Figure S1: principal component (PC) analysis for all samples in the study except METSIM, combined with 1000 genomes samples. PCs have been computed separately in each panel. **Panel a:** modified ExAC dataset, **a.1:** Northern Finnish intellectual disability study, **a.2**: the Swedish Schizophrenia Exome Sequencing project, **a.3:** T2D-GENES/GoT2D/SIGMA consortia, **a.4:** Helmsley IBD Exome Sequencing Project, **a.5:** Myocardial Infarction Genetics Exome Sequencing Consortium. **Panel b:** Finnish - FINRISK**, Panel c:** exome sequencing Danish Blood Spot project**.**

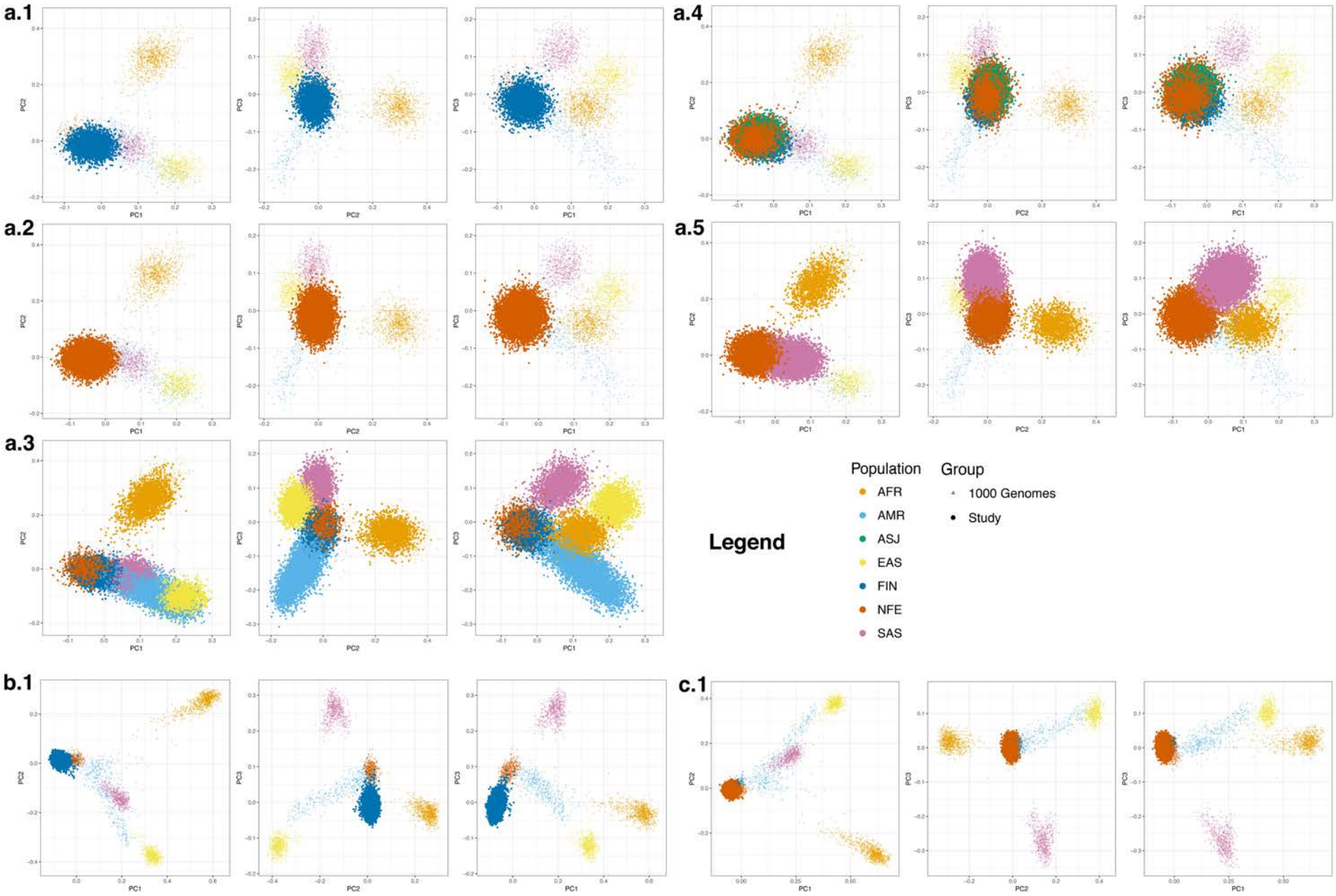


Figure S2: Ethnicity-specific and meta-analyzed association between different classes of variants and age. The signal is specific to PTV and PTV + Damaging missense in PI-genes.

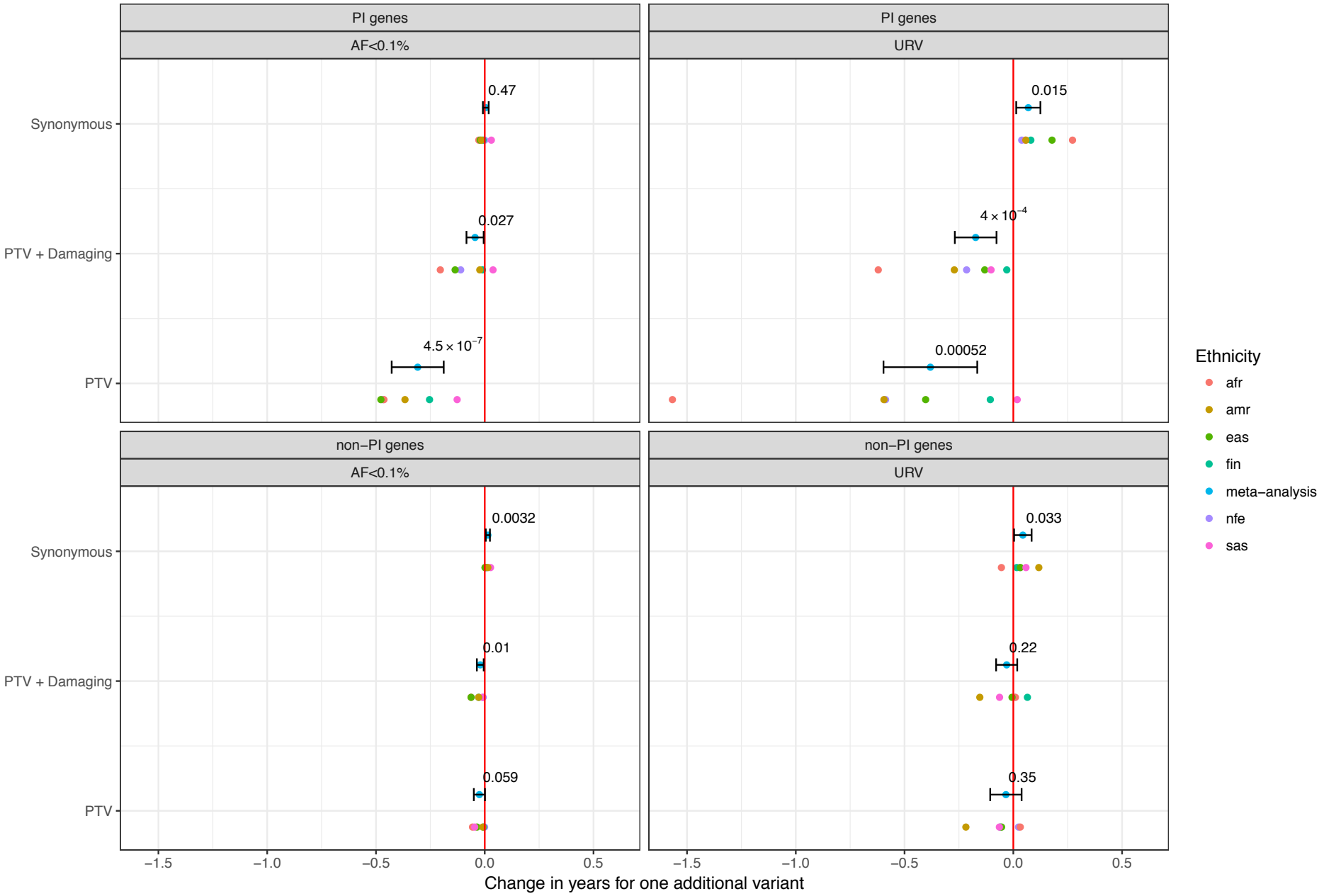


Figure S3: Association between rare PTVs in PI genes and age by sub-study and ethnicity. The signal is consistent across all the studies and ethnicities. Migen: Myocardial Infarction Genetics Exome Sequencing Consortium, Diab: T2D-GENES/GoT2D/SIGMA consortia.

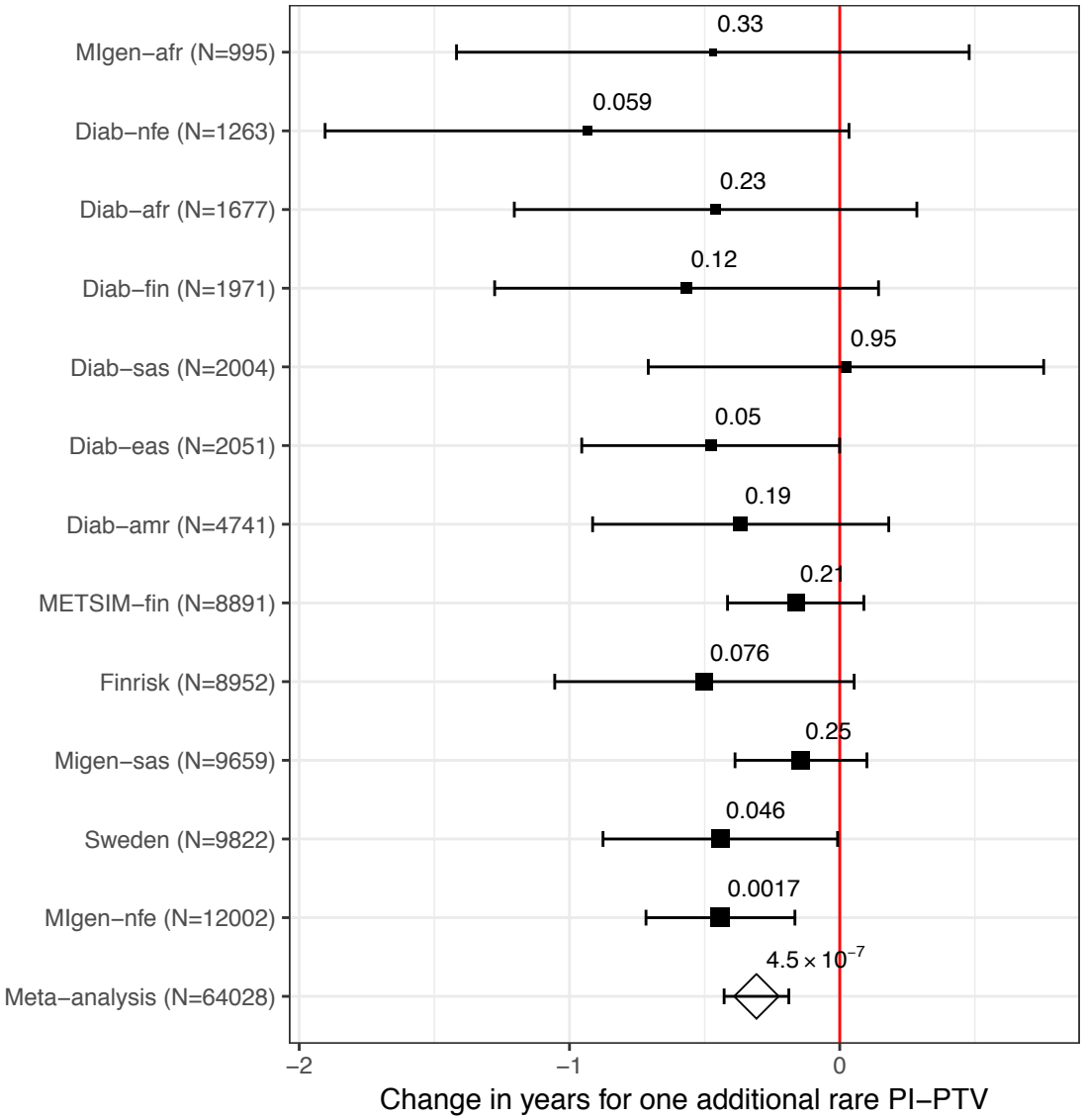


Figure S4: Meta-analyzed association between rare PTVs in PI genes and age for different variant subsets. Signal is consistent within each group. SNPs, no T -> C and G -> A: remove mutations possibly caused by cytosine deamination, SNPs: only SNPs, INDELS: only INDELs, Hi-Quality variants: study-specific call rate > 0.95, allele balance between 30% and 70%, high quality intervals. METSIM study not included.

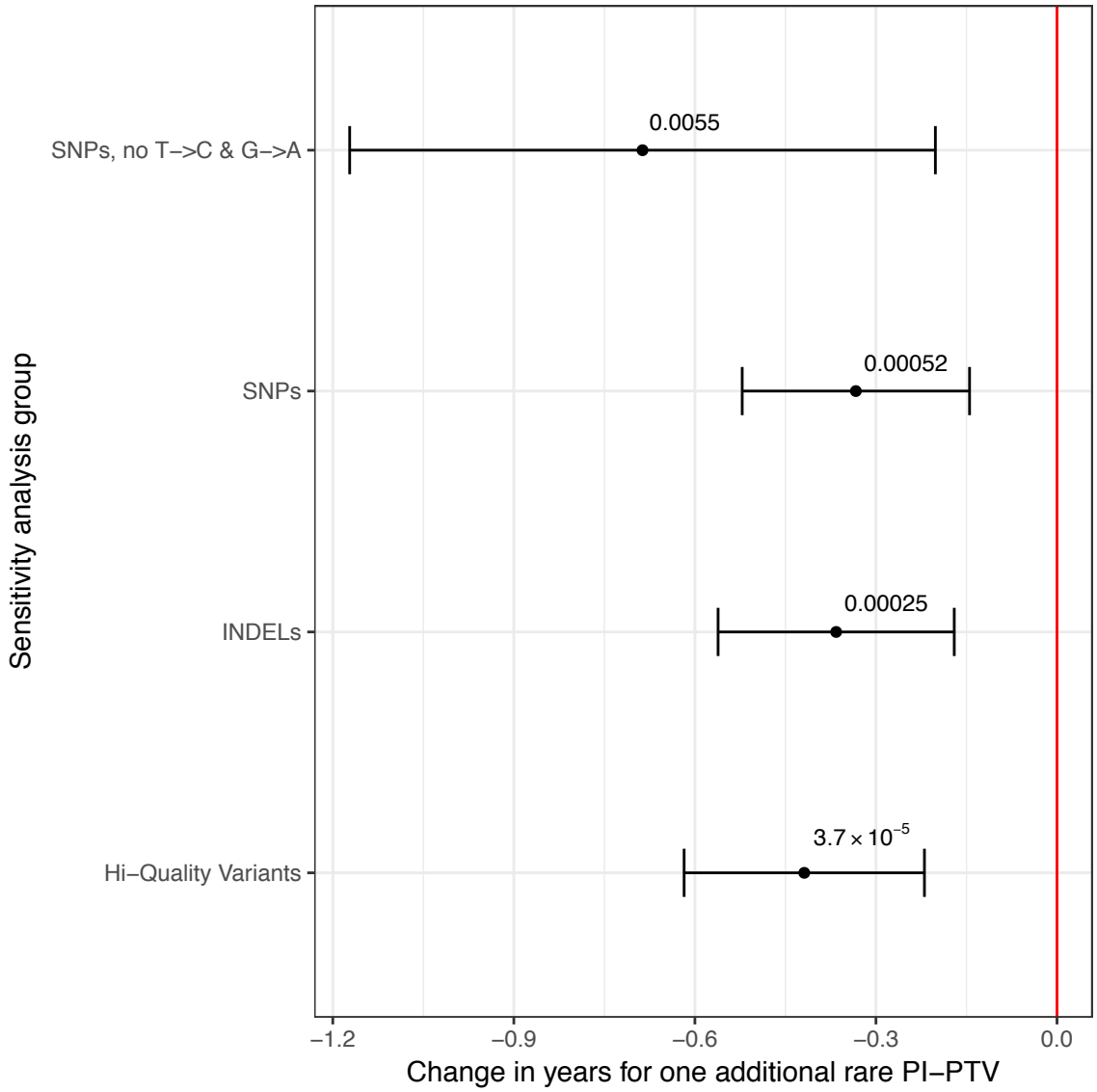


Figure S5: Ethnicity-specific and meta-analyzed association between different classes of variants and age, adjusting for 8 sample-level QC metrics: call-rate, number of SNPs, number of singletons, mean DP, mean GQ, Ti/Tv, Het/Hom and Insertion/deletions. The signal is specific to PTV and PTV + Damaging missense in PI-genes. METSIM study not included.

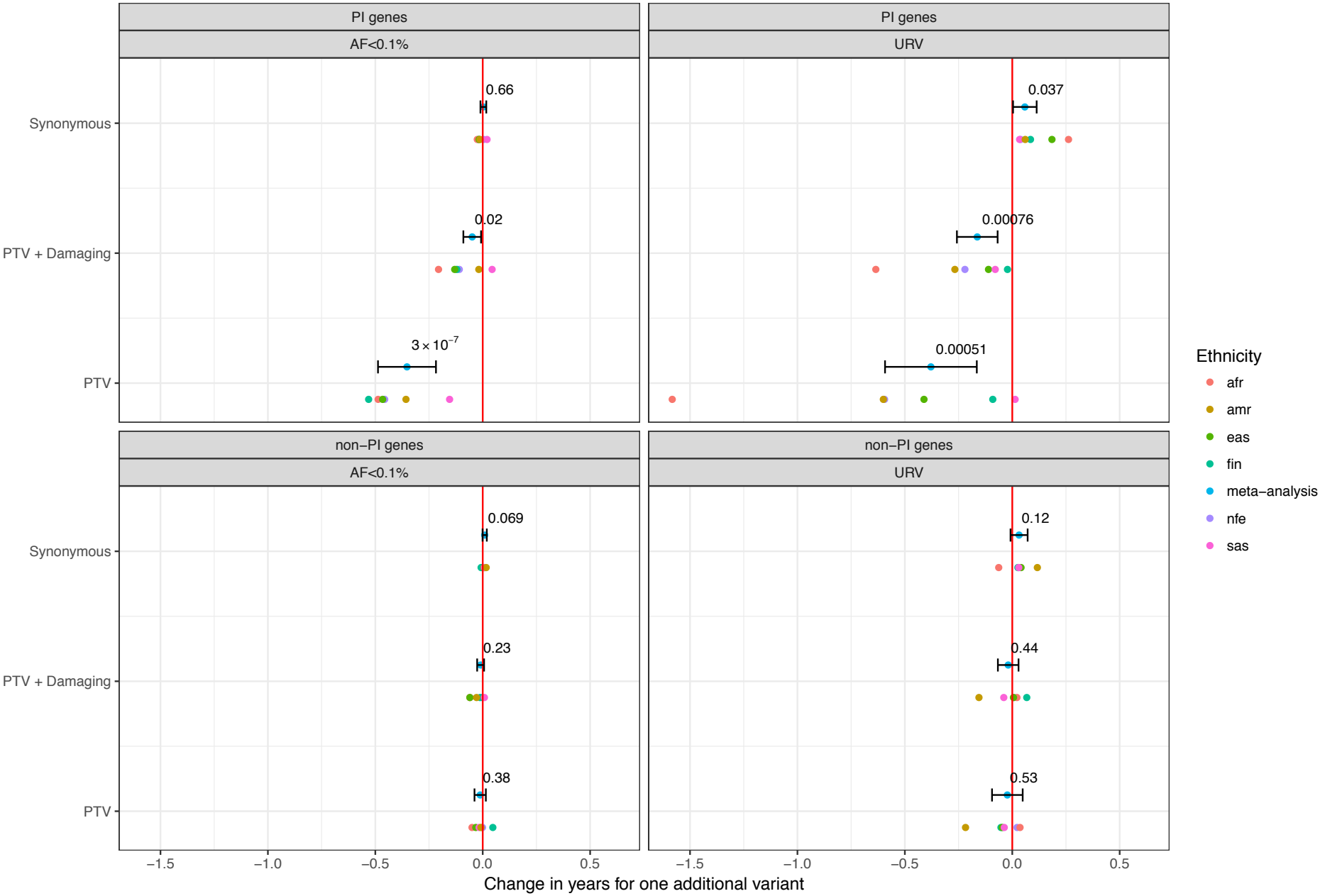
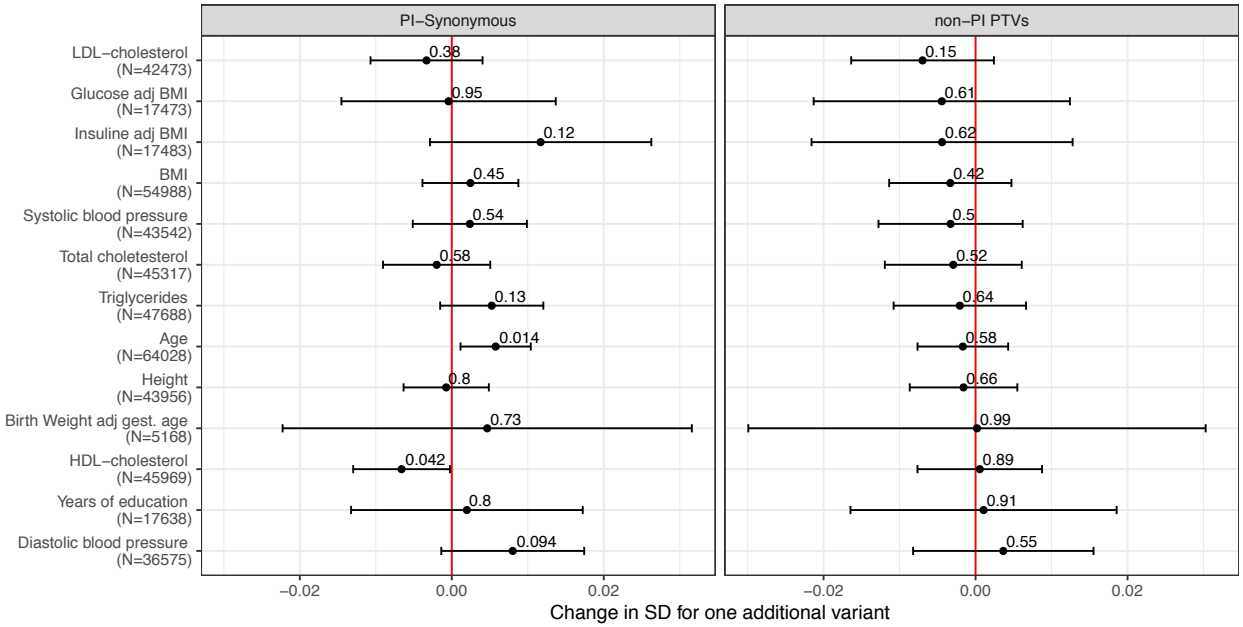


Figure S6: Meta-analyzed associations between ultra-rare synonymous variants in PI genes and ultra-rare PTVs in non-PI genes and 13 quantitative traits (upper panel) and 10 diseases (lower panel). No significant signal.



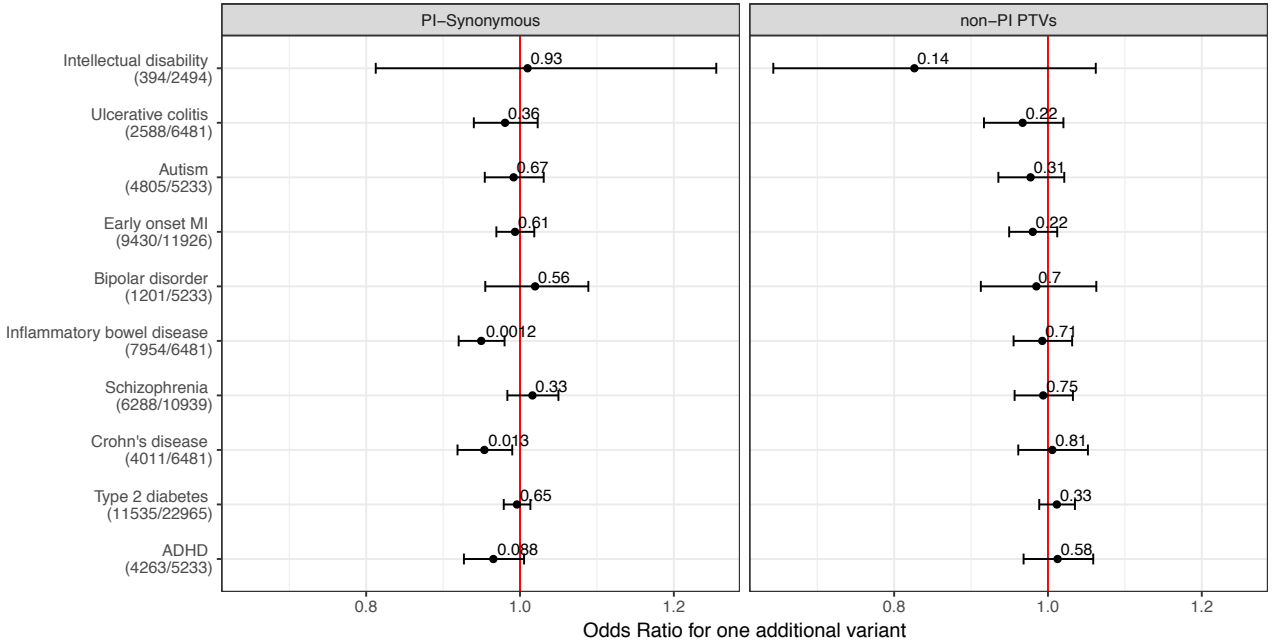
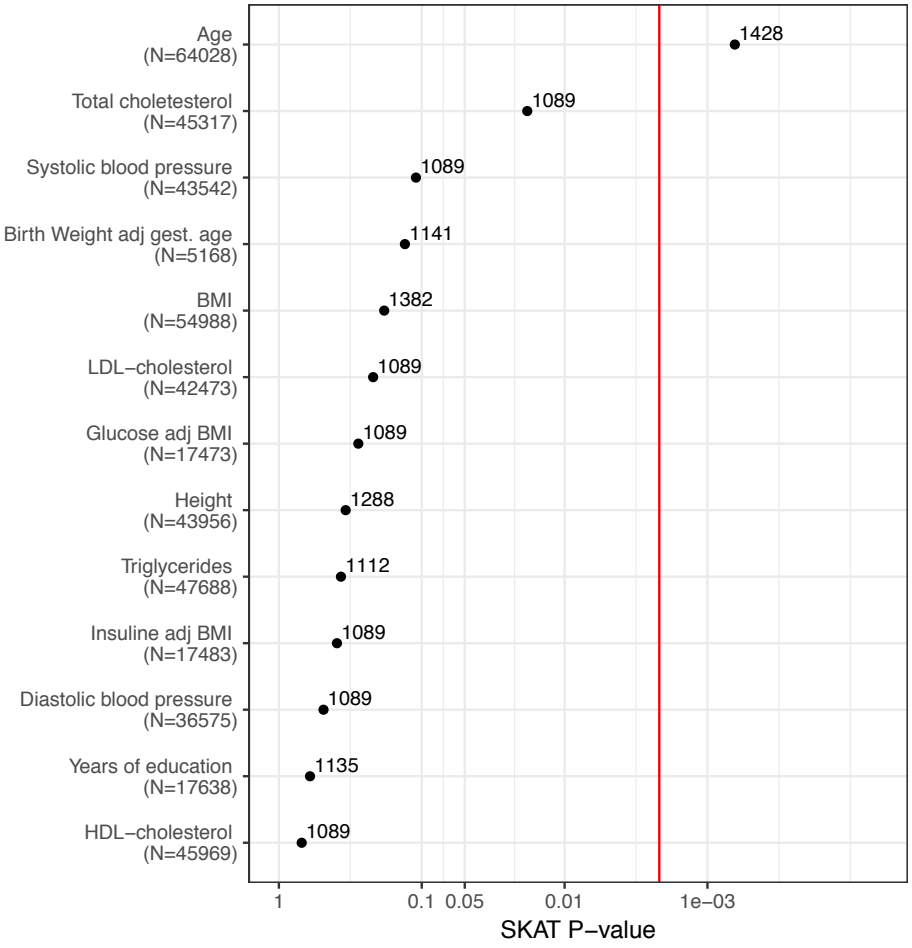


Figure S7: Meta-analyzed associations between rare PTVs in PI genes and 13 quantitative traits (left panel) and 10 diseases (right panel) using SKAT test. The number above each dot represent the number of variants included in the test. We don't observe additional signal compared to what observed using a burden test.



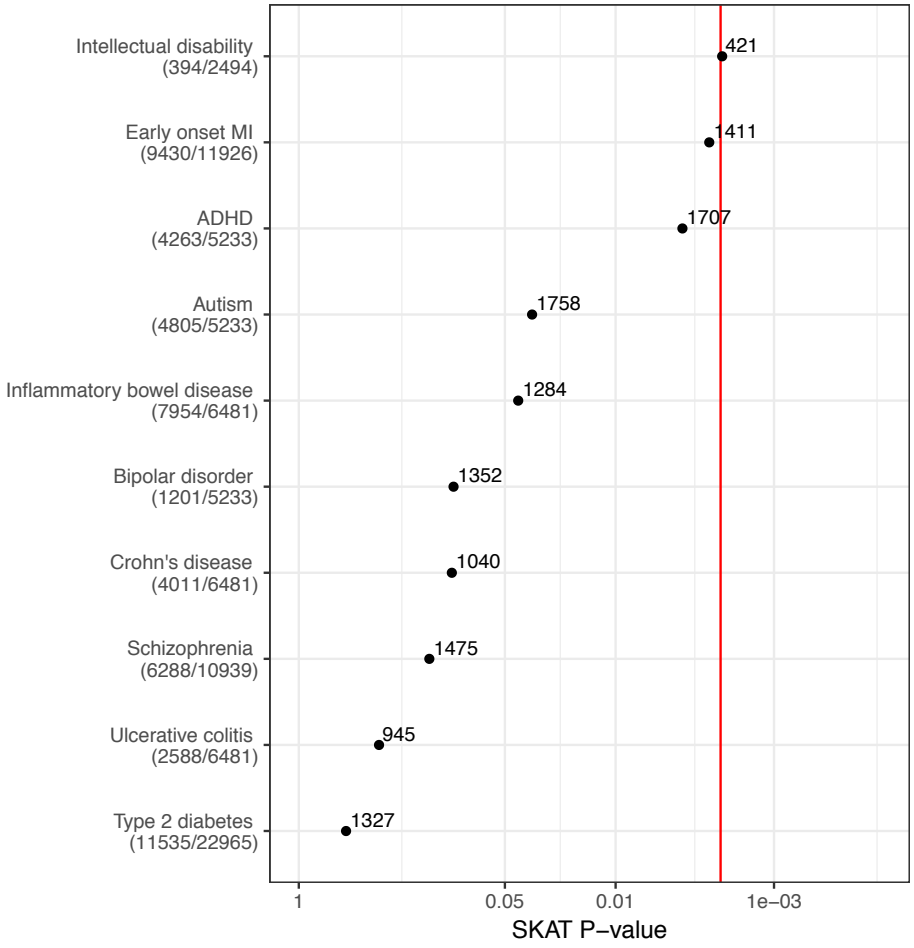
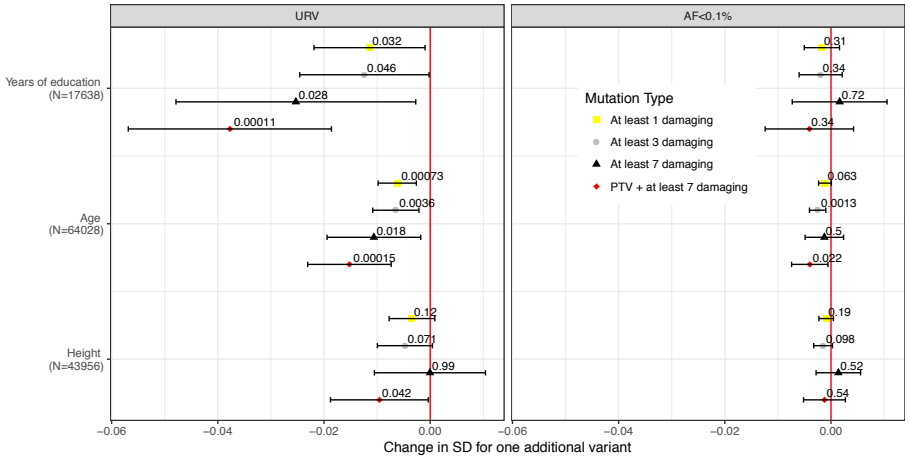
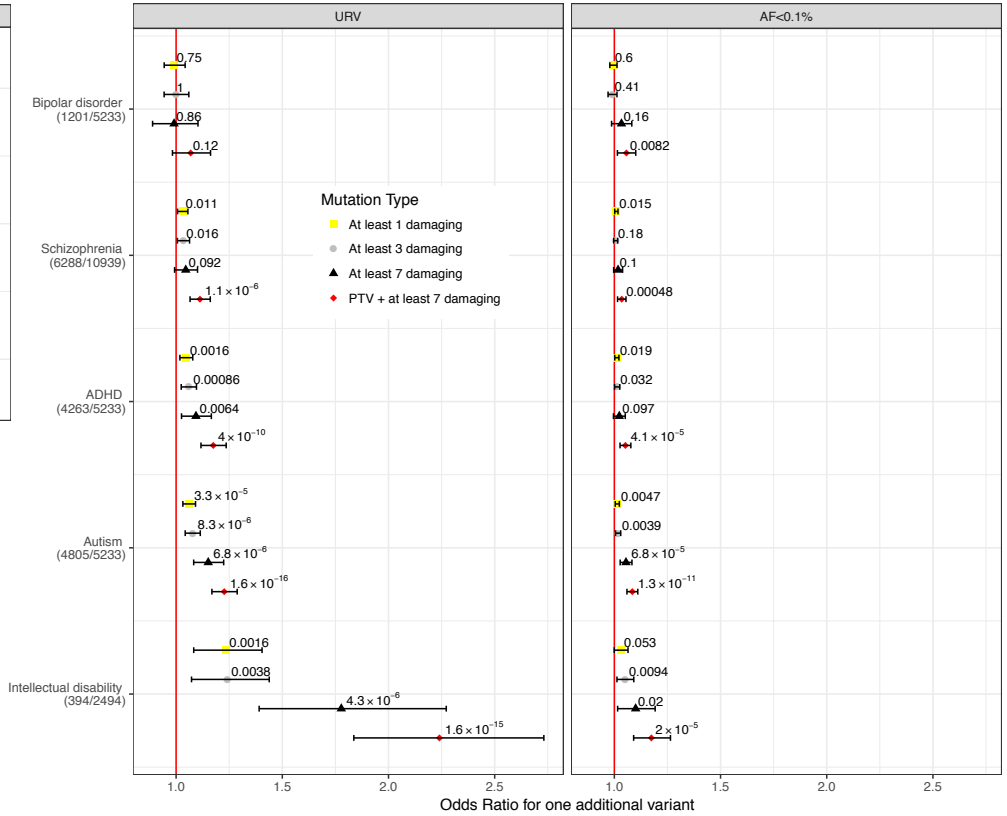
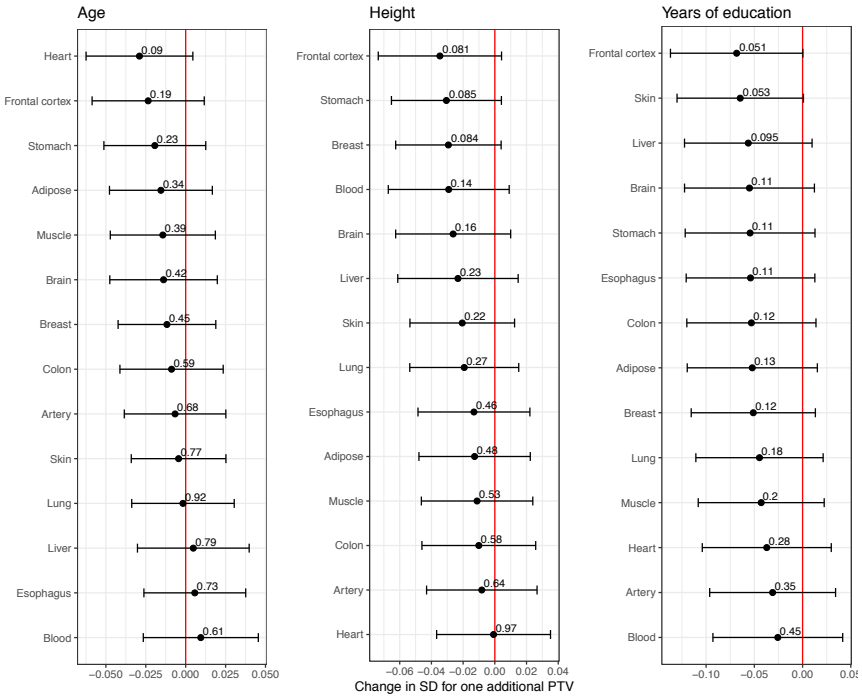


Figure S8: Meta-analyzed association between ultra-rare and rare damaging missense variants, as defined by number of algorithms, in PI-genes and 3 quantitative traits (left panel) and 5 diseases (right panel). The strength of the association increases as function of the number of algorithms and is particularly strong among ultra-rare variants.







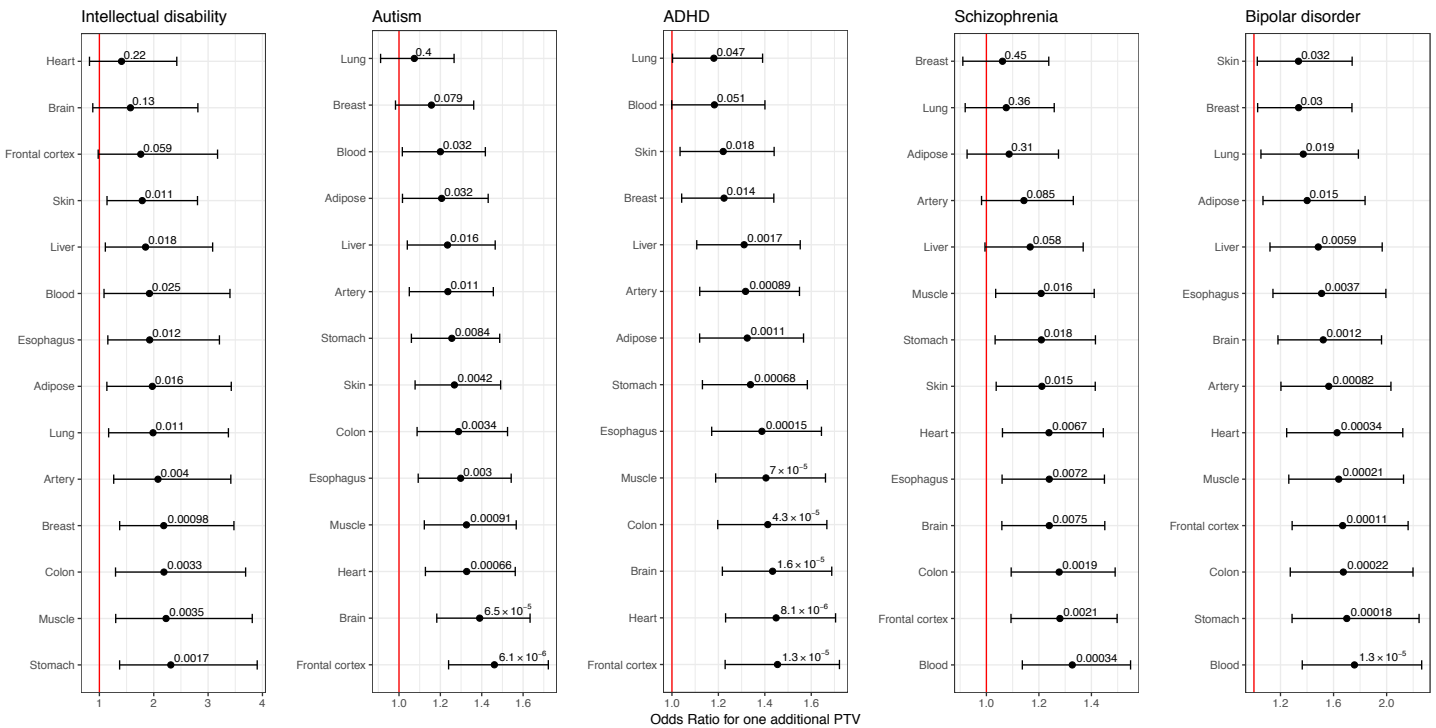


Figure S9: Meta-analyzed association between rare PTVs in PI genes and 3 quantitative traits (upper panel) and 5 diseases (bottom panel) in the top expressed 500 genes for each tissue. METSIM study not included.

Figure S10: Meta-analyzed associations between rare PTVs in PI genes and 3 quantitative traits (left panel) and 5 diseases (right panel) in genes that are expressed in < 20% of the tissues (tissue-specific) or expressed in > 80% of the tissues (expressed in multiple tissues) . METSIM study not included. No major differences are observed.

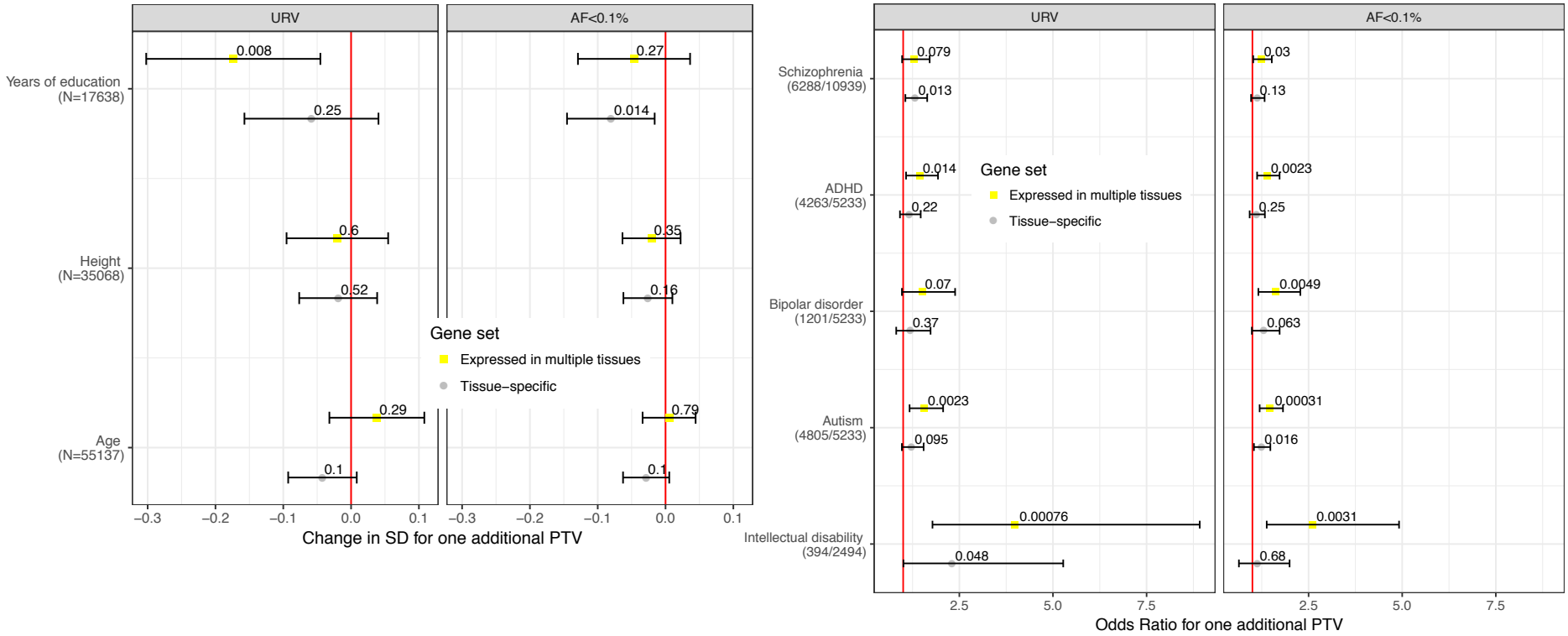


Figure S11: Associations between ultra-rare and rare PTVs in PI genes and 4 diseases from the Danish Blood Spot exome sequencing project. W/O comorbidities: individuals with only the disease reported on the y axis and none of the other investigated diseases, including intellectual disability. W only comorbidities: individuals with the disease reported on the y axis and at least one of the other investigated diseases, including intellectual disability. W only ID: individuals with the disease reported on the y axis and intellectual disability. Significant associations even in individuals without co-morbidities.

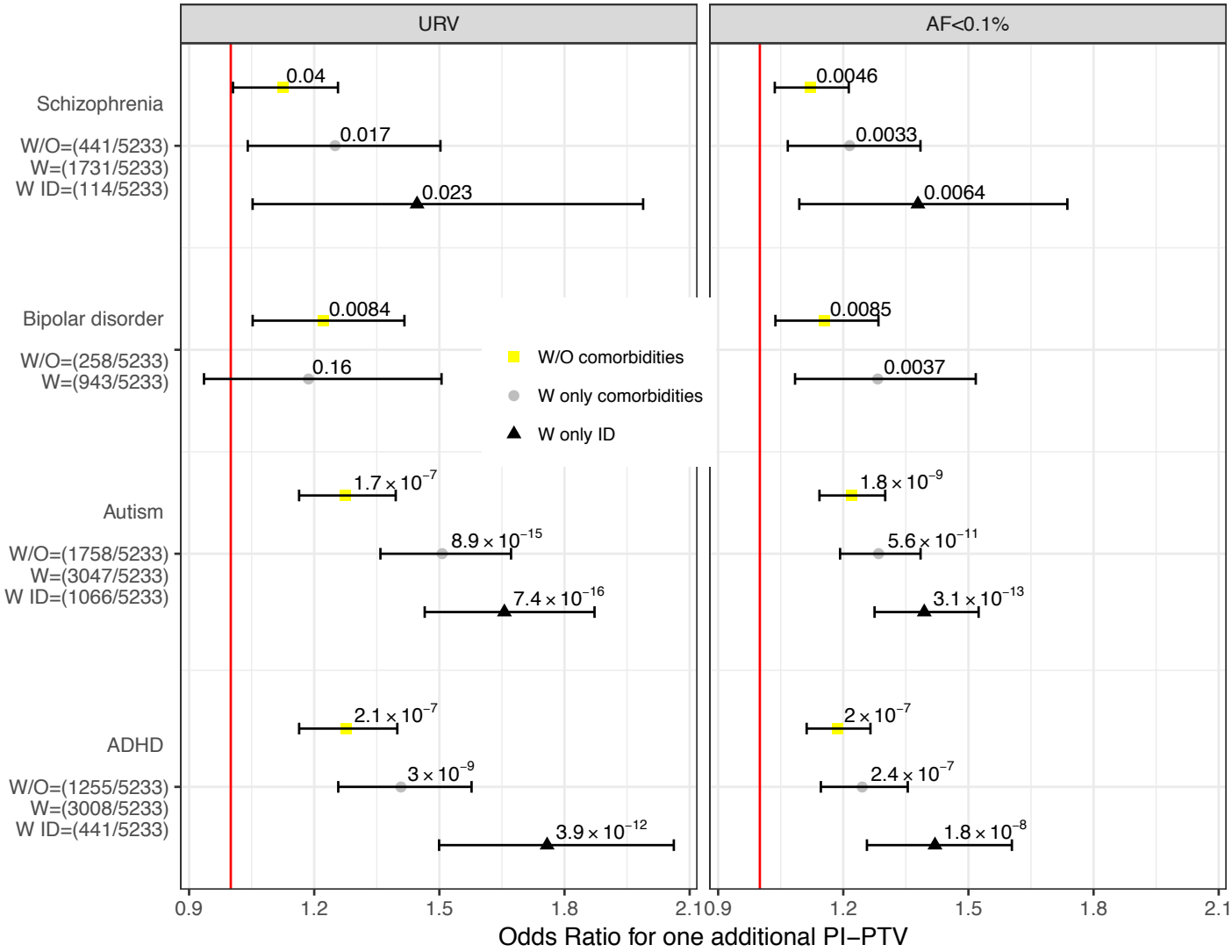
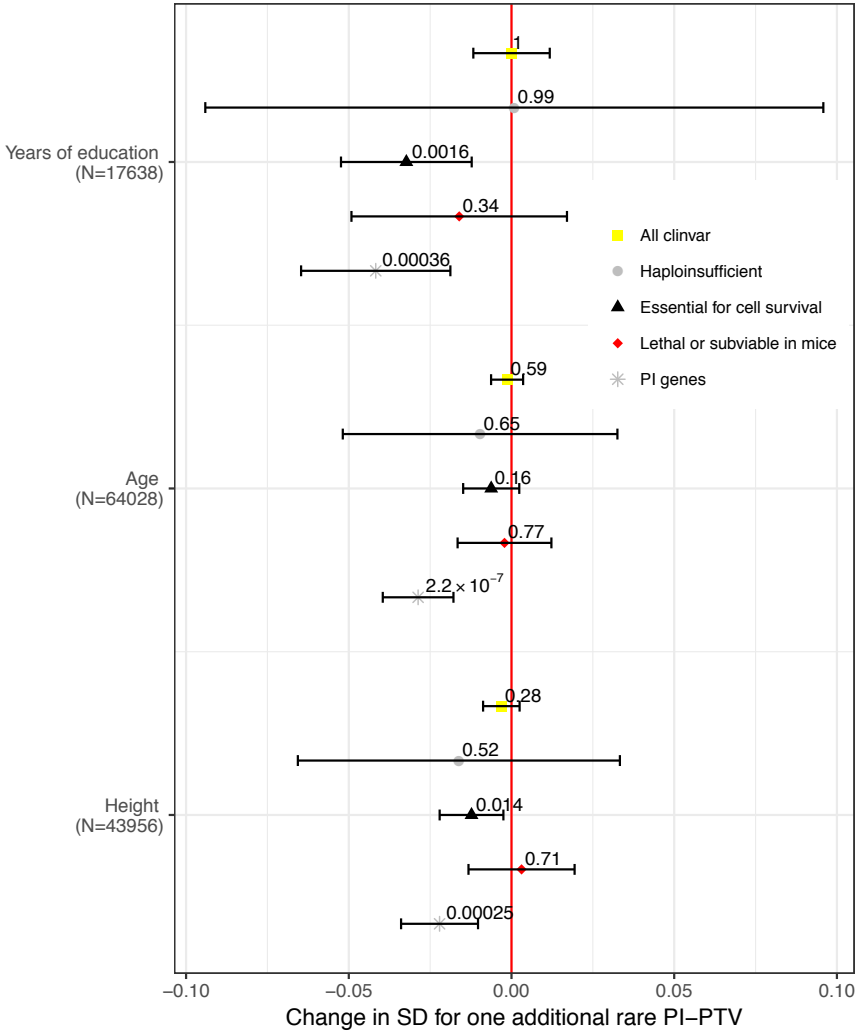


Figure S12: Meta-analyzed association between rare PTVs and 3 quantitative traits (left panel) and 5 diseases (right panel) in gene-sets that are likely to contain functionally relevant genes.



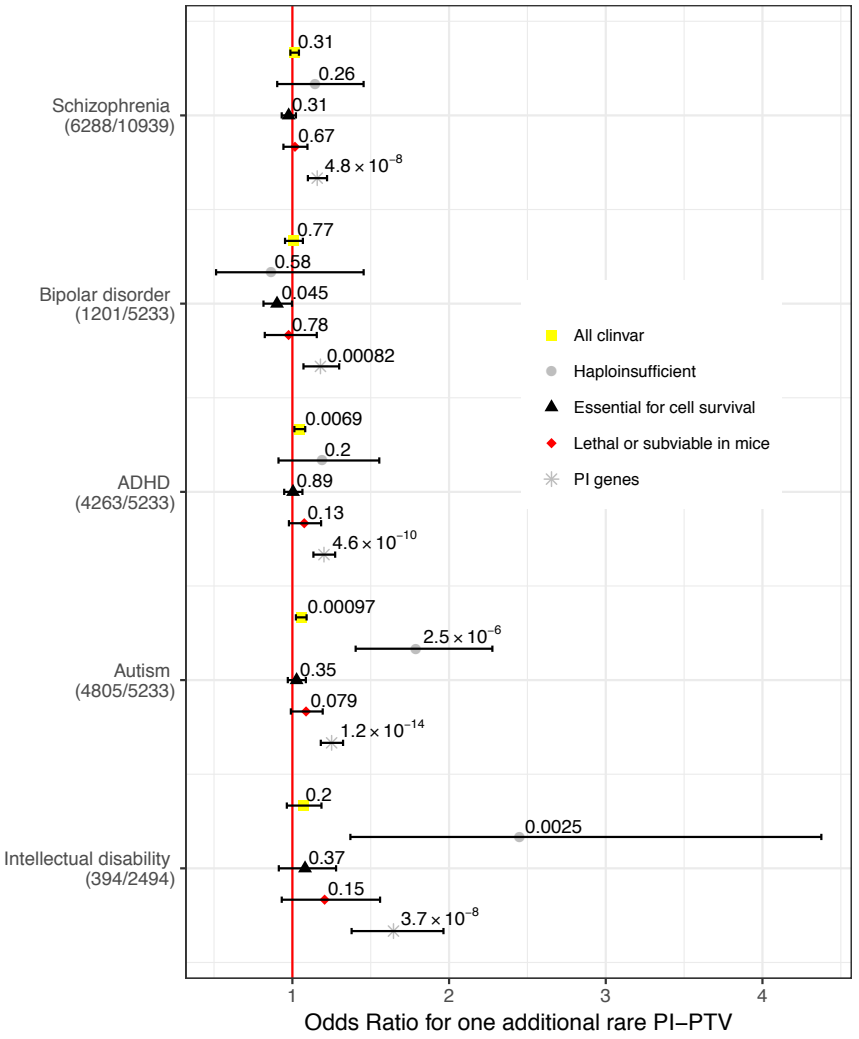


Figure S13: Meta-analyzed association between rare PTVs (**panel a.x**) or rare PTV + damaging missense (**panel b.x**) and phenotypes in genesets defined using GWAS results. For each panel, on the left full associations, on the right associations after removing established genes. **1**: genesets defined using DEPICT on summary statistics with P-value < $5x10^{-8}$, **2**: genesets defined using DEPICT on summary statistics with P-value < $5x10^{-5}$, **3**: manually-curated genesets, **4**: genesets defined using MAGMA gene-based analysis, **5**: genesets defined using FUMA, based on genes within 20Kb from SNPs, **6**: genesets defined using FUMA, based on eQTL signal.

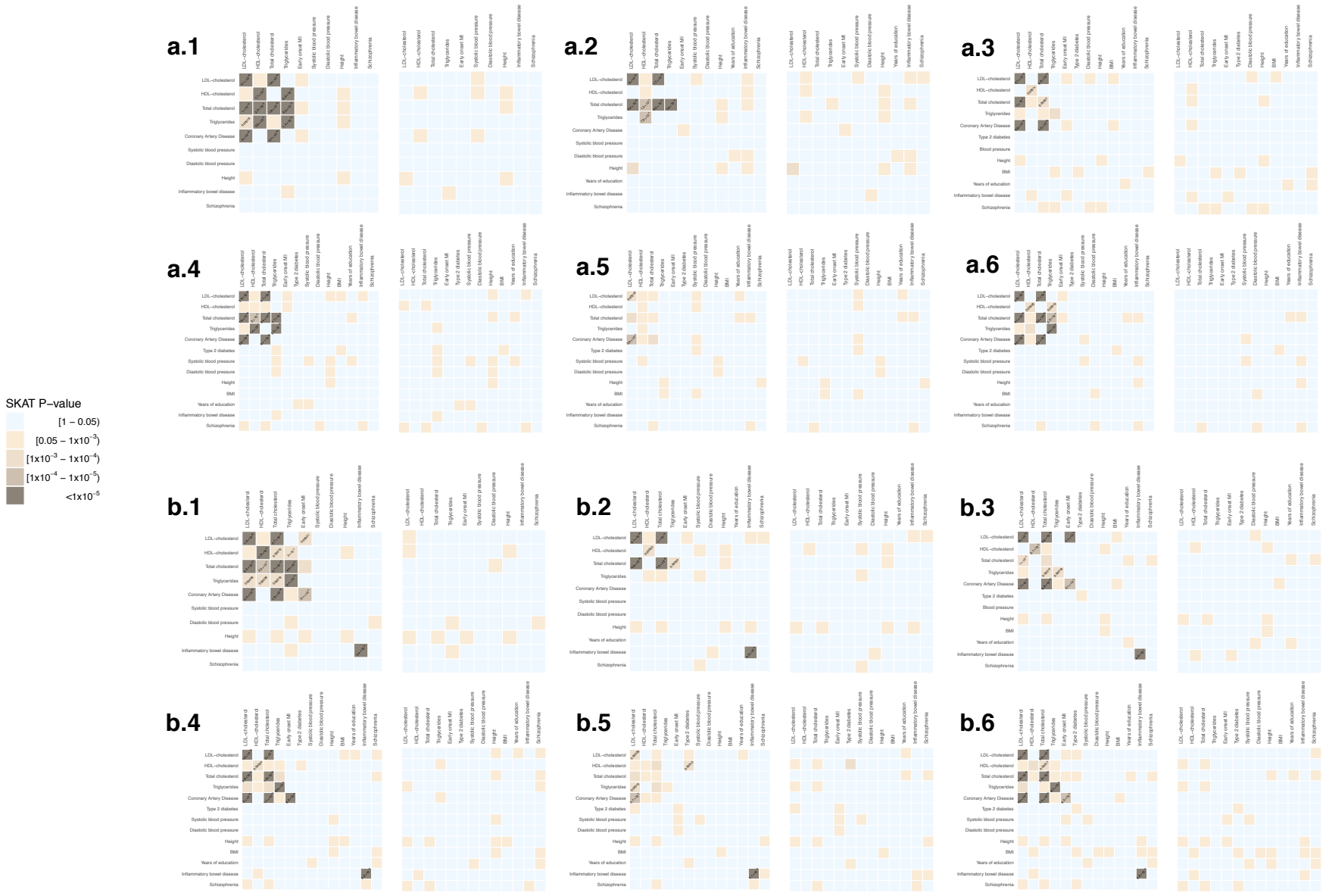


Figure S14: Meta-analyzed association between rare PTVs in PI-genes and 101 diseases in N=14,093 individuals from Finland and Sweden with registry data available. We used survival analysis and included diseases with at least 50 cases. We didn't include individuals with psychiatric disorders. The only association surviving multiple-testing correction is with chronic kidney failure.

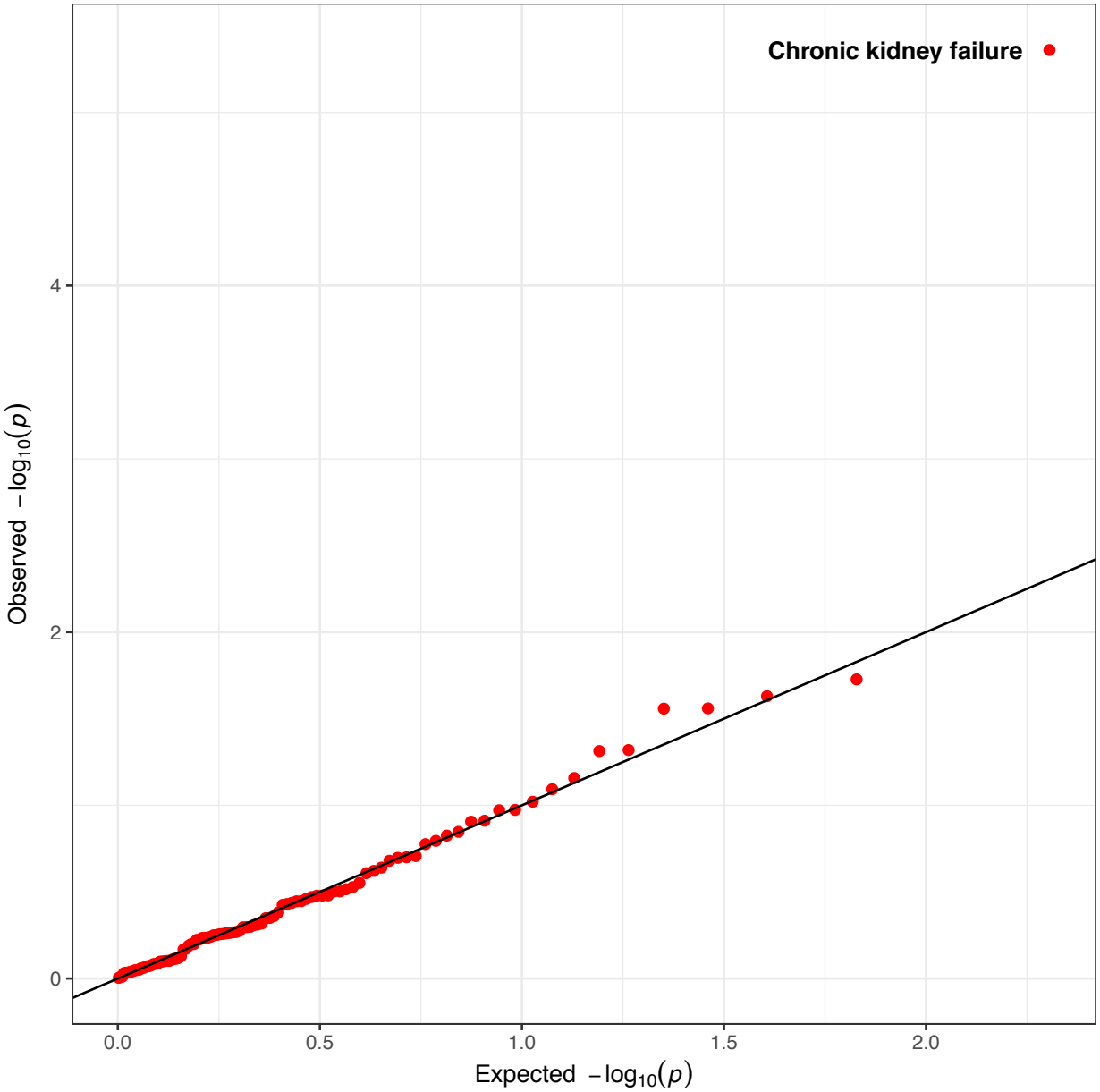


Figure S15: Distribution of number of hospital visits from in-patient registries in Sweden and Finland. We consider only individuals that have at least one visit and, for each individual, we counted the number of unique 3-digits ICD codes.