic Records – Brigham & Women's Hospital (BWH), through Mass General Brigham (MGB) Servers

In utilizing the BWH Sleep Core's support services for Actigraphy and Sleep Diary collection, electronic data is also stored on an access restricted MGB server. Data on this server can be accessed only by approved study staff and investigators. MGB machines are password protected, and passwords must be changed at least every 90 days. Access to MGB's computer systems and file folders are managed by MGB and the BWH Sleep Core. HPHC and BWH have an executed data sharing agreement.

<u>Diary computer resources (eDiary)</u>

The sleep diary is a web-based diary designed for data capture of schedules and sleep timing with customizable questions; real-time subject feedback and data plotting; administrative view for data management and automation and tracking of subject correspondence. The sleep diary is hosted by MGB Research Computing. All connections are encrypted using SSL. The server is secured by running only the services necessary to deliver the application, and by following the procedures outlined in the ISPO Linux Server Security Standard Draft. The application is developed in-house and run through Veracode analysis for security vulnerabilities. Data are stored on the MySQL servers provided by MGB Research Computing and have 30-day snapshots.

To maintain confidentiality of information obtained from the research participants, the computer systems containing confidential data will have a level and scope of security that equals or exceeds those required by HIPAA guidelines. Data are collected and stored centrally and securely at the institution and under the auspices of the institutional IT security team. Only IRB approved investigators and study staff will have access to these identified data. A RISO audit report is available upon request.

e. Electronic Records – Ripple Science Inc.

Ripple™ is a secure web application designed for the storing and management of personally identifying information of research participants. Project Viva will be using Ripple to store meta-data about our participants (contact information, consent status, participation status, etc.). Use of the Ripple platform allows us to more efficiently recruit and track cohort members for our

surveys and visits, as it is a platform specifically intended for participants recruitment and tracking, and is designed to house this type of frequently updated meta-data (participant contact information, communication attempt details, communication preferences, etc.).

Authorized Project Viva staff will have the ability to export and import data from/to the Ripple™ platform, and we can restrict access to different sections and functionality of the platform by user account as needed. HPHCI IT has reviewed and approved the software for use in our department. Ripple will only be accessed by approved Project Viva on HPHC-owned computers while on the HPHC server (either in the office or through the VPN). Ripple Science, Inc. staff have access to subject ID numbers and PHI solely for the purpose of administering our use of their platform and providing technical support, and HPHC and Ripple have jointly executed a Data Confidentiality Agreement.

Ripple was initially developed at the University of Michigan to provide a user-friendly, web-based secure interface where research teams can centralize the storage and management of research participants' personal information, including name, participant ID, demographics, and study workflow (e.g., appointments). Participant information managed with ripple is private and secure. This information is kept in fully encrypted format inside dedicated databases that are segregated from other Ripple accounts and thus only authorized study staff will have access to the study data. Likewise, Ripple infrastructure complies with the privacy and security guidelines of the Health Insurance Portability and Accountability Act (HIPAA), including 2048-bit data encryption in transit and at rest, automatic logoff, audit trail, daily backups in triplicate dedicated servers, firewall, custom access permission for lab members, zxcvbn password strength estimation, and enterprise administrative safeguards to prevent unauthorized staff from accessing participant information.

f. Paper Records

Paper records of Project Viva are stored in our offices at 401 Park Drive, Suite 401, Boston, MA 02215 in locked file cabinets, behind access-restricted doors. Only Project Viva staff knows where the keys are to access these cabinets. Identifiable information is stored in separate locked cabinets from the other information we collect. Cabinets are locked nightly by Research Assistants. Project Viva has a rotating schedule of who will lock cabinets, including a back-up person. Old or archived paper forms are stored at Iron Mountain.

B. Data Access & Transmission

a. Data Access

Project Viva staff have access to all data as a result of their engagement with participants. Project Viva's Principal Investigator, Dr. Emily Oken, and Co-Principal Investigator, Dr. Marie-France Hivert, also have participant contact at times and may see identifiable information. All other investigators have access only to de-identified data (unless otherwise approved) and do not have access to the linking codes. Project Viva policies prohibit staff and investigators from disclosing the linking code under any circumstances.

b. Data Transmission & Types

For specific analyses led by non-DPM investigators, Project Viva's Senior Programmer or Data Manager emails data sets to investigators using HPHC's PGP send feature. These emails include a disclosure statement indicating the recipient is expected to abide by our policies and only use the data for approved purposes.

Project Viva may release the following types of data in the following circumstances:

Personal Health Information (PHI)

PHI is defined by federal law as a data set that includes one of the 18 HIPAA identifiers. Project Viva will release PHI to a non-HPHC investigator only if a Data Security Agreement has been executed between HPHC and the investigator's institution, and HPHC's and the investigator's IRBs have reviewed and approved the research. PHI is sometimes, but very seldom, required for Project Viva analyses. PHI by outside investigators is most likely to be required for substudies or ancillary studies.

Limited Data Sets (LDS)

An LDS is also defined by federal law. It is a data set that includes PHI, but is limited to dates and city, state or zip code. Project Viva will release an LDS to a non-HPHC investigator only if a Data Use Agreement has been signed, and HPHC's and the investigator's IRBs have reviewed and approved the research. LDS are sometimes, but very seldom, required for Project Viva analyses.

De-identified Data Sets or De-identified Aggregate Data

De-identified data sets are the most common type of data used for Project Viva analyses both for internal and external investigators. The Senior Programmer or Data Manager may provide de-identified data sets to Co-Is at their request for Viva work approved at a Co-Investigator Meeting. De-identified data sets may be provided for substudies, ancillary studies or data repository studies after the appropriate HSC/IRB approvals are in place.

De-identified aggregate summary tables are often needed for proposals, including grant proposals or analysis proposals. Project Viva also sometimes provides them to investigators who do not have extensive programming experience and need help completing their analysis. They will be released at the discretion of Viva's Senior Programmer for approved Project Viva work. If the investigator is to use the table for substudies or ancillary studies, they need to obtain appropriate HSC/IRB approvals prior to data release.

C. Certificate of Confidentiality

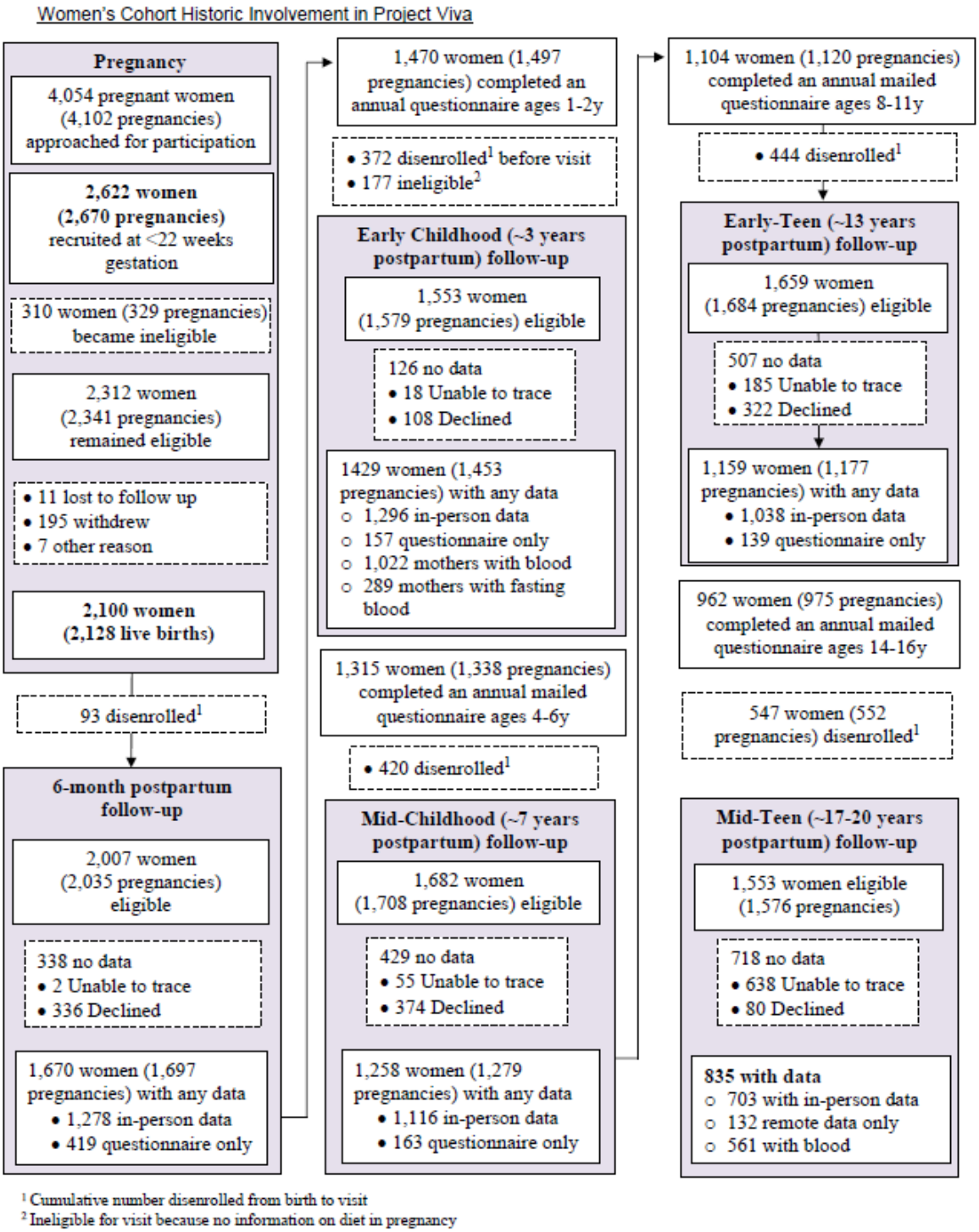
NIH-funded research is automatically covered by a Certificate of Confidentiality from the Department of Health and Human Services (DHHS), that further protects the privacy of our participants. With this certificate, the investigators cannot be forced to disclose information that may identify participants in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. Disclosure will be necessary, however, upon request of DHHS for audit or program evaluation purposes.

Appendix A: Current Grants Supporting Project Viva

An active grant list is found in Table 3. These grants support ongoing or upcoming data collection related to this protocol.

Table 3. Active grants supporting Project Viva Women's Health Data Collection			
Grant name	**HPHCI PI**	**Prime Institution (Overall PI(s))**	**IRBNet Project #**
A lifecourse approach to women's cardiometabolic and bone health: from fertility to perimenopause	Emily Oken	HPHCI (Emily Oken and Jorge Chavarro)	1368189
Per- and polyfluoroalkyl substances mixtures and maternal cardiovascular disease risk across the reproductive life course	Emily Oken	HSPH (Tamarra James-Todd and Ami Zota)	1662413

Appendix B: Visit Completion Breakdowns and Summaries



[1] Cumulative number disenrolled from birth to visit
[2] Ineligible for visit because no information on diet in pregnancy