

HIGHLIGHTS OF LARGE DATABASE RESOURCES/COHORTS AVAILABLE FOR SEX DIFFERENCES STUDIES AT BWH

The list of database resources, below, is a compilation of data from studies ongoing at BWH that can be used as potential resources for future studies on sex and gender-based medicine. We are currently collecting information from investigators on other available resources that will be added to this list. The list will be a component of our website for the Connors-BRI Center for Women's Health research and available to investigators at BWH working in women's health and sex differences research.

- **Women's Health Study (WHS):** Trial of Aspirin and Vitamin E in Women (HL 43851, CA 47988), was a randomized, double-blind, placebo-controlled trial of the balance of benefits and risks of low-dose aspirin (100 mg on alternate days) and vitamin E (600 IU on alternate days) in the primary prevention of cardiovascular disease and cancer among 39,876 US female health professionals. This study, which has now converted to an observational follow-up study, has been ongoing since 1992. Blood samples, including plasma and DNA, are available on ~70% of participants. A large number of lipid, inflammatory, and thrombotic biomarkers have been measured on all plasma samples and genome-wide scanning is completed. (Contact Person: Julie Buring)
- **Physicians' Health Study II (PHS II):** Trial of Vitamins in the Chemoprevention of Cancer, Cardiovascular Disease and Eye Disease (funded by multiple institutes at the NIH and BASF), is a randomized, double-blind, placebo-controlled trial of vitamin E (400 IU on alternate days), vitamin C (500 mg daily), and a multivitamin (Centrum Silver daily) among 15,000 participants in the prevention of prostate cancer, cardiovascular disease, cataract, and age-related macular degeneration. A beta-carotene component was included in the early years of the study. This trial has been ongoing since 1997. Blood samples, including plasma and DNA, are available on ~70% of participants. (Contact Person: Mike Gaziano)
- **The VITamin D and Omega-3 Trial (VITAL)** is a large-scale randomized, double-blind, placebo-controlled, 2x2 factorial trial of vitamin D (in the form of vitamin D₃ [cholecalciferol], 2000 IU/day) and marine omega-3 fatty acid (eicosapentaenoic acid [EPA] + docosahexaenoic acid [DHA], 1 g/day) supplements in the primary prevention of cancer and CVD in a multi-ethnic population of 25,874 U.S. men and women aged ≥60 and ≥65, respectively. The mean treatment period will be 5 years. Baseline blood samples have been collected in approximately 17,000 participants, with follow-up blood samples in ~6,000 participants. In-clinic visits involving in-depth phenotyping are being conducted in ~1000 participants at baseline and at 2 years of follow-up.
Ancillary studies are investigating whether these supplements affect risk for diabetes and glucose intolerance; hypertension; cognitive decline; depression; osteoporosis and fracture; falls; asthma and other respiratory diseases; anemia; infections; autoimmune disorders, and several other outcomes (contact person: JoAnn Manson)
- **Women's Antioxidant Cardiovascular Study (WACS):** Trial of Antioxidant Therapy of CVD in Women (HL46959), a randomized, double-blind, placebo-controlled trial of the balance of benefits and risks of beta-carotene (50 mg on alternate days), vitamin E (600 IU on alternate days), vitamin C (500 mg daily), and a combination of folic acid (2.5 mg daily), vitamin B6 (50 mg daily), and vitamin B12 (1 mg daily) in the prevention of cardiovascular events among 8,171 female health professionals (5,442 participated in the B-vitamin trial) with a prior history of cardiovascular disease or at high risk due to three or more risk factors. This trial began in

1993 and randomized treatment ended in 2005. Blood samples, including plasma and DNA, are available on ~70% of participants. (Contact Person: JoAnn Manson)

- **Women's Health Initiative (WH32109):** This is a nationwide, multicenter, randomized trial sponsored by the National Institutes of Health to assess the benefits and risks of hormone replacement therapy, low-fat diet, and calcium/vitamin D supplementation in the prevention of cardiovascular disease, cancer, and osteoporosis-related fractures in postmenopausal women. Begun in 1993, the Division was one of the 16 original vanguard clinical centers and assisted in the development of the design and protocol for the trial. The clinical trial component of this project has ended, and is now in an observational follow-up phase. The study includes ~161,000 women (~68,000 in one or more clinical trials and ~93,000 in the observational component). Baseline blood samples, including plasma, serum, and DNA, are available on all 161,000 participants and follow-up blood samples are available on a large subset. (Contact Person: JoAnn Manson)
- **Nurses' Health Study:** This is an ongoing cohort of 120,000 women currently aged 70-95 years, and followed since age 30-55 years, with data on wide variety of diseases including cancers, cardiovascular disease, diabetes, neurologic disorders, urinary incontinence, and others. Biospecimens are also available in many participants. (Contact Person: Fran Grodstein)
- **Nurses' Health Study II:** This is an ongoing cohort of 100,000 women currently aged 51-68, and followed since age 25-42 years, with data on wide variety of diseases including cancers, cardiovascular disease, diabetes, hypertension, infertility, urinary incontinence and many others. Biospecimens are also available in many participants. (Contact Person: Heather Eliassen)
- **Health Professionals Follow-up Study:** This is an ongoing cohort of 50,000 men in the allied health professions, designed as a male companion study to the Nurses' Health Study. Participants are currently age 69-104, and have been followed since age 40-75 years. Data are available on a wide variety of diseases, including cancers, cardiovascular disease, diabetes, neurologic disorders, and others. Biospecimens are also available in many participants (Contact: Walter Willett).
- **Nurses' Health Study III**
This is an open, web-based longitudinal cohort of 35,000 nurses age 20-45, recruited since 2010. The cohort is still enrolling, and aims to enroll 100,000 nurses. Participants complete an online survey regarding occupational exposures, lifestyle exposures, and health outcomes every 6 months; the study includes a subsample, the Maternal Health Survey, with added data collection regarding fertility and pregnancy.
<http://www.nhs3.org/> (contact persons: Janet Rich-Edwards/ Fran Grodstein)
- **Health Professionals Follow-up Study**
The Health Professionals Follow-up Study began in 1986 and is now an ongoing all-male study that evaluates a series of hypotheses regarding men's health as it relates to nutritional factors to the incidence of serious illnesses such as cancer, heart disease, and other vascular diseases. This group is composed of 29,683 dentists, 4,185 pharmacists, 3,745 optometrists, 2,220 osteopath physicians, 1,600 podiatrists, and 10,098 veterinarians (contact person: Walter Willett).

- **The National Collaborative Perinatal Project (NCPP)** of the NINDS was initiated nearly 50 years ago to investigate prospectively the prenatal and familial antecedents of pediatric, neurological, and psychiatric disorders of childhood. The NCPP involved the systematic collection of data through the prospective observation and examination of over 55,000 pregnancies from twelve university-affiliated medical centers in the United States, including 17,741 pregnancies from two New England sites (BWH and Brown University). Pregnant women (G1 generation) were recruited for the study between 1959 and 1966 and were largely representative of patients receiving prenatal care in each participating center. Extensive prenatal and maternal data were systematically collected by trained staff throughout pregnancy and at birth, along with repeated medical, neurological, and psychological examinations of the children (G2 generation) at 4 and 8 months and 1, 4, and 7 years of age. Reproductive and gynecological history, current and past medical history, socioeconomic interview, and family history were recorded. In addition to detailed clinician evaluations, blood/serum and/or tissue samples were obtained at each prenatal visit and on the day of delivery and stored in a repository for further analyses. Follow-up of the G1 and adult G2s, along with the enrollment and evaluation of G3 (i.e., offspring of the G2s) subjects of the NCPP is ongoing in a number of current studies (e.g. among others, by BWH investigators such as Drs. Jill Goldstein and Karen Michels) providing three generations of information that include diagnostic assessments for psychiatric disorders, neuropsychological evaluations, cardiovascular risk indicators, reproductive disorders, breast cancer, and clinic visits that also include structural and functional MRI in studies of fetal antecedents to adult brain abnormalities. (Contact Person: Jill Goldstein)

- **Estrogen-regulated Gene Expression in Library:** A link to potentially useful datasets for the sites of ER binding and estrogen regulated gene expression in MCF7 cells. (Provided by: Myles Brown) <http://research.dfci.harvard.edu/brownlab/datasets/index.php>

- **Women with Epilepsy: Pregnancy Outcomes and Deliveries (WEPOD)**
 Milken Family Foundation, Epilepsy Therapy Project, and Epilepsy Foundation
 This 3-center study will prospectively compare pregnancy rates and live-birth rates between women with epilepsy and healthy controls. Women with epilepsy will also be studied for seizure frequency in relation to menstrual cycles and during pregnancy, with analysis of key co-variables including type of epilepsy syndrome and type of anti-epileptic drug prescribed (contact person: Page Pennell).

- **Pharmacogenomics and Pharmacokinetics of Lamotrigine in Early Pregnancy (P-PEP)**
 Epilepsy Foundation Targeted Research Initiative
 This supplement to the WEPOD study will examine the impact of genetic variations in drug transporter ABCB1 and glucuronidating enzymes on baseline and accelerated lamotrigine clearance during early pregnancy, and describe the time course of change in lamotrigine concentrations during the first trimester of pregnancy and relate it to seizure frequency (contact person: Page Pennell).

- **Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD)**
 NIH/ NINDS and NICHD
 This multi-center, observational cohort study will enroll pregnant women with epilepsy, non-pregnant women with epilepsy, and pregnant healthy controls. Primary aims include maternal seizure frequency, obstetric complications, neonatal outcomes, maternal depression, and

cognitive outcomes of the offspring, with consideration of AED pharmacokinetics and maternal and fetal exposure to AEDs (contact person: Page Pennell).

- **Metabolomic Indicators of Risk in the MONEAD Cohort**

NIH Common Fund Initiative, administered by NCI on behalf of NIH

This supplement will enhance the MONEAD research team's knowledge of advanced metabolomics tools and approaches, apply high-resolution metabolomics to MONEAD samples as part of a broader, long-term initiative to create a metabolomics resource for at-risk pregnancies, and establish feasibility for use of metabolomics for mechanistic studies through specific analysis of folate, hormone metabolites, and antioxidant pathways along with unbiased evaluation of the metabolome in biological samples from the unique MONEAD cohort. This study will focus on potential mechanisms underlying small for gestational age outcomes (contact person: Page Pennell).

- **Heart Health 4 Moms funded by PCORI**

The purpose of this study is to determine whether a web-based healthy lifestyle program based on DASH can increase self efficacy for healthy eating and physical activity in women with recent preeclampsia. (PIs: Janet Rich-Edwards and Ellen Seely)

- **Preeclampsia: A Marker of Future Cardiovascular Risk in Women funded by NIH**

The purpose of this study is to determine whether women with prior preeclampsia have activation of the angiotension II type 1 receptor leading to salt sensitivity of blood pressure and eventual hypertension. (PI: Ellen Seely)

- **The COcoa Supplement and Multivitamins Outcomes Study (COSMOS)**

COSMOS is a randomized, double-blind, placebo-controlled, 2x2 factorial trial of a cocoa flavanol supplement and multivitamins in reducing risks of cardiovascular disease (CVD) and cancer in 12,000 women aged ≥ 65 years and 6,000 men aged ≥ 60 years (N=18,000 total) with 4 years of treatment and follow-up. The trial is beginning recruitment in spring 2015.

The trial utilizes an innovative and highly time- and cost- efficient approach leveraging the existing infrastructure of the Women's Health Initiative (WHI) and the VITamin D and OmegaA-3 Trial (VITAL). We plan to collect baseline and follow-up blood and urine samples on a subset of participants to assess changes in important nutritional and vascular/metabolic biomarkers related to the interventions. The design of the trial also allows for the development of multiple ancillary studies, including collection of information on secondary outcomes and in-clinic visits at Clinical and Translational Science Centers. (contact person: JoAnn Manson) (COSMOS Trial PIs: Dr. JoAnn Manson and Dr. Howard Sesso at Brigham and Women's Hospital, Harvard Medical School, and Dr. Garnet Anderson at the CCC, Fred Hutchinson Cancer Research Center.)

- **The Harvard Epigenetic Birth Cohort**

The Harvard Epigenetic Birth Cohort comprises about 1900 mother-infant dyads annotated with a rich library of data (maternal, prenatal, neonatal) and biospecimens (placenta, cord blood, maternal blood). We have done extensive epigenetic work in this cohort which reveals striking sex differences in the effect of intrauterine exposure to endocrine disrupting chemicals on DNA methylation and miRNA expression in the placenta. This resource is of particular interest given the recent announcement of the Human Placenta Project by NIH (Contact Person: Karin Michels).

- **Psychological and Autonomic Hyperarousal in Menopausal Hot Flash-Associated Insomnia**
This mechanistic study is examining the psychological and physiologic profiles of hyperarousal among peri/postmenopausal women with nocturnal hot flashes by contrasting those who do or do not have hot flash-related sleep-maintenance insomnia. (contact person: Hadine Joffe)
- **Predicting Hot Flash Response to Tamoxifen and Aromatase Inhibitors**
This study of women planning to start tamoxifen or an aromatase inhibitor (AI) for treatment for ER+ breast cancer or high-risk conditions aims to identify clinical predictors of the development of hot flashes as part of an examination of psychological and genetic predictors of endocrine therapy tolerability. (contact person: Hadine Joffe)
- **Effects of Estradiol and Hot Flashes on Mood in Perimenopausal Women**
This study investigates the hormonal dynamics of depressive symptoms in perimenopausal women using close monitoring of mood, serum reproductive hormones, hot flashes and sleep patterns. (contact person: Hadine Joffe)
- **Partners Biobank (previously known as OurGenes)**
The Partners HealthCare Biobank is an ongoing study which seeks to cultivate collaborations among investigators, physicians and the patients seen at any of the Partners HealthCare hospitals. Data samples are maintained in an institution-wide archive which is an expanding resource available to Partners investigators and research groups. Currently, more than 24,000 patients have consented to participate in this study at both Brigham and Women's Hospital and Massachusetts General Hospital. Partners has committed to GWAS of 25,000 participants. (contact person: Beth Karlson)
- **Specialized Center of Research (SCOR) in Newborn Lung Biology**
The SCOR database initially was established as a repository of information for laboratory and clinical investigators (HL#67669); PI: Stella Kourembanas) focused on Brigham and Women's Hospital (BWH) extremely preterm inborn infants. The study cohort consists of >1500 BWH infants born before 29 completed weeks of gestation. The database captures demographics, major neonatal outcomes, disposition, and detailed information on respiratory management of the infants at key points during their hospitalizations. Biological specimens (i.e., urine samples, tracheal aspirate secretions, dried blood spots) are available on a subset of subjects. (Contact Person: Linda J. Van Marter)
- **VITamin D and OmegA-3 Trial (VITAL): Effects on Fractures**
This study is an ancillary study conducted among participants enrolled in the parent VITAL study. VITAL is a double-blind, placebo-controlled trial assessing the role of vitamin D3 ([cholecalciferol], 2000 IU/day) and marine omega-3 fatty acid (eicosapentaenoic acid [EPA] + docosahexaenoic acid [DHA], 1 g/day) supplements in reducing risks of cancer and cardiovascular disease among U.S. men aged ≥50 and women aged ≥55. To test the effects of supplemental vitamin D and/or omega-3 fatty acid on fracture risk, this ancillary study is determining among 25,874 men and women the role of these supplements in the primary prevention of incident total, hip and non-vertebral fractures. Self-reported incident fracture events are being adjudicated through detailed review of medical records. Hip and femur fractures are further adjudicated using radiological images. (Contact Person: PI Meryl LeBoff)
- **VITamin D and OmegA-3 Trial (VITAL): Effects on Bone Structure and Architecture**

This is an ancillary study conducted among a subcohort of VITAL participants with detailed in-clinic assessments. VITAL is a double-blind, placebo-controlled trial assessing the role of vitamin D3 ([cholecalciferol], 2000 IU/day) and marine omega-3 fatty acid (eicosapentaenoic acid [EPA] + docosahexaenoic acid [DHA], 1 g/day) supplements in reducing risks of cancer and cardiovascular disease among U.S. men aged ≥ 50 and women aged ≥ 55 . To comprehensively test the effects of supplemental vitamin D and/or omega-3 fatty acid on bone health, this ancillary study is completing detailed measurements of bone mineral density, body composition, bone structure as assessed by peripheral quantitative computed tomography (pQCT), and bone turnover markers at baseline and 2 years of follow-up, and high-resolution pQCT (HR-pQCT) at year 2. (Contact Person: PI Meryl LeBoff)