Introduction: Epidemiological estimates indicate fibromyalgia affects up to 8% of the population, is underdiagnosed, and frequently lasts a lifetime. The heritability of chronic pain conditions is estimated at 50%. Small sample sizes have precluded finding significant genetic loci to date, despite investigations using methods including linkage and candidate gene studies, genome-wide association methods, and exome sequencing approaches. Thus, to more fully elucidate the genetic architecture of fibromyalgia, we examine sex differences and provide estimates of prevalence, comorbidities across the phenome, polygenic overlap between fibromyalgia and other traits, and perform a genome-wide association study (GWAS) of fibromyalgia from the largest sample to date.

Methods: Fibromyalgia cases were identified by the ICD10 code M79.7. Controls were identified by presence of any ICD10 code, together with the absence of ICD9 code 729.1 and ICD10 code M79.7. Ancestry classification was based on principal component clustering. We calculated polygenic risk scores (PRSs) for eight comorbid phenotypes with PRSice2 in BioVU (Vanderbilt biobank) and BioMe (Mount Sinai biobank). We fitted multivariable logistic regression models to test the association between fibromyalgia diagnosis and each component PRS while controlling for median age and genetic PCs 1-10. We perform GWAS using Saige v0.42.1 with PCs1-10, age, BMI, and sex, as covariates and meta-analyze using METAL.

Results: Swedish register data indicate enrichment among fibromyalgia cases of comorbidities including major depression, anxiety, back pain, inflammatory bowel disease, asthma, rheumatoid arthritis, osteoarthritis, and decreased subjective well-being. In our analyses, fibromyalgia case status was significantly associated with PRSs for back pain, inflammatory bowel disease, major depression, neuroticism, rheumatoid arthritis, and subjective well-being. The PRS for rheumatoid arthritis demonstrated the strongest positive association with fibromyalgia (OR per standard deviation of risk: 1.9-2.2) while subjective well-being yielded the strongest negative association (OR: 0.84-0.91). The first genome-wide significant locus is identified by two separate SNPs and will also be reported.

Discussion: In this work, we improve the field's understanding of fibromyalgia, a pain condition linked with anxiety, depression, and subjective well-being, among other commonly comorbid traits and we make advances towards understanding shared genetic architecture of these related traits.