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Background: Polycystic ovary syndrome (PCOS) is a heterogeneous condition that affects 6-10% of women of reproductive age. PCOS is often characterized by a triad of ovulatory dysfunction, hyperandrogenism, and cardiometabolic dysfunction. Both ovarian-related and ovarian-independent factors have been implicated in the pathogenesis of PCOS, but it remains to be determined which are the inciting events and which are the secondary consequences. Studies of male relatives of women with PCOS have proposed a male counterpart of PCOS, which suggests that PCOS is not always a primary disorder of female reproduction, but rather can be, at least in part, a condition of cardiometabolic dysregulation and hyperandrogenism, with ovarian dysfunction as a secondary consequence.
Methods: To investigate a genetically defined male counterpart of PCOS, we optimized a polygenic risk score (PRS) algorithm for predicting PCOS based on 206,851 unrelated women of European ancestry in the UK Biobank, then used this algorithm to calculate PCOS PRS for 176,360 men in the UK Biobank. We used logistic regression to calculate odds ratios for dichotomous outcomes by comparing men with high and low PRS (testing a variety of percentile cutoffs) and ANCOVA to compare continuous outcomes across deciles of PRS. All analyses were adjusted for age, age^2, assessment center, genotyping array, and the first 10 principal genetic components to account for ancestry.
Results: Men who carried a high PCOS PRS (top 20%) had a 17% increased risk of obesity defined as BMI ≥30 kg/m^2 (OR 1.17, 95% confidence interval [CI] 1.14-1.20, p=1.3x10^{-30}), 15% increased risk of type 2 diabetes mellitus (OR 1.15, 95% CI 1.09-1.20, p=5.3x10^{-8}), 5% increased risk of coronary artery disease (OR 1.05, 95% CI 1.01-1.09, p=0.03), and 5% increased risk for androgenic alopecia (OR 1.05, 95% CI 1.01-1.08, p=0.01). BMI, hemoglobin A1c, triglycerides, and the free androgen index all increased across deciles of the PRS, while HDL and SHBG decreased across PRS deciles (p all <0.001). The relationship between the PCOS PRS and coronary artery disease, HDL, and triglycerides appeared to be mediated by BMI. In contrast, the associations between the PCOS PRS and type 2 diabetes mellitus and hemoglobin A1c remained significant after adjusting for BMI, suggesting independent mechanisms of pathogenesis.
Conclusions: By demonstrating associations between PCOS genetic risk factors and cardiometabolic dysfunction and androgenic conditions in men, we have shown that these genetic risk factors can act independently of ovarian function. Thus, at least in some cases, the reproductive dysfunction of PCOS in women may arise secondarily from disruption of biological pathways common to both men and women. Future dissection of these biological pathways will further inform efforts to identify pathological mechanisms underlying PCOS.

Reproductive Endocrinology
RECIPROCAL EFFECTS OF OVARIAN AND METABOLIC DYSFUNCTION

Effect of Experimentally Induced Sleep Fragmentation and Hypoestrogenism on Fasting Nutrient Utilization in Pre-Menopausal Women

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Background: Both sleep disturbance and menopause have independently been associated with weight gain in women. Possible mechanisms contributing to this weight gain may be changes in resting energy expenditure (REE) and/or nutrient utilization. Therefore, in the current study we aimed to examine the effects of experimentally induced sleep fragmentation and pharmacologic estradiol (E2) withdrawal on REE and nutrient utilization in the fasted state. *Design:* We studied pre-menopausal women during 5-night inpatient studies repeated in the mid-to-late follicular phase (high-E2; n=21) and following leuprolide-induced hypoestrogenism (low-E2; n=9 completed second visit). During each admission there were two nights of unfragmented sleep [8-h time in bed (TIB)] and three nights of fragmented sleep [9-h TIB]. Sleep was fragmented using an auditory stimulus delivered every 15 minutes that sustained wake for 2 minutes, producing 1 hour of wake after sleep onset. Study diets consisted of 3 meals and a snack each day and were iso-caloric across the two visits. REE and nutrient utilization were assessed in the fasted state via indirect calorimetry and compared between E2 states following unfragmented and fragmented sleep using linear mixed models. **Results:** Sleep fragmentation in the high-E2 state increased the respiratory quotient (RQ; +3%; p=0.03) with an accompanying increase in carbohydrate oxidation (+20%; p=0.02) and decrease in fat oxidation (-16%; p=0.03). The same effect was observed in response to E2-withdrawl during unfragmented sleep [increased RQ (+5%; p=0.01) and carbohydrate oxidation (+33%; p=0.01), and decreased fat oxidation (-26%; p=0.01)]. There was no additive effect of sleep fragmentation on nutrient utilization in the low-E2 state suggesting a possible ceiling (RQ and carbohydrate oxidation) and floor (fat oxidation) effect. There was no effect of sleep fragmentation or E2 state on REE. **Conclusion:** Both sleep fragmentation and hypoestrogenism were shown to alter fasting nutrient utilization, but not REE, in a manner that may contribute to weight gain in menopausal women. These findings are important for understanding weight gain during menopause, which is characterized by estrogen withdrawal and often accompanied by sleep disturbances.

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Heterozygous Eif4nif1 Stop Gain Mice Replicate the Primary Ovarian Insufficiency Phenotype