SPECIFIC AIMS

The menstrual cycle is a marker of physiologic and reproductive health and is tightly controlled by hormone signals between the hypothalamus, pituitary, and ovaries. The menstrual cycle can be disrupted by environmental and biological factors via hormone dysregulation and ovarian dysfunction. The most common cause of irregular menses in reproductive-age women is **polycystic ovary syndrome (PCOS)**; hallmark features include ovarian dysfunction and androgen excess[1]. PCOS poses a huge burden of disease including increased risk of infertility, diabetes[2], hypertension[3], dyslipidemia, obesity, and metabolic syndrome[4-6]. Even in the absence of clinically defined ovarian disease, variations in **menstrual cycle characteristics (MCC)** such as cycle length and cycle irregularity are associated with increased risk of chronic non-communicable disease and premature death[7]. While multiple studies have evaluated environmental exposures and male reproductive health, specifically the effect of **air pollution (AP)** on semen quality[8, 9], little is known about the environmental impact of AP on menstrual health, particularly in the context of disparities in exposure or outcomes[10]. Furthermore, the extremely limited literature on non-tobacco air pollutants and MCC variation[11, 12] are conflicting. Our **overarching goal** is to fill this knowledge gap and determine the impact of environmental factors on MCC, focusing on the association of life course exposure to AP and climate factors with MCC and PCOS.

Climate factors such as temperature has been shown to affect reproductive function in mammals[13]. AP exposure has been associated with other reproductive outcomes in women and their offspring[14-17]. We previously reported associations between (1) higher AP exposures in *high school-age* girls and menstrual irregularity[18], and (2) proximity to major roadways and infertility risk in *adult* women[19]. The underlying cellular and pathophysiological mechanisms are thought to include endocrine disruption[18, 20-24], inflammation, oxidative stress, direct toxicity[25], and impaired DNA repair[26]. Assessment of AP exposures and MCC are limited by studies of heterogenous populations with limited racial/ethnic diversity, incomplete city-level census tract level monitoring, retrospective collection of cycle history, and lack of MCC and PCOS ascertainment[11, 12].

We propose to use data from three large cohort studies to test our **overall hypothesis** that AP exposures are associated with MCC and increased risk of PCOS: (1) the Nurses' Health Study 3 (**NHS3**), an open cohort of nurses born after 1964 within the United States (current n=46,360); and (2) the Growing Up Today Study (**GUTS**) consisting of 15,035 daughters of participants in the Nurses' Health Study II (NHSII) enrolled in 1996 and 2004 when they were 9-15 years of age, with prenatal exposure assessments available (n=5,140). Though these cohorts are predominantly White, they offer a rich dataset that includes ascertainment of MCC, clinical ovarian dysfunction, and androgen excess, as well as prospective time-varying residential history data that will allow us to estimate AP exposures across the life course. We will evaluate cumulative lifetime exposure and life course exposure to AP during the sensitive time windows of (1) gestation, (2) childhood/premenarche, and (3) adulthood to determine which exposure window confers greatest risk. We will additionally evaluate life course exposure to climate factors, including temperature and humidity, to understand their contribution to MCC outcomes and risk for PCOS. Finally, we will include the (3) Boston Medical Center Electronic Health Record (**BMC-EHR**) cohort of 37,959 women with time-varying geocoded home address and diagnostic codes (including menstrual irregularity, androgen excess features, and PCOS). BMC is a safety net hospital with a predominantly minority (Black and Hispanic) population; and provides a unique opportunity to evaluate disparities in AP exposures and MCC outcomes.

Aim 1: Determine the association between life course exposures to AP and climate factors and physiological variation in MCC. *We hypothesize that long-term exposures increase menstrual cycle length and irregularity.*

Aim 2: Determine the association between life course exposures to AP and climate factors and PCOS risk. *We hypothesize that gestational or lifetime exposures disrupt endocrine function and increase the risk of PCOS, defined by irregular menses and androgen excess (clinically manifesting as hirsutism, acne).*

Aim 3: Evaluate disparity in environmental exposure distribution and risk of PCOS. *We hypothesize that the absolute risk of irregular menses and PCOS is higher among the population at BMC compared to other cohorts, due to disparities in exposure to AP and other environmental risk factors.*

This study will fill a major gap in our understanding of the effect of AP and climate-related exposures on menstrual health and disease. Our findings will help inform clinical counseling on health promotion and risk reduction across the lifespan to support menstrual health.

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