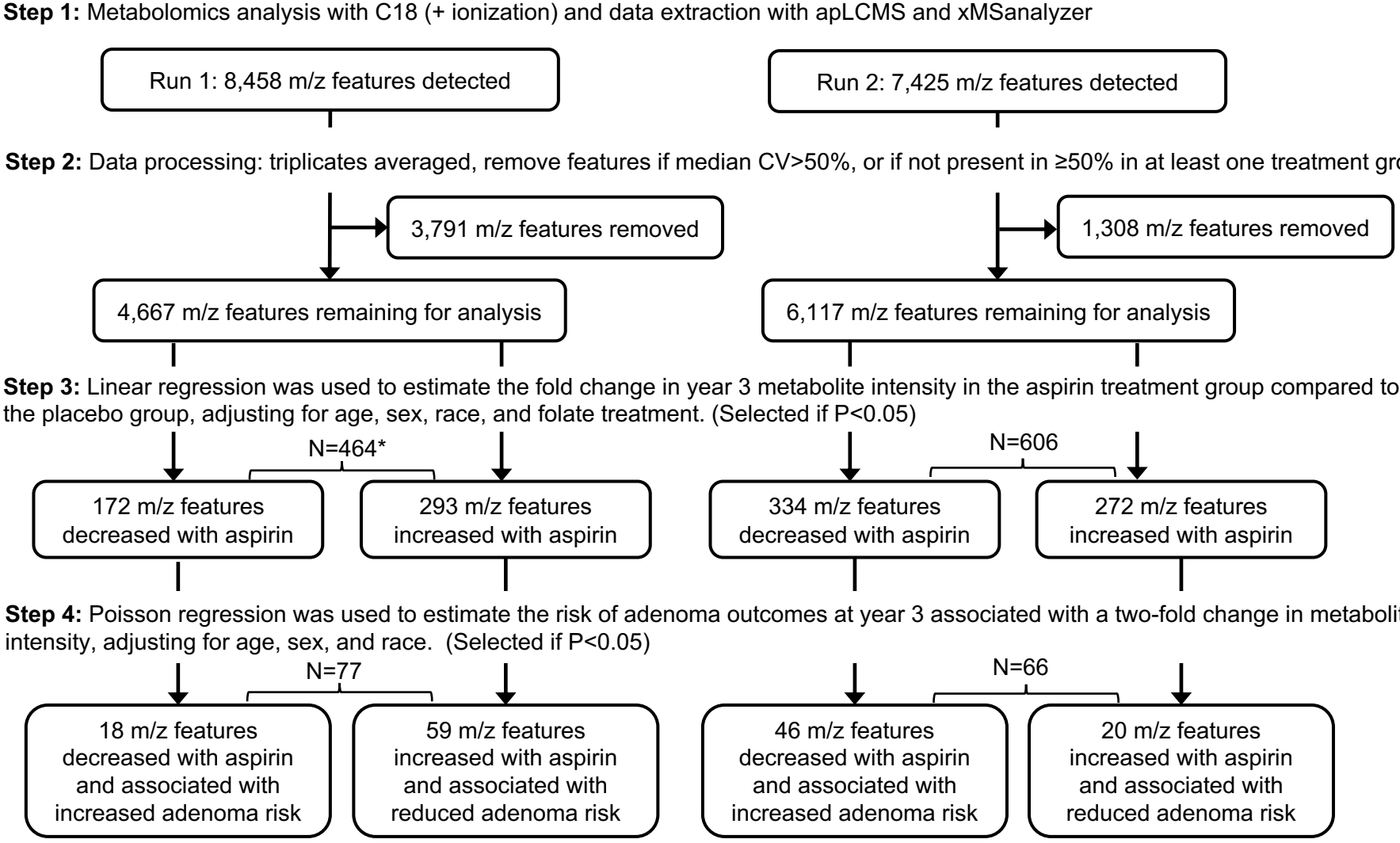
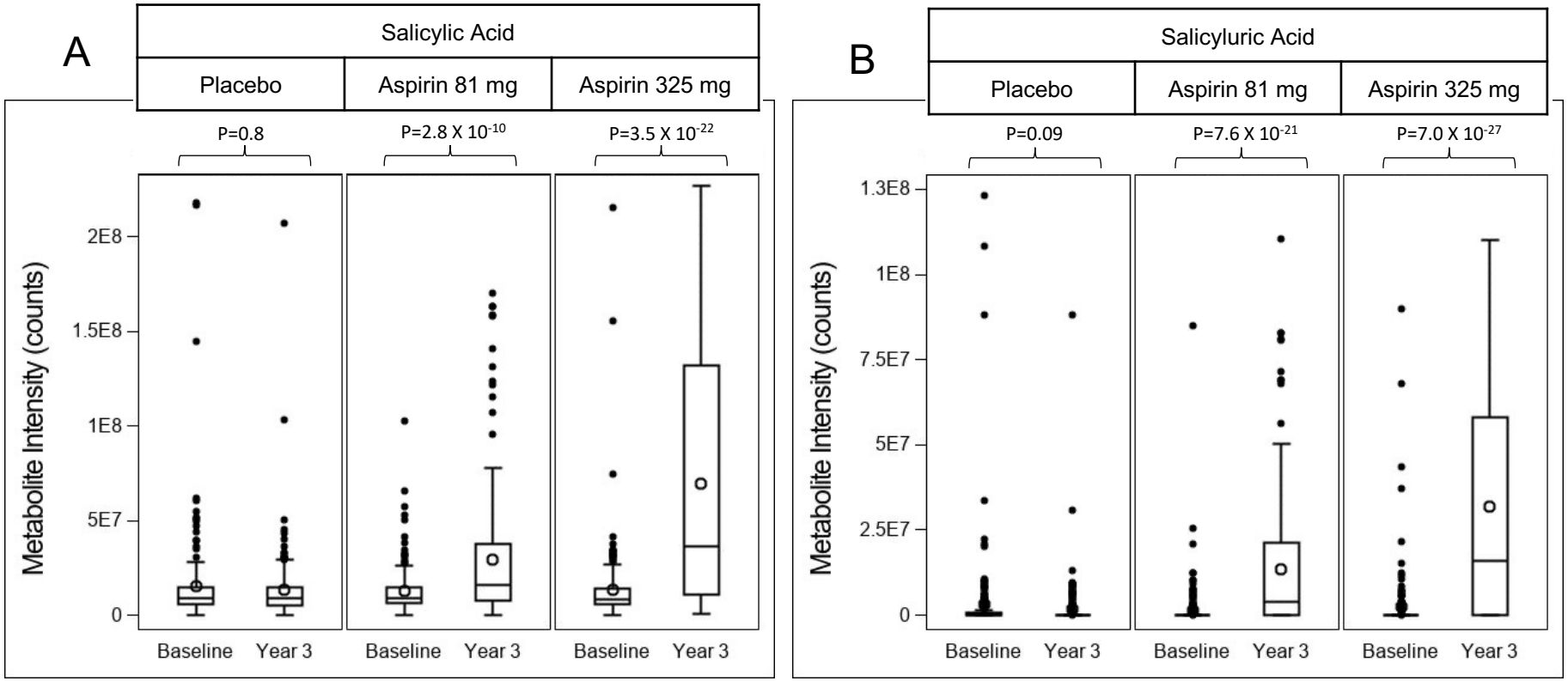
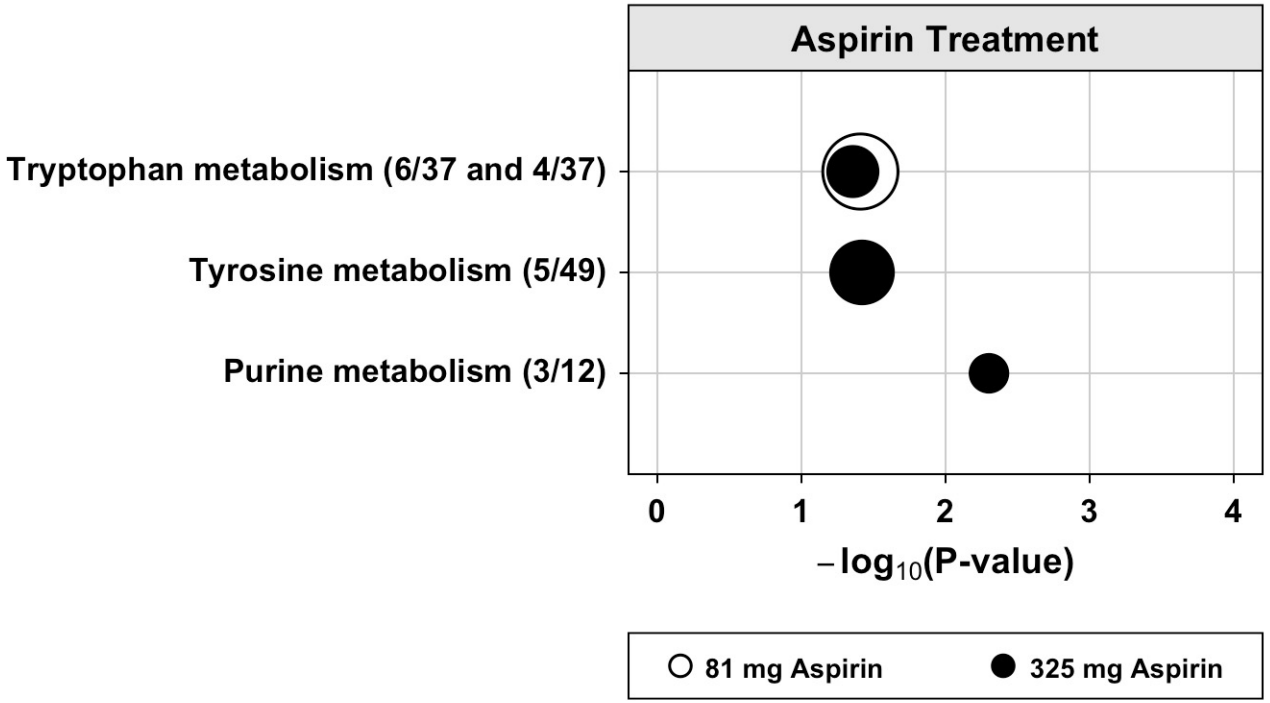


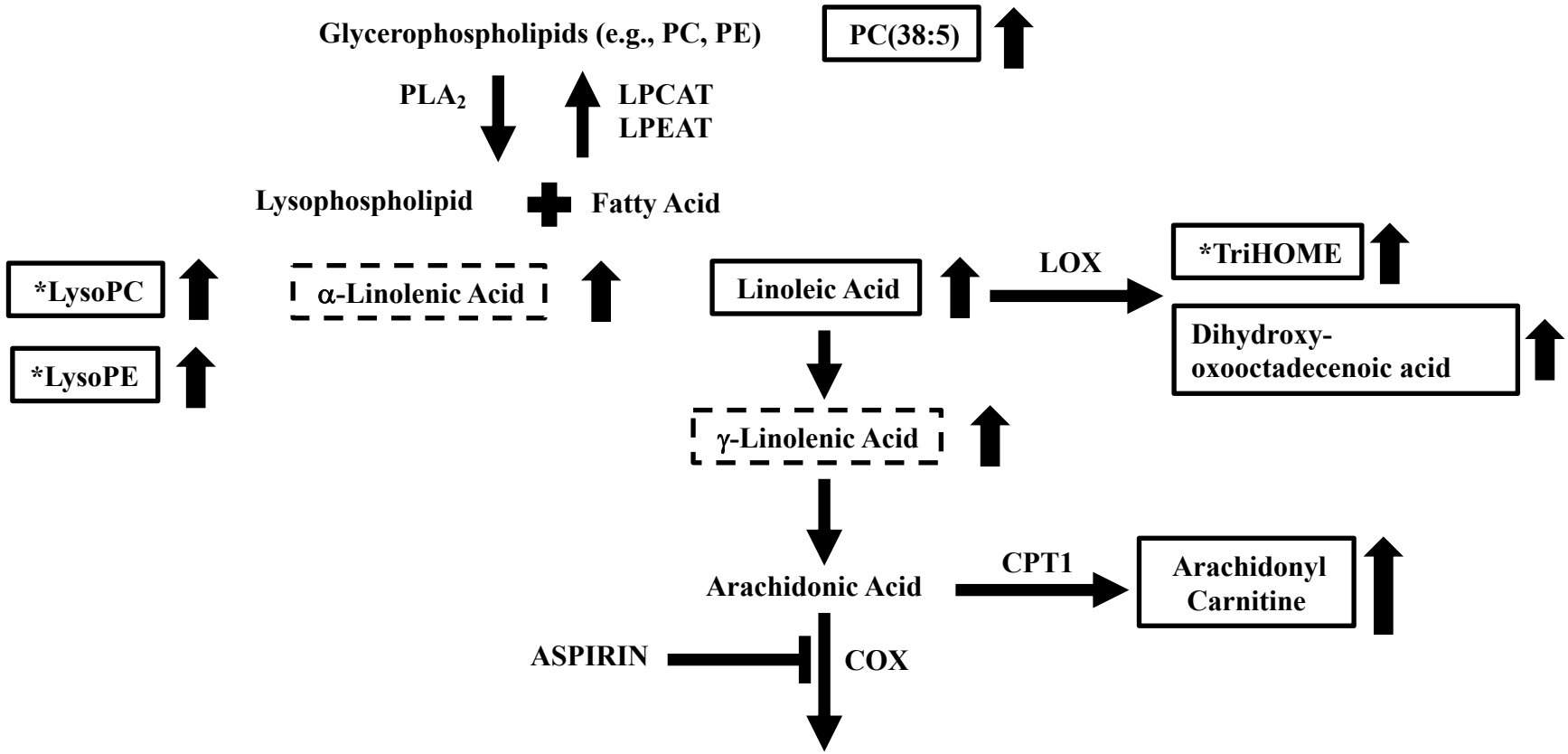
Supplementary Figure S1. Workflow for metabolomics data analysis. In step 3, separate linear models were run for metabolic features associated with 81 or 325 mg doses of aspirin treatment versus placebo, and total number of metabolic features associated with either dose are shown. In Run #1, one feature was both increased with 81 mg aspirin and decreased with 325 mg aspirin, so total number of features associated with aspirin treatment is N=464 instead of N=465. In step 4, separate Poisson regression models were run for three types of adenoma outcomes (any adenoma, advanced adenoma, or high-risk findings) and total numbers of metabolic features associated with any of these three outcomes are shown in the last row.



Supplementary Figure S2. Changes in aspirin catabolite intensities between baseline and year 3 blood plasma samples from participants selected for blood metabolomics analysis, by aspirin treatment group. **A**, Salicylic Acid, [M+H], m/z=139.0389. **B**, Salicyluric Acid, [M+H], m/z= 196.0604. P-values are for comparisons between raw baseline and year 3 intensities using Wilcoxon signed-rank tests. N=521; samples from two participants failed quality control and were excluded (N=1 assigned to 81 mg and N=1 assigned to 325 mg aspirin).

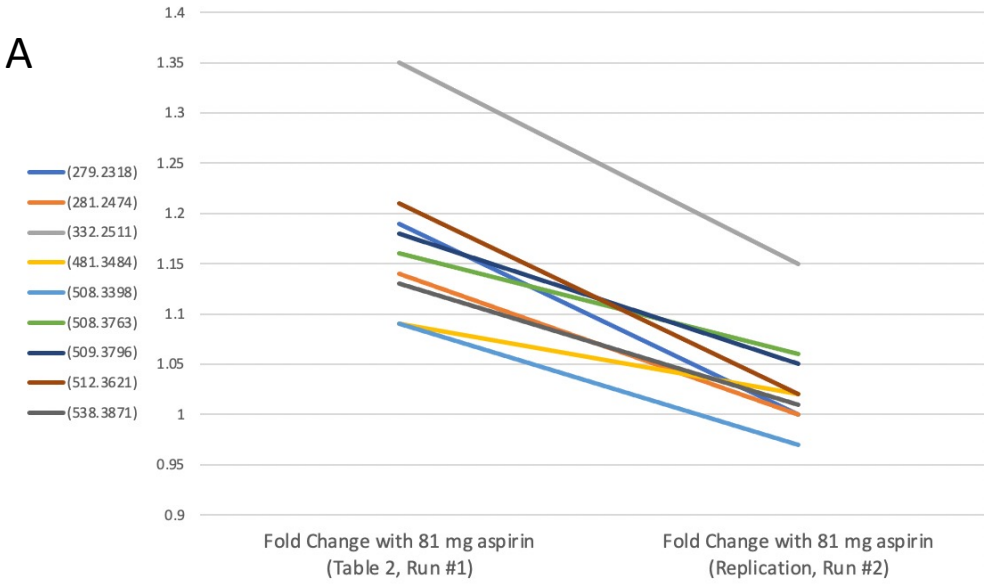


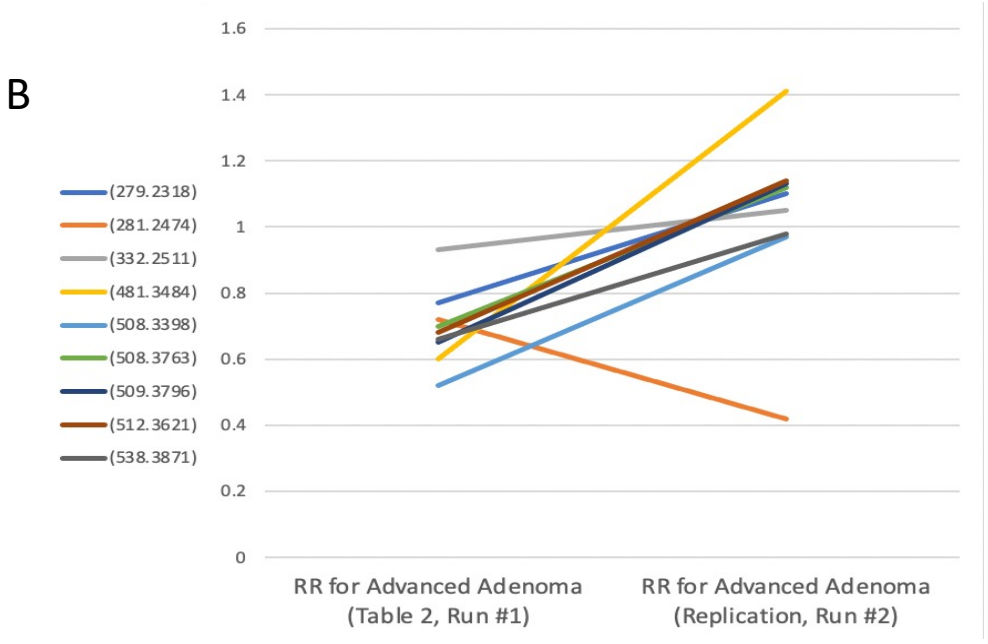
Supplementary Figure S3: Dysregulated metabolic pathways associated with aspirin treatment in blood plasma in run 2. The vertical axis represents the pathways (circles) with the radius representing the number of hits (significant metabolic features). The horizontal axis represents the negative $\log_{10}$ of the gamma adjusted P-values for each pathway with at least 3 hits. The open circles are for 81 mg aspirin and the solid circles are for 325 mg aspirin treatment. In parentheses next to each pathway name is the number of hits divided by the pathway size (total number of features detected in the pathway).



Abbreviations:
PC = Phosphotidylcholine
PE = Phosphotidylethanolamine
PLA2 = phospholipase A2
LPCAT = lysophosphatidylcholine acyltransferase
LPEAT = lysophosphatidylethanolamine acyltransferase
LOX = lipoxygenase
TriHOME = trihydroxyoctadecenoic acid
CPT1 = carnitine palmitoyltransferase I
COX = cyclooxygenase

Supplementary Figure S4: Fatty acid metabolic pathways linking metabolites that increased with aspirin treatment and were also associated with reduced risk of colorectal adenoma outcomes. Levels of metabolites shown in boxes were increased in plasma samples from participants treated with 81 mg aspirin compared to placebo. As shown, these metabolites are upstream of aspirin inhibition of COX, which catalyzes the formation of prostanoids from arachidonic acid. Dashed boxes indicate uncertainty as to whether the identity of one metabolite is α- or γ-Linolenic acid. Asterisks (*) indicate metabolites with statistically significant associations with reduced adenoma risk after adjusting for multiple testing.





Supplementary Figure S5: Replication of Effect Estimates for Metabolites Across Runs.
A: Comparison of effect estimates for fold change in metabolite level due to 81 mg/day aspirin treatment for nine of the metabolic features from run #1 that we were also able to identify in run #2 .
B: Comparison of effect estimates for relative risks for advanced adenomas for associations with metabolite level for the same nine metabolic features as above.