Written abstracts (300 words or less) along with a description (150 words or less) of how this work applies to sex difference, gender biology, or women’s health research will be judged to select featured talks.

**Abstract**

While epidemiological research has found multiple risk factors of COVID-19 severity, including sex, cardiometabolic status, and social determinants of health, the interaction between risk factors of COVID-19 have not been thoroughly investigated. Leveraging known COVID-19 risk factors as exposures has the potential to shed light on COVID-19 biology and susceptible communities. In this genome-wide interaction study in the UK Biobank, we investigate the interaction between genetic variants of sex, obesity, T2D, and social determinants of health and their impact on COVID-19 severity. Using GxE analysis and GWAS post-processing methods, we found significant loci that uncover some biological underpinnings of variable COVID-19 severity. A genome-wide significant intron variant (rs2268616) identified in the sex joint interaction and cardiometabolic interaction analyses was associated with the placental growth factor gene and testosterone in GWAS analyses. Interestingly, other studies have found that SARS-CoV-2 can enter the testis and delay viral RNA clearance in males, possibly contributing to differential immune responses between sex. Our work analyzing the gene-environment interaction provides insight into the relationship between variants associated with COVID-19 severity, and it contributes to the biological and genetic research done to uncover the underpinnings of COVID-19. Future studies investigating the stratified effects of sex, T2D and BMI, and social determinants of health on COVID-19 susceptibility, as well as analysis with a wider array of ancestries may further uncover underlying the genetic interaction effects that place individuals at higher risk.

**Description**

Studies have shown males to be independently associated with higher mortality and worse COVID-19 outcomes. Different sex genes and hormones, as well as differences in environmental factors between the sexes, contribute to differential immune responses between sexes and may mediate the association of male sex and worse COVID-19 outcomes. Our work seeks to explore the gene-environment interactions that are associated with worse COVID-19 outcomes, specifically interactions between genetic variants of sex, obesity, T2D, and social determinants of health. Exploring the genetics behind these sex differences offer novel understanding of the underlying mechanisms, adding to the current epidemiological research conducted to explore biological differences.