Disease comorbidities and longer-term complications, occurring as a result of biologically related associations across phenotypes, can lead to increased risk of severe health burdens and patient morbidity. Given that many individual diseases exhibit sex-specific differences in their genetic underpinnings, our objective was to determine whether associated pairs of diseases are similarly influenced by genotype-by-sex (GxS) interactions.

Through the comparison of sex-stratified disease-disease networks (DDNs) – graphs where nodes represent diseases and edges represent relationships between diseases – we investigate differences across the sexes in patterns of genetic polygenicity and pleiotropy between diseases. Using sex-stratified phenome-wide association study summary data from the UK Biobank, we built male- and female-specific DDNs for 103 disease phenotypes.

Comparing the two graphs reveals that the diseasomes of males and females behave similarly to one another in terms of topology and key central diseases (such as hypertensive, chronic respiratory, and thyroid-based disorders). Some phenotypes, however, are found to exhibit sex-specific influence in cross-phenotype associations. For instance, autoimmune and inflammatory disorders including multiple sclerosis and osteoarthritis are centrally involved only in the female-specific DDN, while cardiometabolic diseases and skin cancer are more prominent only in the male-specific DDN. A comparison of edges present in the two graphs indicates similar patterns of polygenicity across the sexes relative to a random model of genetic associations between diseases. Notably, discrepancies in embedding distances and clustering patterns across the networks imply a more expansive genetic influence on multimorbidity risk for females than males.

We further validated these observations by evaluating the pleiotropic contributions of two sexually-dimorphic single-nucleotide polymorphisms related to thyroid disorders, highlighting a distinct genetic architecture across the sexes that influences associations. Our examination of corresponding gene expression profiles from the GTEx Portal confirmed these sex-specific associations. In sum, our analysis affirms the presence of GxS interactions in cross-phenotype associations, emphasizing the continued need for investigation of the role of sex in disease onset and its importance in biomedical discovery and precision medicine research.