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Title: Mitochondrial nutrient utilization underlying the association between metabolites and insulin resistance in adolescents.

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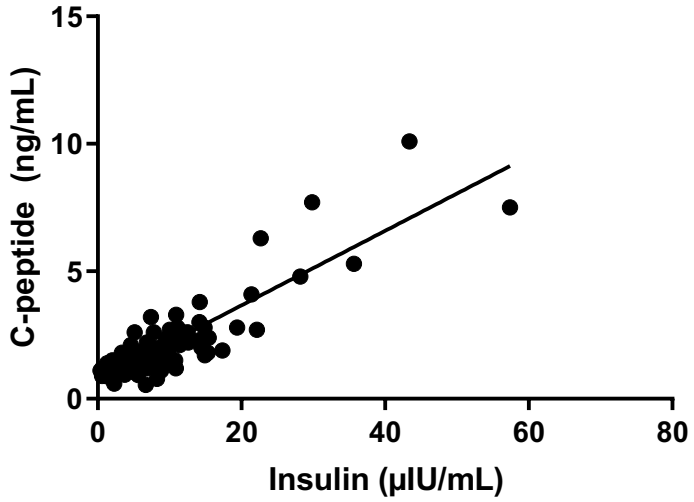

Figure S1. Relationship between insulin and c-peptide at baseline (n=120, linear trendline $y=0.1461x+0.7379$, $r^2 = 0.7689$, $p<0.0001$).

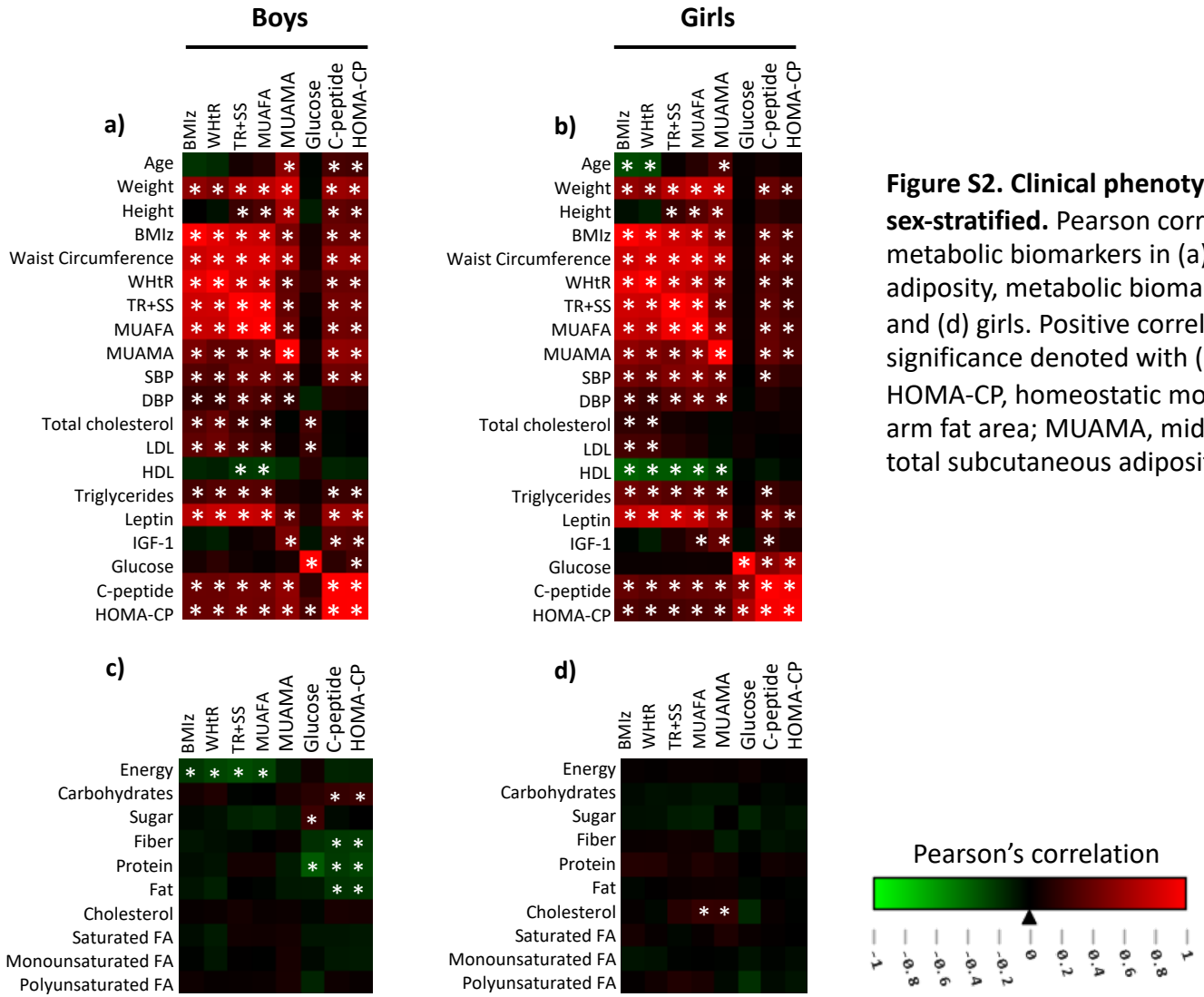

Figure S2. Clinical phenotypes and metabolic biomarkers exhibit strong correlations, sex-stratified. Pearson correlations identified connectivity between adiposity and metabolic biomarkers in (a) boys (n=98) and (b) girls (n=108) and connectivity between adiposity, metabolic biomarkers, and energy-adjusted dietary macronutrients in (c) boys and (d) girls. Positive correlation in red and negative correlations in green. Nominal significance denoted with (*) (α=0.05). DBP, diastolic blood pressure; FA, fatty acid; HOMA-CP, homeostatic model assessment index using C-peptide; MUAFA, mid-upper arm fat area; MUAMA, mid-upper arm muscle area; SBP, systolic blood pressure; TR+SS, total subcutaneous adiposity; WHtR, waist-to-height ratio.

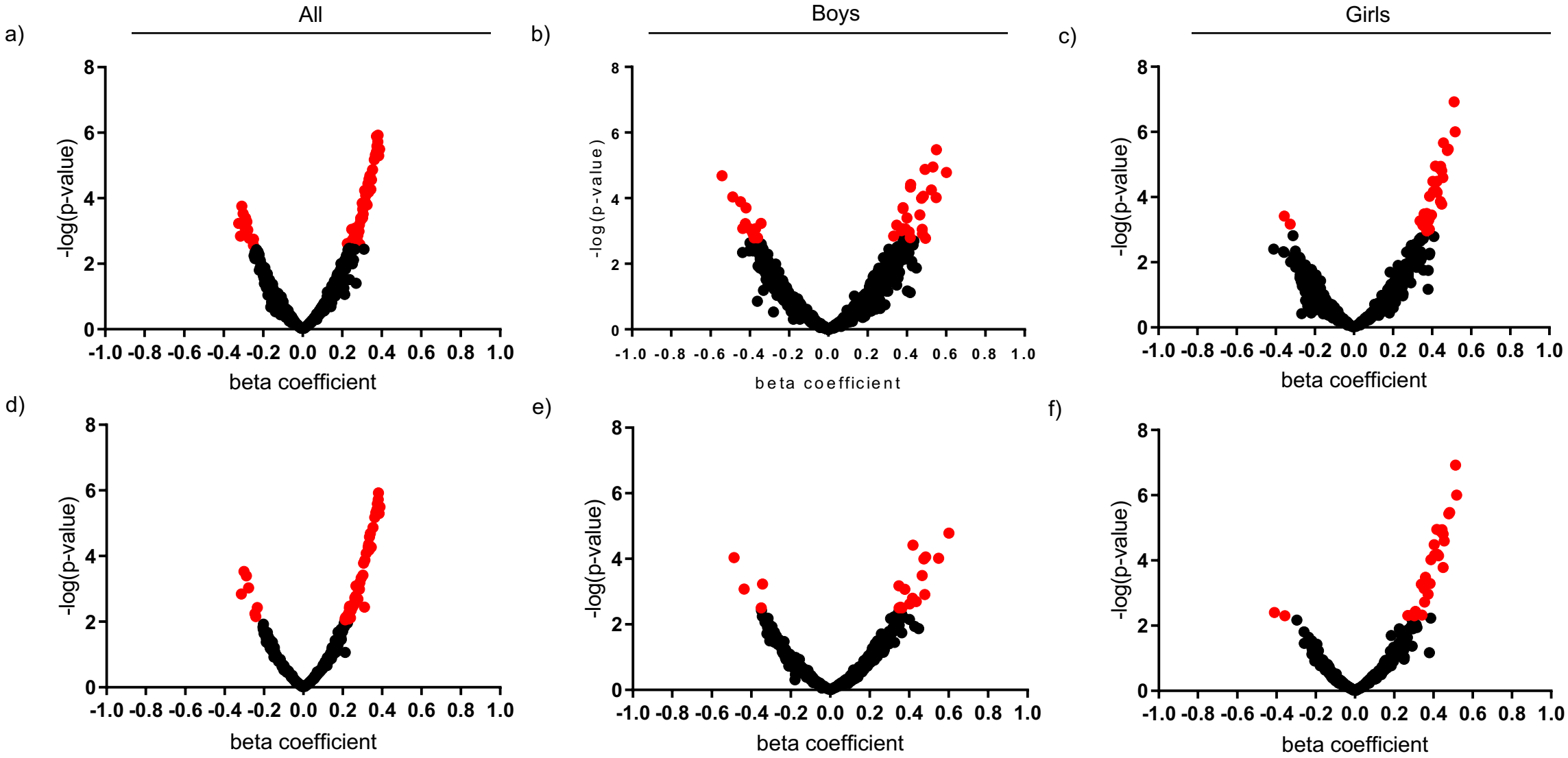

Figure S3. Association of metabolite features with BMIz, within the entire cohort and sex-stratified. Beta coefficients from linear models are plotted on the x-axis and negative log transformed p-values are plotted on the y-axis. Association between BMIz and both annotated and unannotated features (p=3272) (a) within entire cohort (n=206), accounting for age, sex, and puberty onset, and sex stratified in (b) boys and (c) girls, accounting for age and puberty onset (Model 1). Using solely annotated metabolites (p=550), representing the relationship between metabolites and BMIz (d) within the entire cohort and sex stratified in (e) boys and (f) girls (Model 1). Features in red indicate significant associations after FDR correction (FDR<0.10). FDR, false discovery rate.

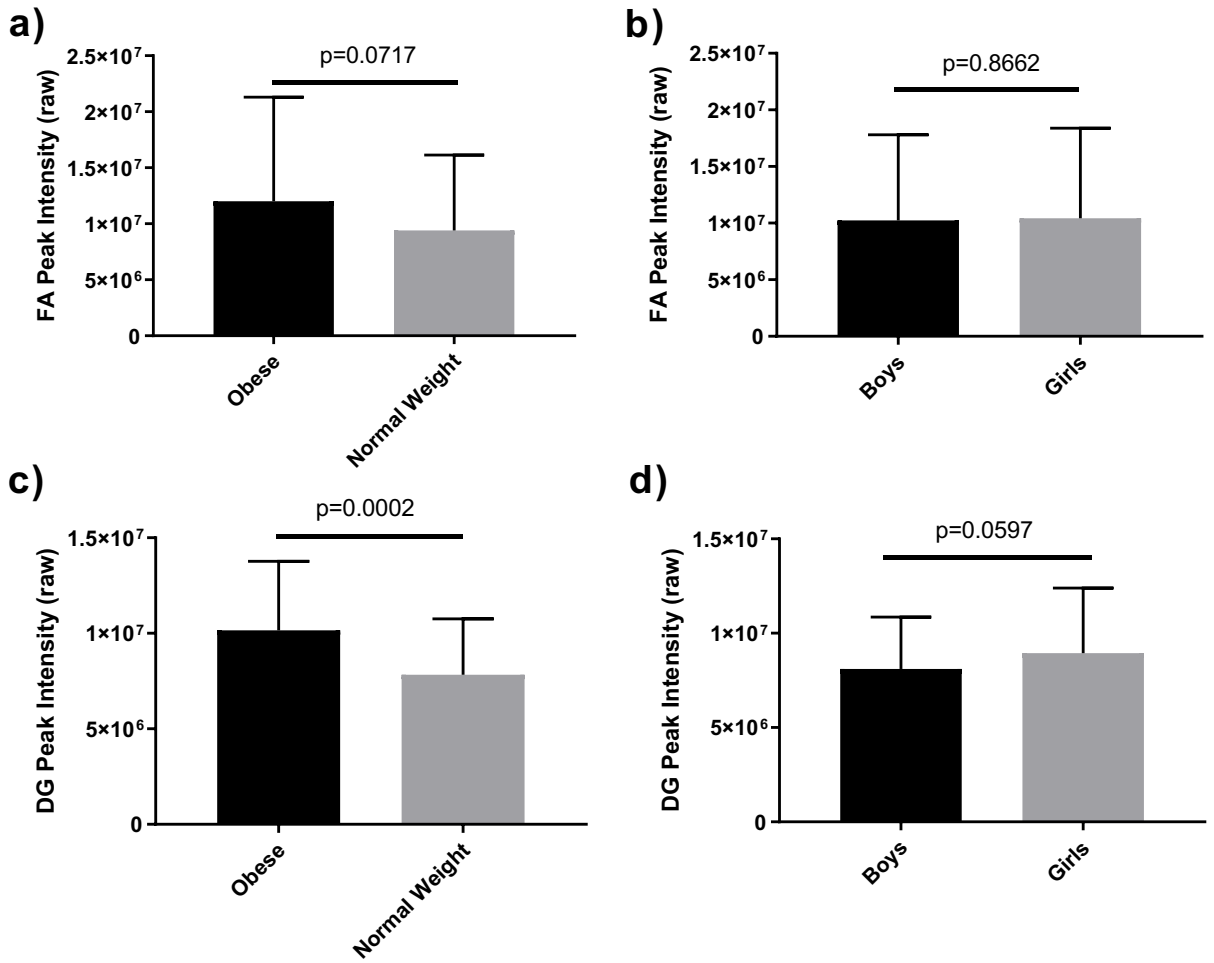

Figure S4. Fatty acids and diglycerides stratified by sex and obese (BMIz >2) vs. normal weight (-2< BMIz ≤1). T-tests were used to distinguish differences between metabolite groups. Sum of raw peak intensity values of FA (p=55) stratified by (a) obese and normal weight (p=0.0717) and (b) by sex (p=0.86662). Sum of raw peak intensity values of DG metabolites (p=19) significantly differs between (c) obese and normal weight (p=0.000154) and (d) trended to be elevated in girls (p=0.0597). DG, diglyceride; FA, fatty acid.

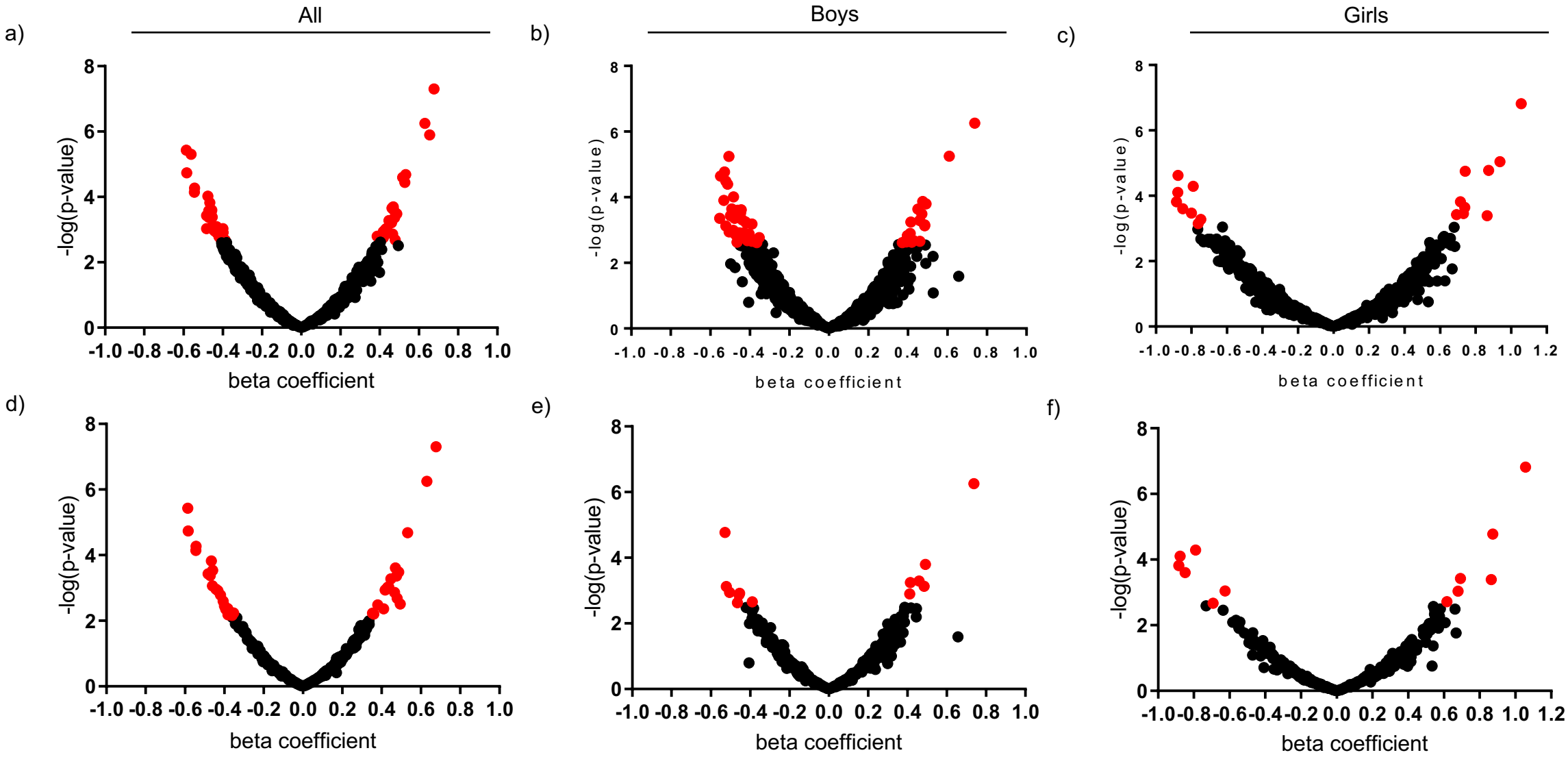

Figure S5. Association of metabolite features with HOMA-CP, within the entire cohort and sex-stratified. Beta coefficients from linear models are plotted on the x-axis and negative log transformed p-values are plotted on the y-axis. Association between HOMA-CP and both annotated and unannotated features (p=3272) (a) within entire cohort (n=206), accounting for age, sex, and puberty onset, and sex stratified in (b) boys and (c) girls, accounting for age and puberty onset (Model 1). Using solely annotated metabolites (p=550), representing the relationship between metabolites and HOMA-CP (d) within the entire cohort and sex stratified in (e) boys and (f) girls (Model 1). Features in red indicate significant associations after FDR correction (FDR<0.10). FDR, false discovery rate; HOMA-CP, homeostatic model assessment index using C-peptide.