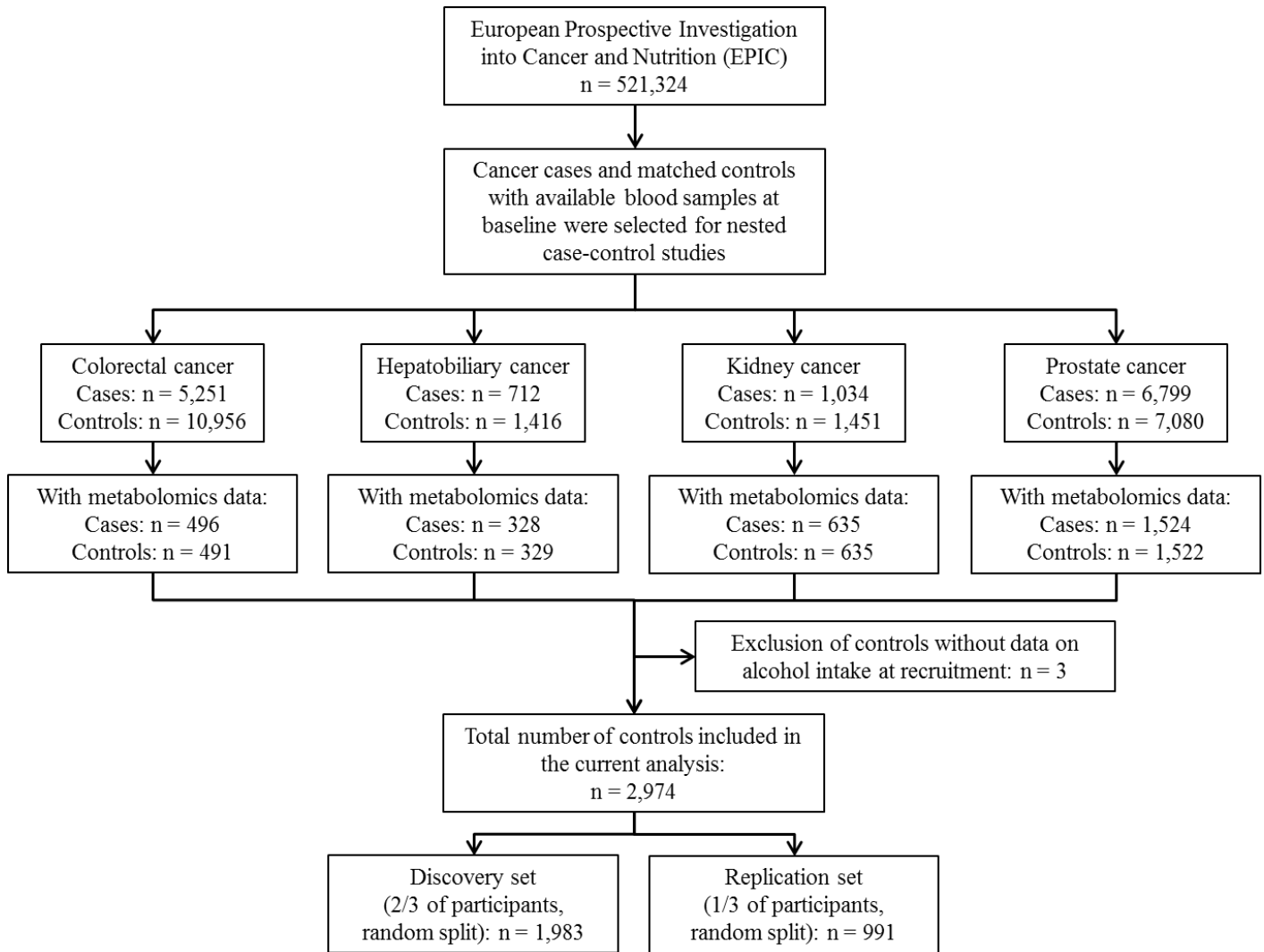
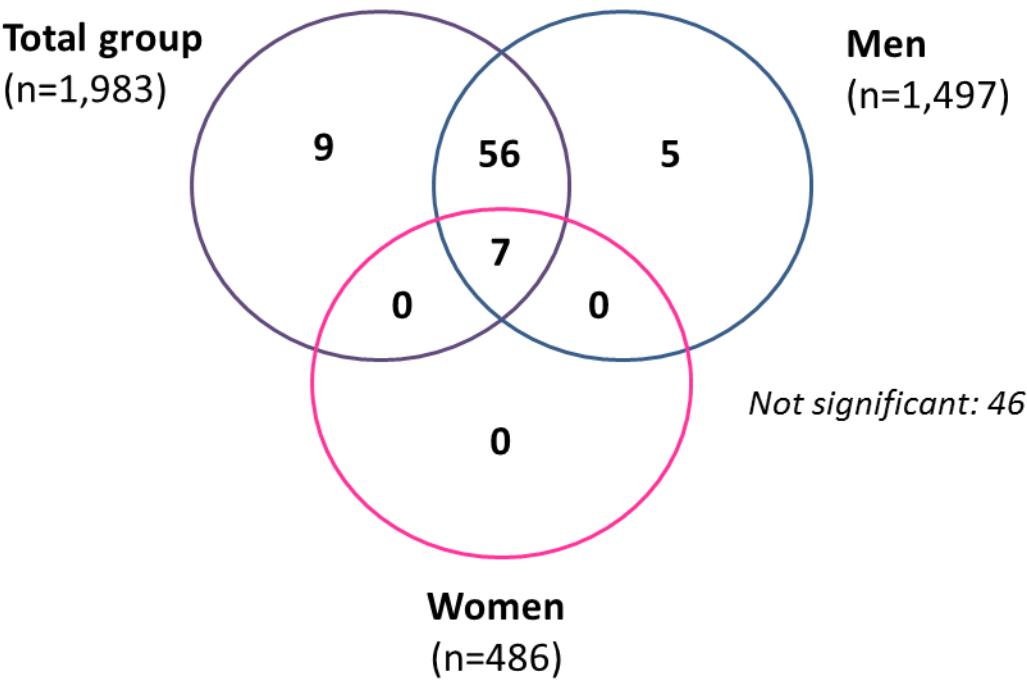


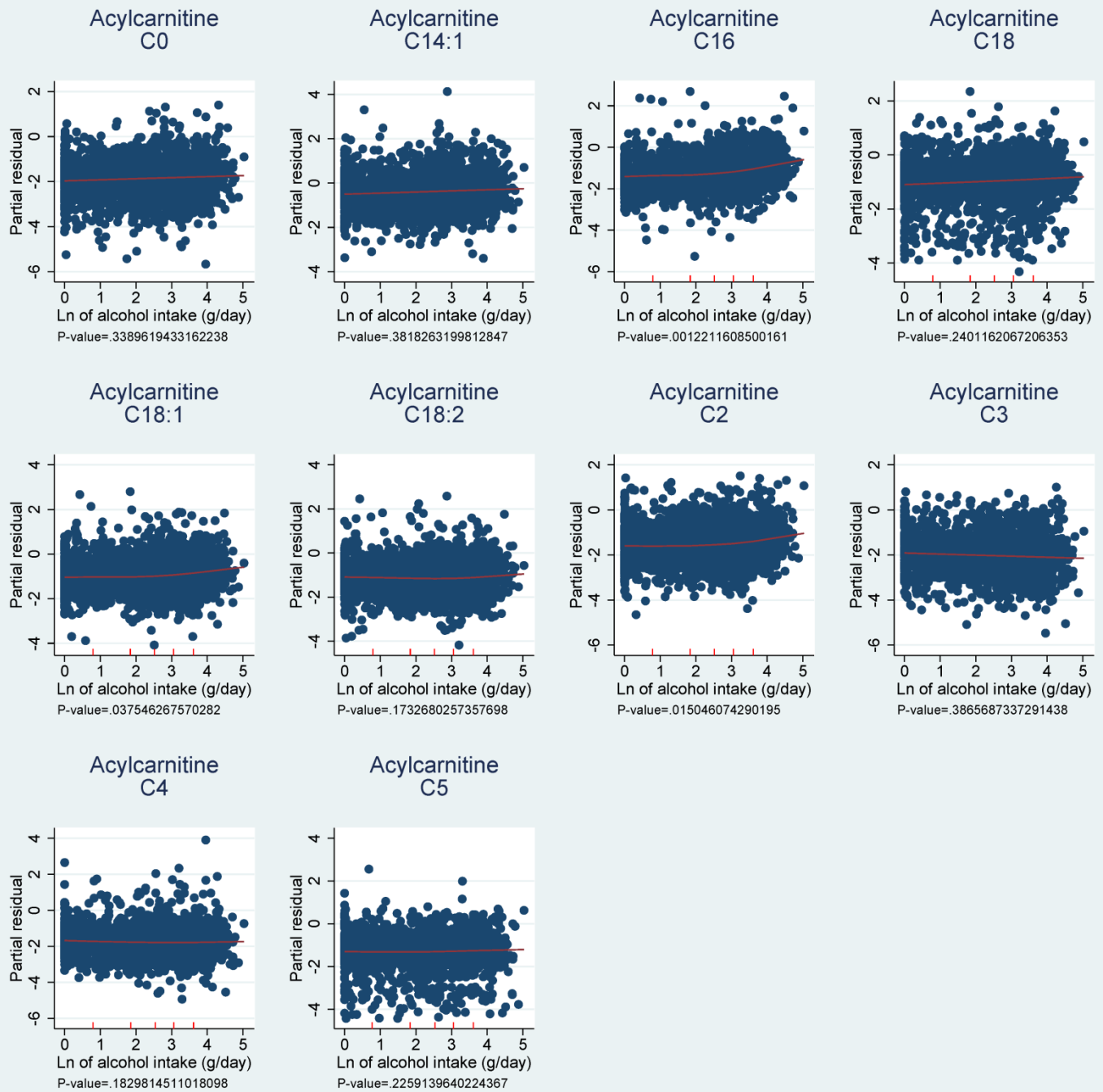
Supplementary Figure 1. Flow chart of participant inclusion into the European Prospective Investigation into Cancer and Nutrition (EPIC) study and into the current analysis.



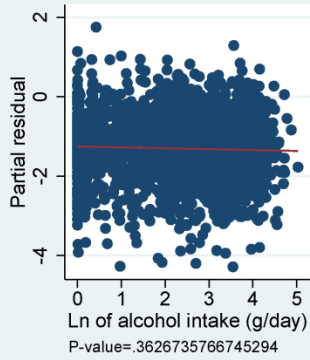
Supplementary Figure 3. Venn diagram showing overlap in metabolites identified as being statistically significantly (FDR-adjusted q-value<0.05) associated with alcohol intake (ln-transformed) in the total discovery set, and in subgroups of men and women (stratified analyses).



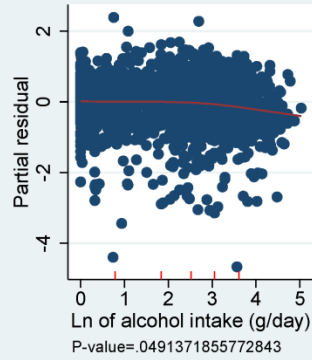
Supplementary Figure 4. Smoothened scatterplots obtained from penalized spline regression of the metabolite outcome variables against ln-transformed alcohol and covariates (same as in main analysis). Scatterplots were generated using 5 knots and goodness-of-fit tests were performed, of which P-values are reported below the plots (lower p-value suggests more evidence against parametric model).



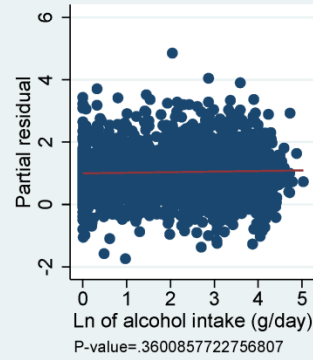
Alanine



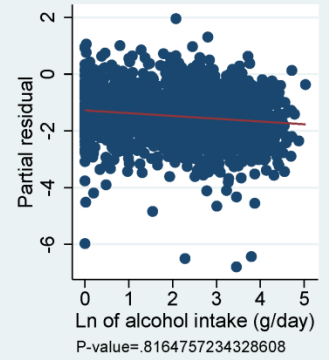
Arginine



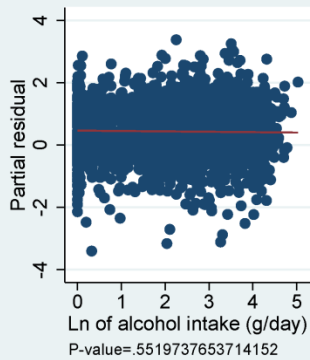
Asparagine



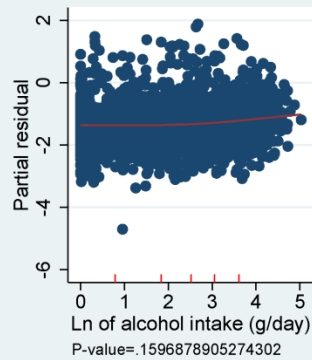
Citrulline



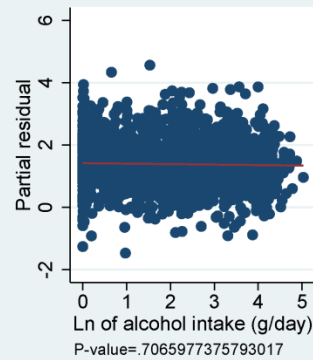
Glutamine



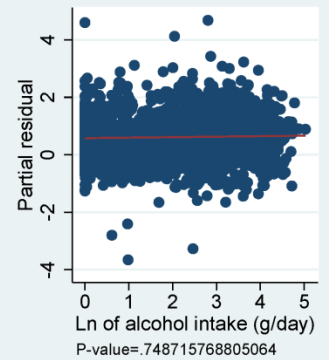
Glutamate



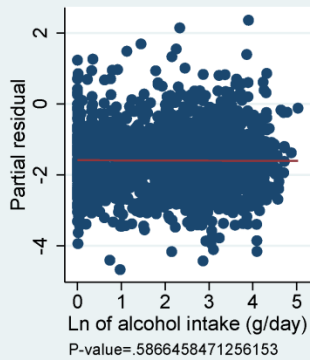
Glycine



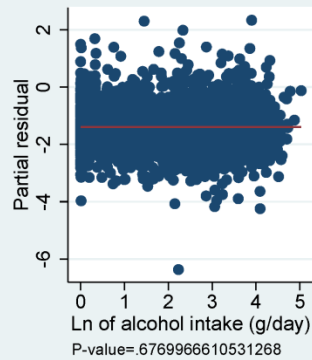
Histidine



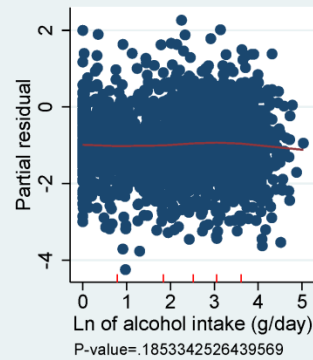
Isoleucine



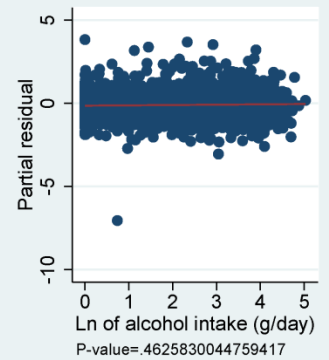
Leucine



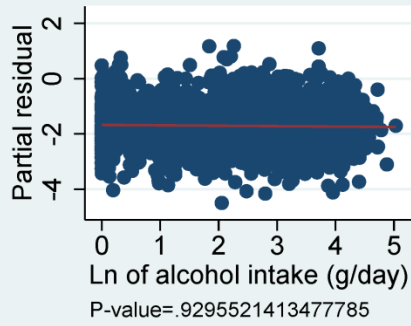
Lysine



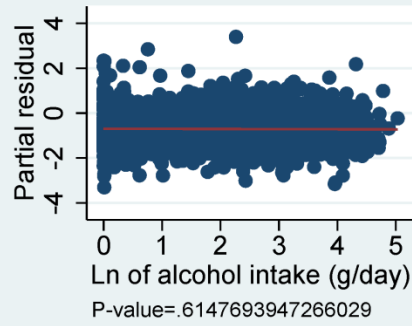
Methionine



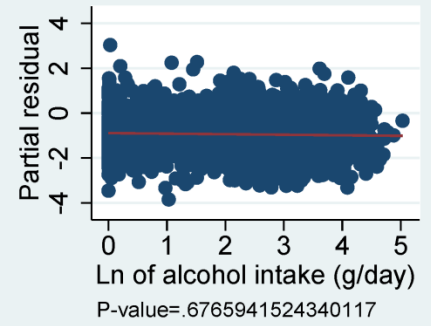
Ornithine



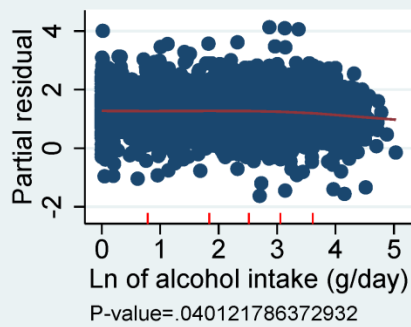
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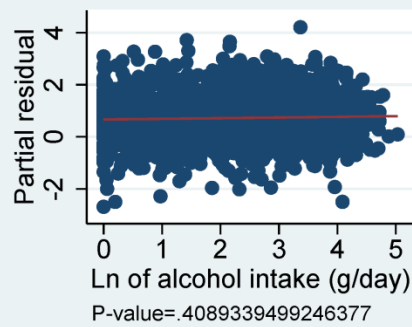
Proline



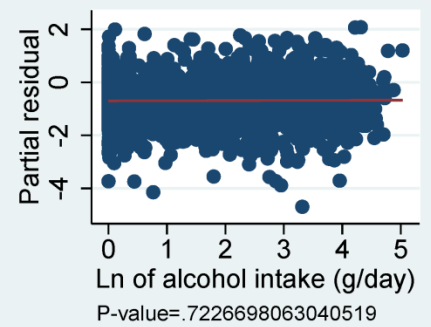
Serine



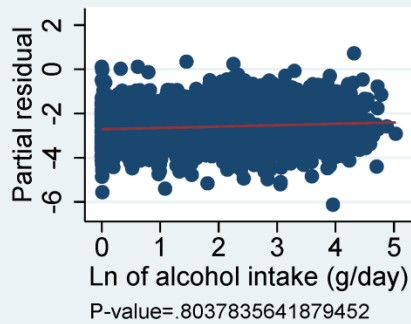
Threonine



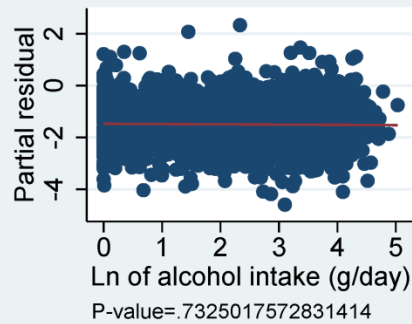
Tryptophan



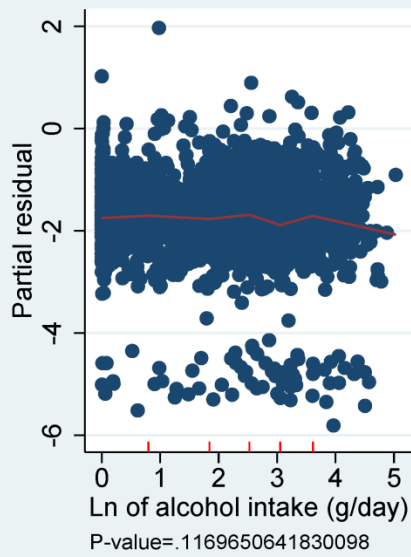
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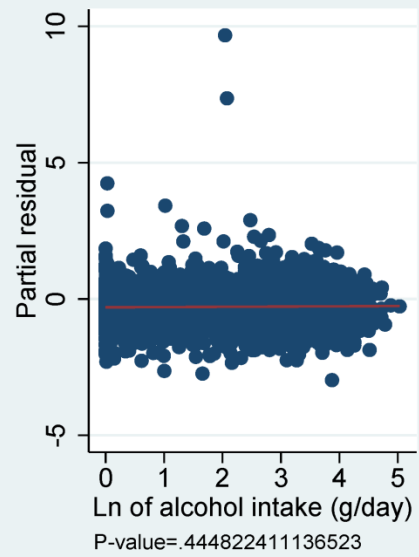
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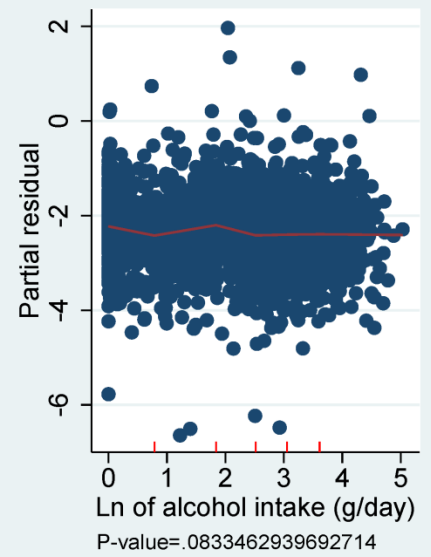
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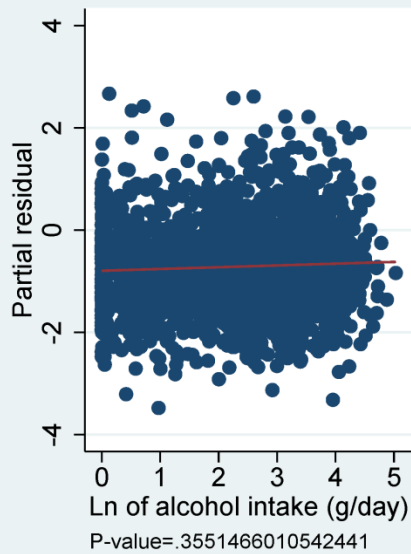
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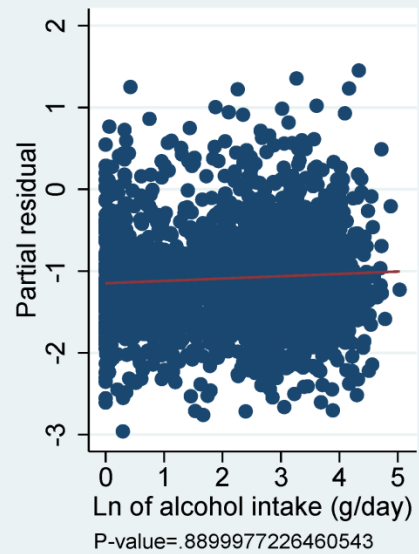
Kynurenine



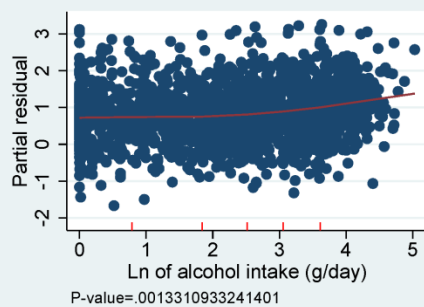
t4-hydroxyproline



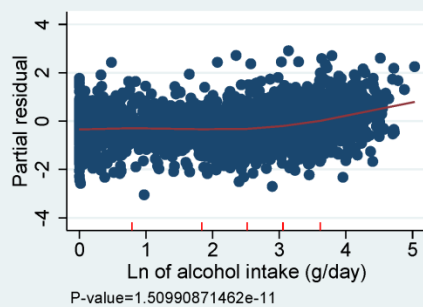
Taurine



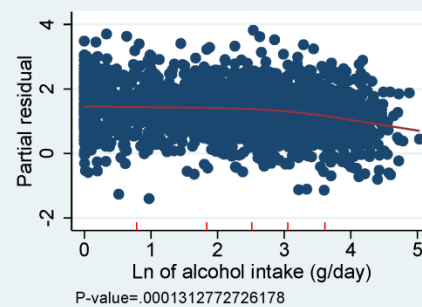
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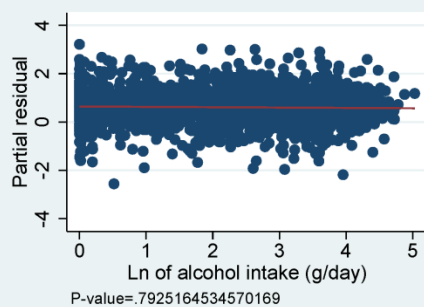
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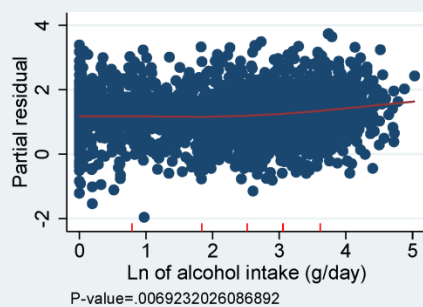
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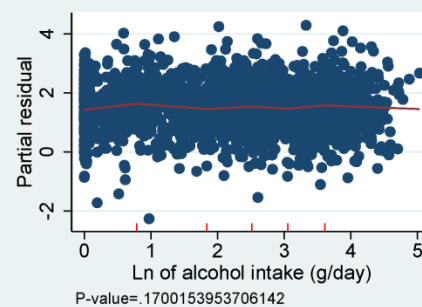
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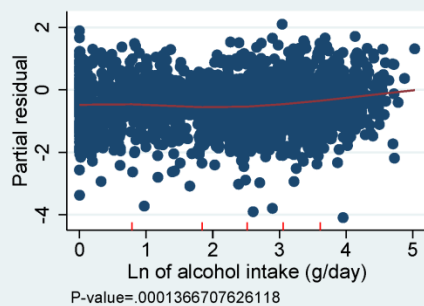
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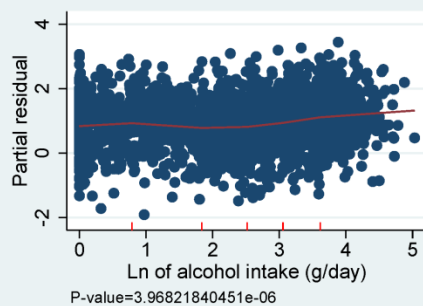
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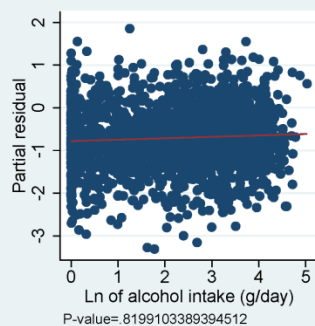
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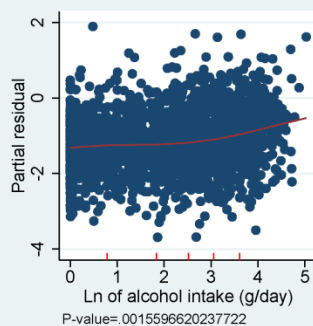
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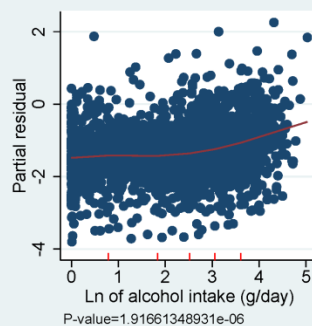
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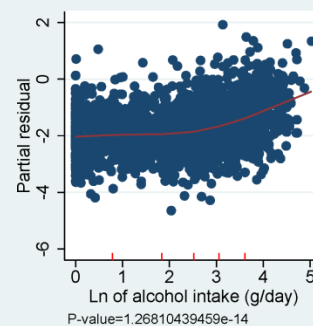
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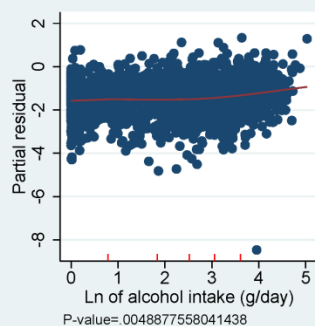
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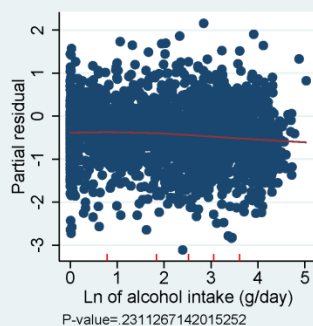
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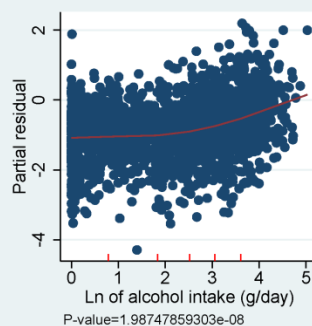
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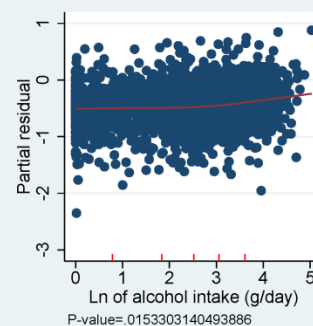
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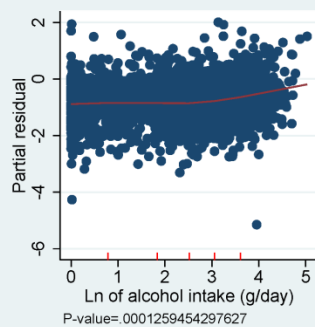
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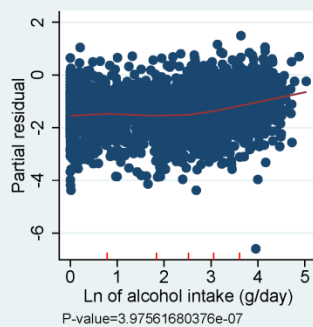
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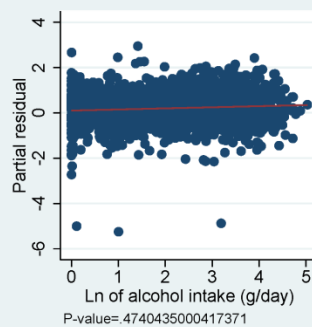
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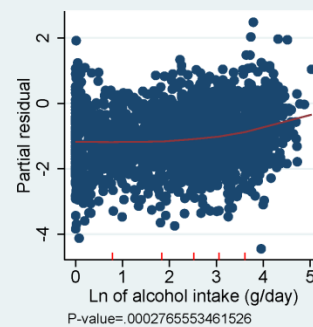
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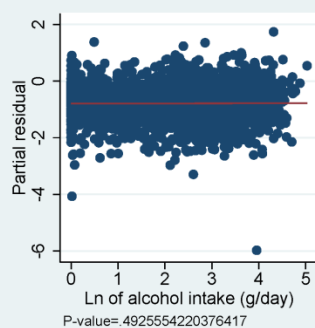
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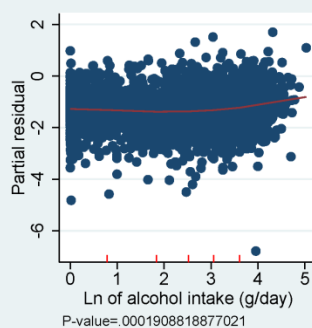
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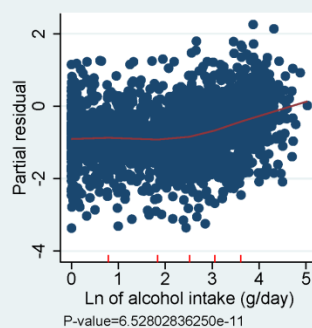
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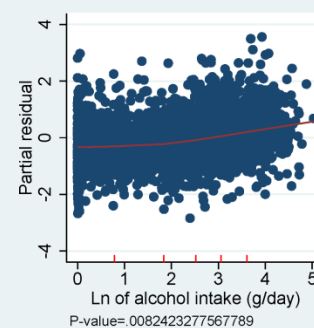
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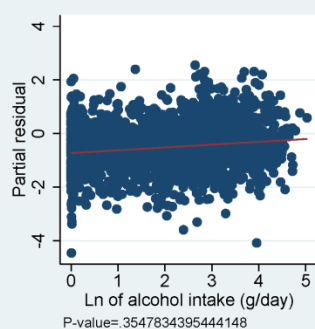
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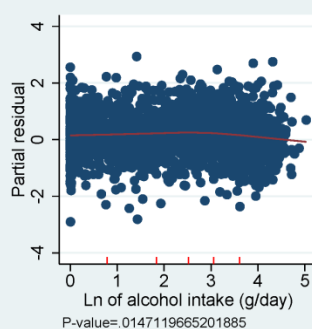
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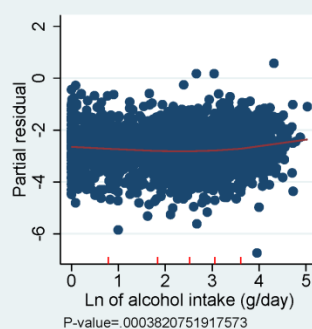
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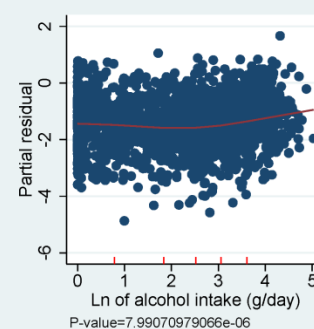
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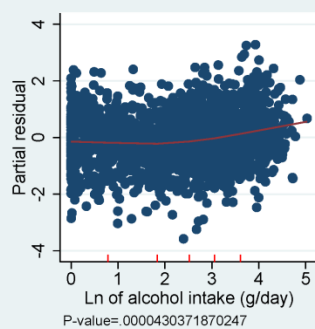
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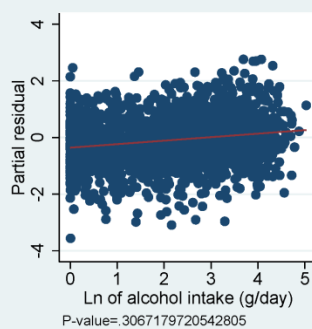
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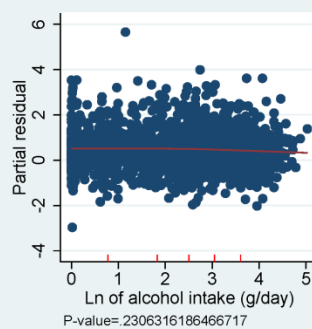
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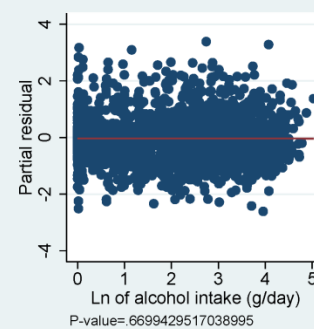
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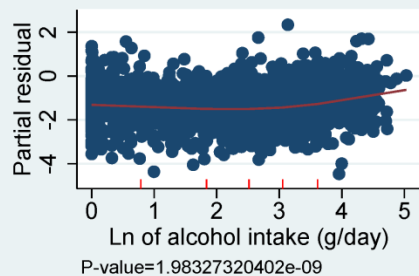
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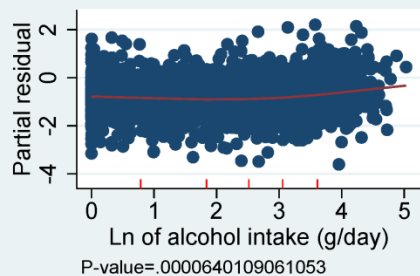
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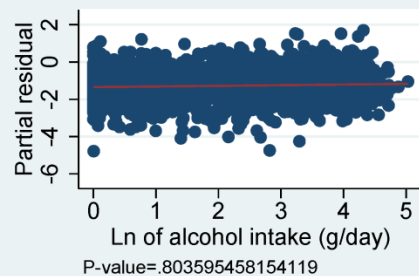
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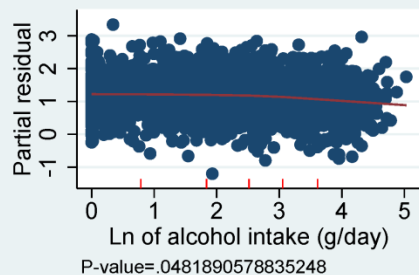
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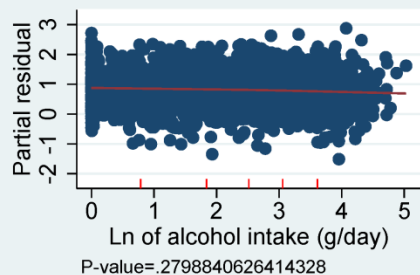
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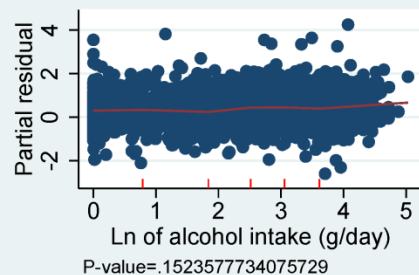
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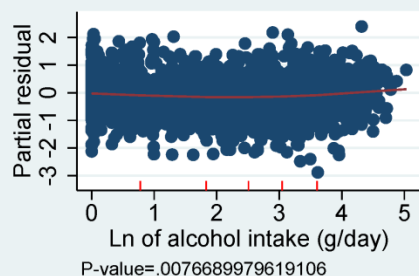
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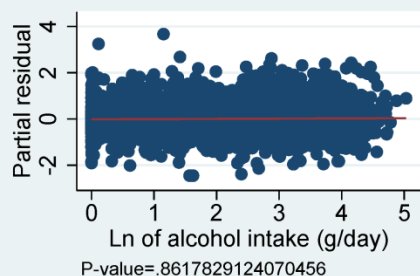
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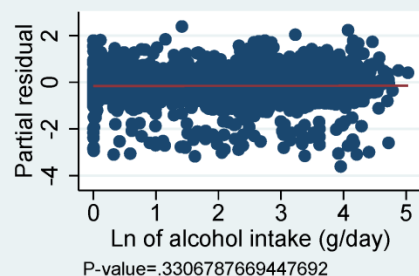
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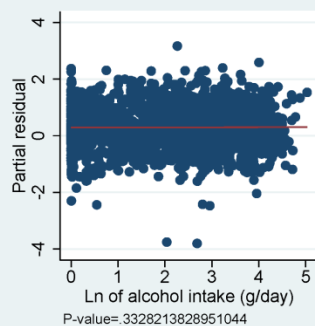
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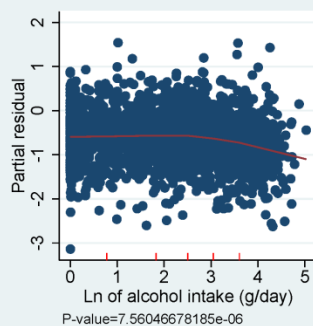
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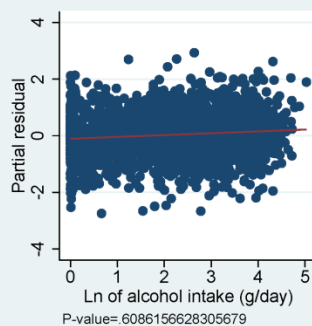
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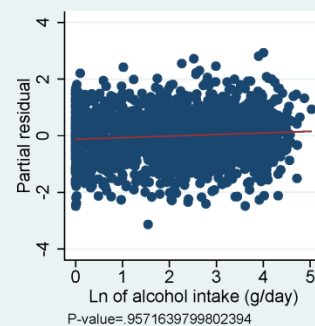
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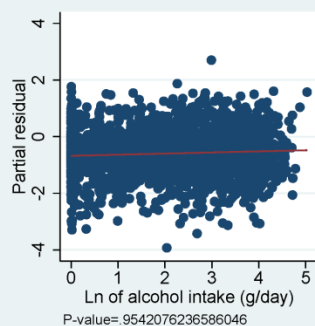
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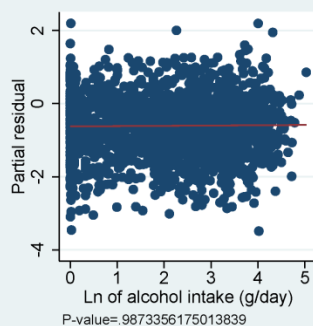
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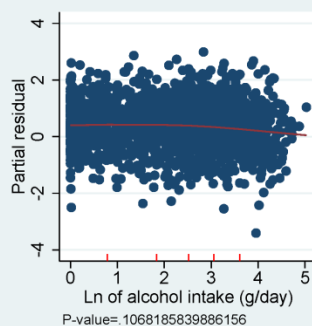
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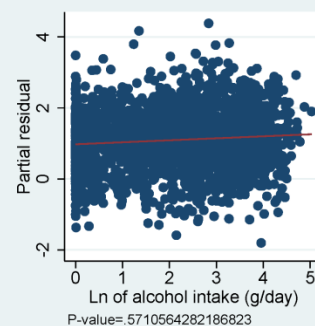
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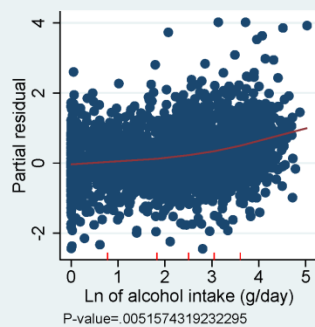
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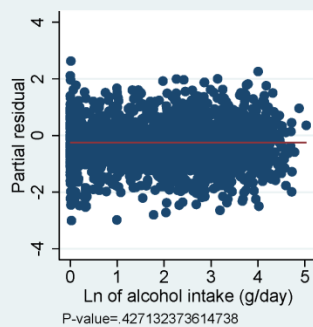
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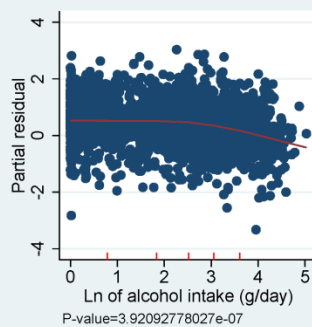
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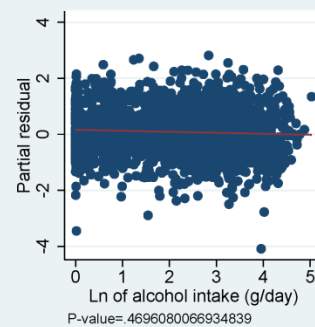
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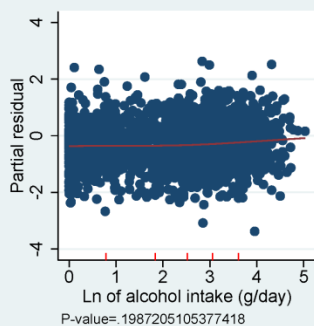
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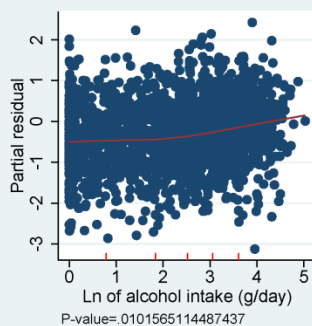
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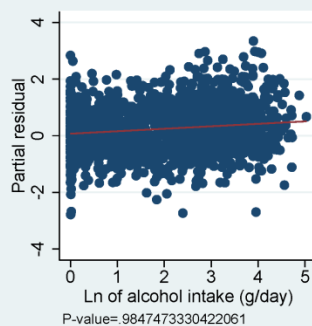
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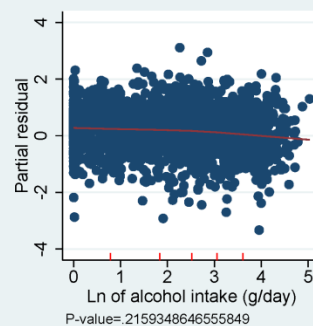
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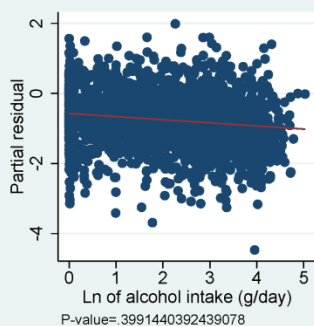
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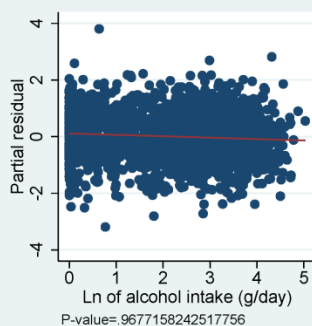
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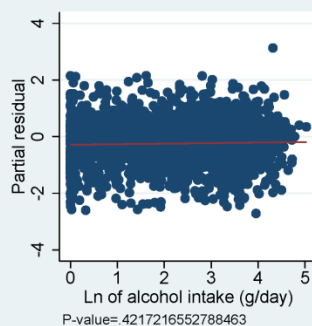
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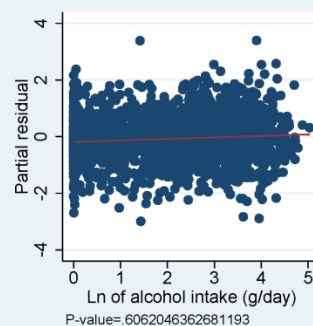
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C38:4



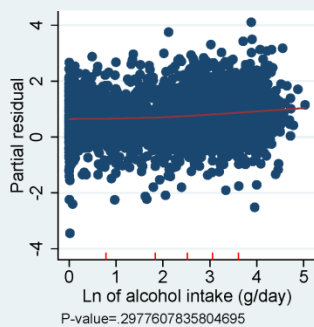
PC
ae
C38:5



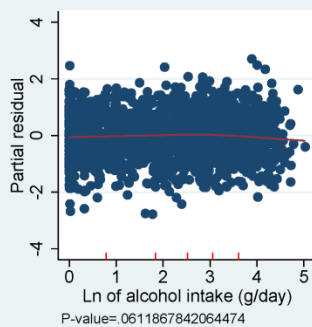
PC
ae
C38:6



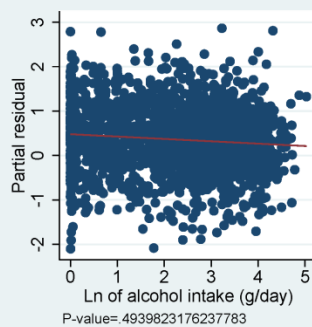
PC
ae
C40:1



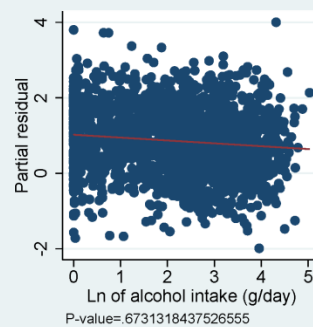
PC
ae
C40:2



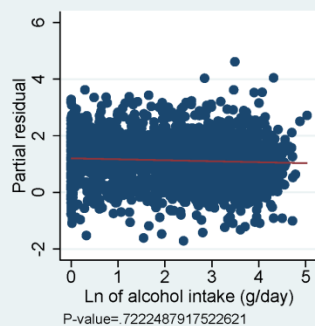
PC
ae
C40:3



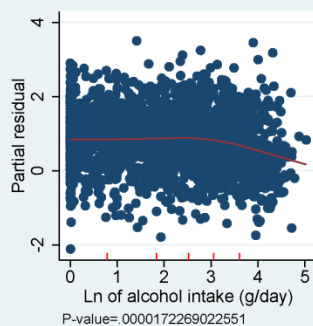
PC
ae
C40:4



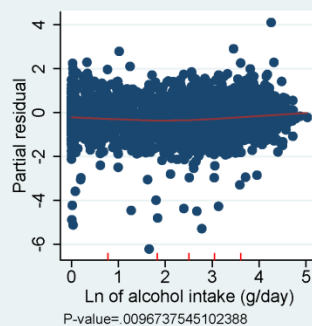
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ae
C40:5



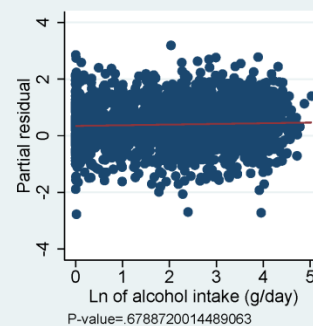
PC
ae
C40:6



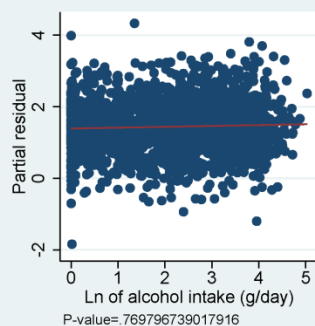
PC
ae
C42:1



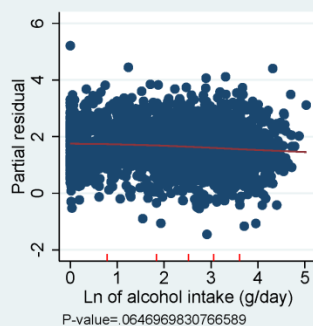
PC
ae
C42:2



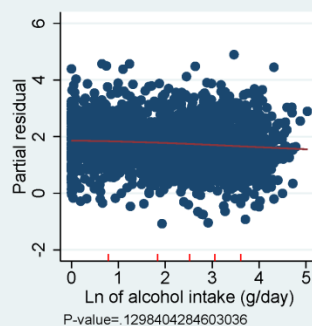
PC
ae
C42:3



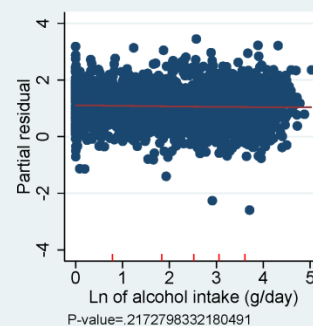
PC
ae
C42:4



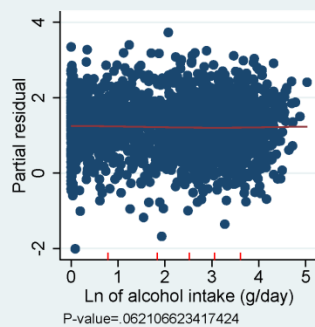
PC
ae
C42:5



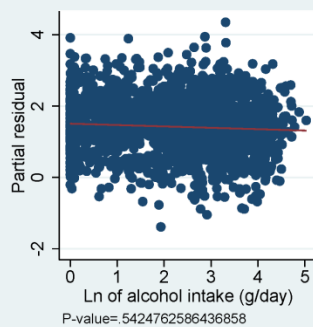
PC
ae
C44:4



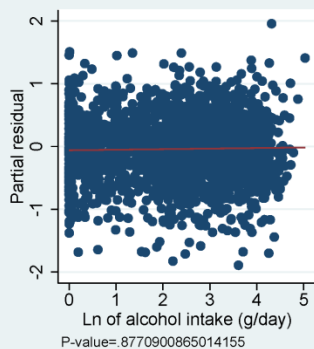
PC
ae
C44:5



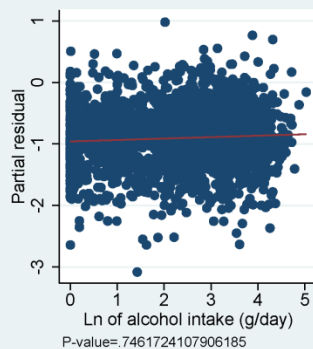
PC
ae
C44:6



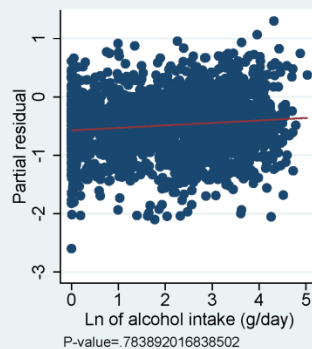
SM
C16:0



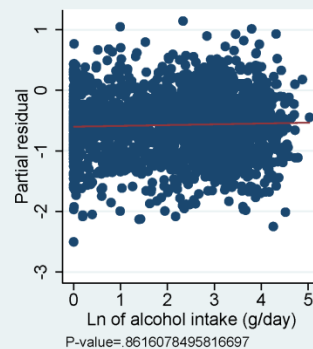
SM
C16:1



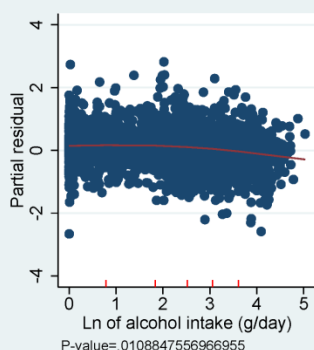
SM
C18:0



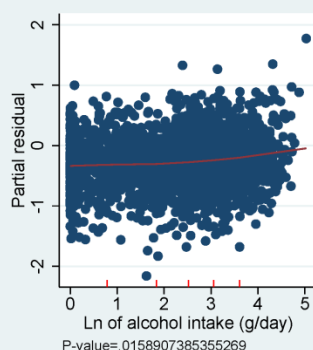
SM
C18:1



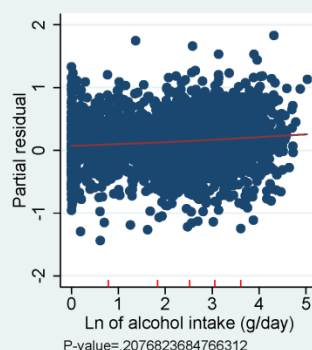
SM
C20:2



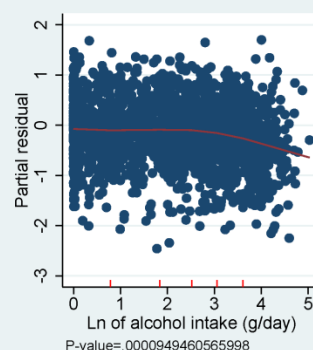
SM
C24:0



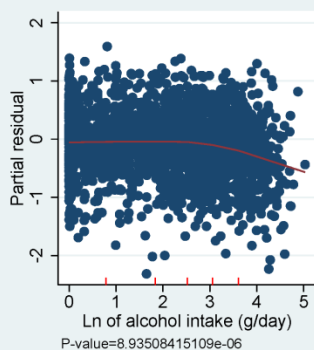
SM
C24:1



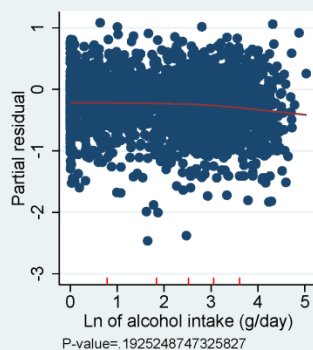
SM(OH)
C14:1



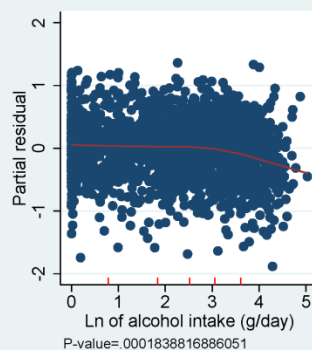
SM(OH)
C16:1



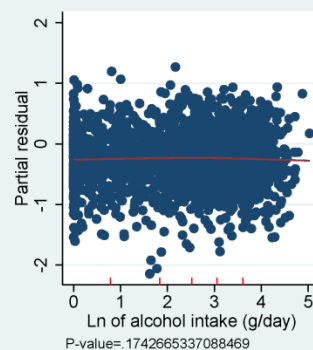
SM(OH)
C22:1



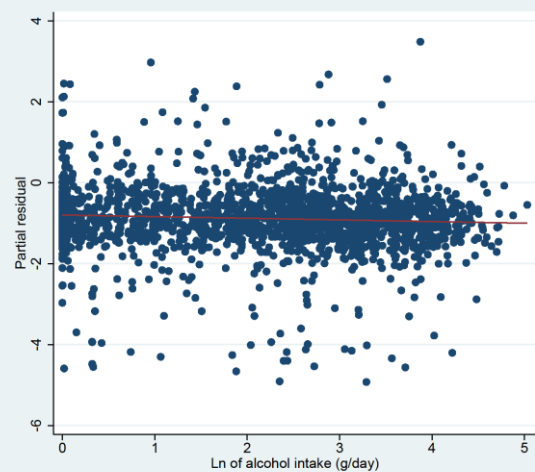
SM(OH)
C22:2



SM(OH)
C24:1



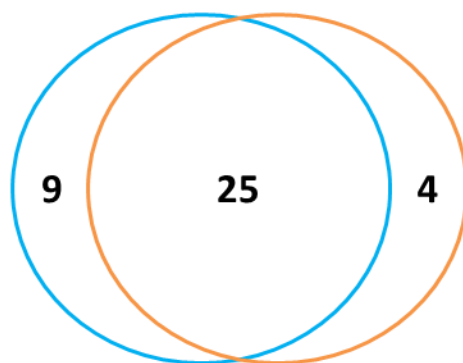
Hexoses



P-value= .6782714613255829

Supplementary Figure 5. Venn diagram showing overlap in metabolites identified as being statistically significantly (Bonferroni-adjusted p -value <0.05) associated with continuous ln-transformed alcohol intake (main analysis) and with heavy drinking (≥ 40 g/day of alcohol) vs. light drinking (0.1-4.9 g/day of alcohol) in replication analysis.

Main analysis
(continuous ln-transformed alcohol intake)



Sensitivity analysis
(heavy vs. light alcohol consumption)

Supplementary Figure 6. Regression coefficients obtained from analysis of associations of alcohol intake with metabolites in the discovery dataset, stratified by sub-study, i.e. colorectal cancer (CRC), kidney cancer (KC), hepatobiliary cancer (HC), and prostate cancer (PC) case-control study.

Footnote: Analyzed with multivariable linear regression analyses analyzing associations of alcohol consumption (ln-transformed alcohol intake + 1) as main independent variable and as dependent variables the residuals obtained from linear mixed models with Z-standardized ln-transformed metabolite concentrations as dependent variables, sex as independent variable, and random intercepts for analytical batches nested within studies. Adjusted for: sex; age (y; continuous), body mass index (kg/m²; continuous), self-reported physical activity levels (Cambridge physical activity index [22]: inactive, moderately inactive, moderately active, active, unknown), fasting status (≥6 hours, 3-5.9 hours, <3 hours, unknown), meat intake (g/day; continuous), fish intake (g/day; continuous), energy intake (kcal/day; continuous), country, and smoking status (current, former, never, unknown).

