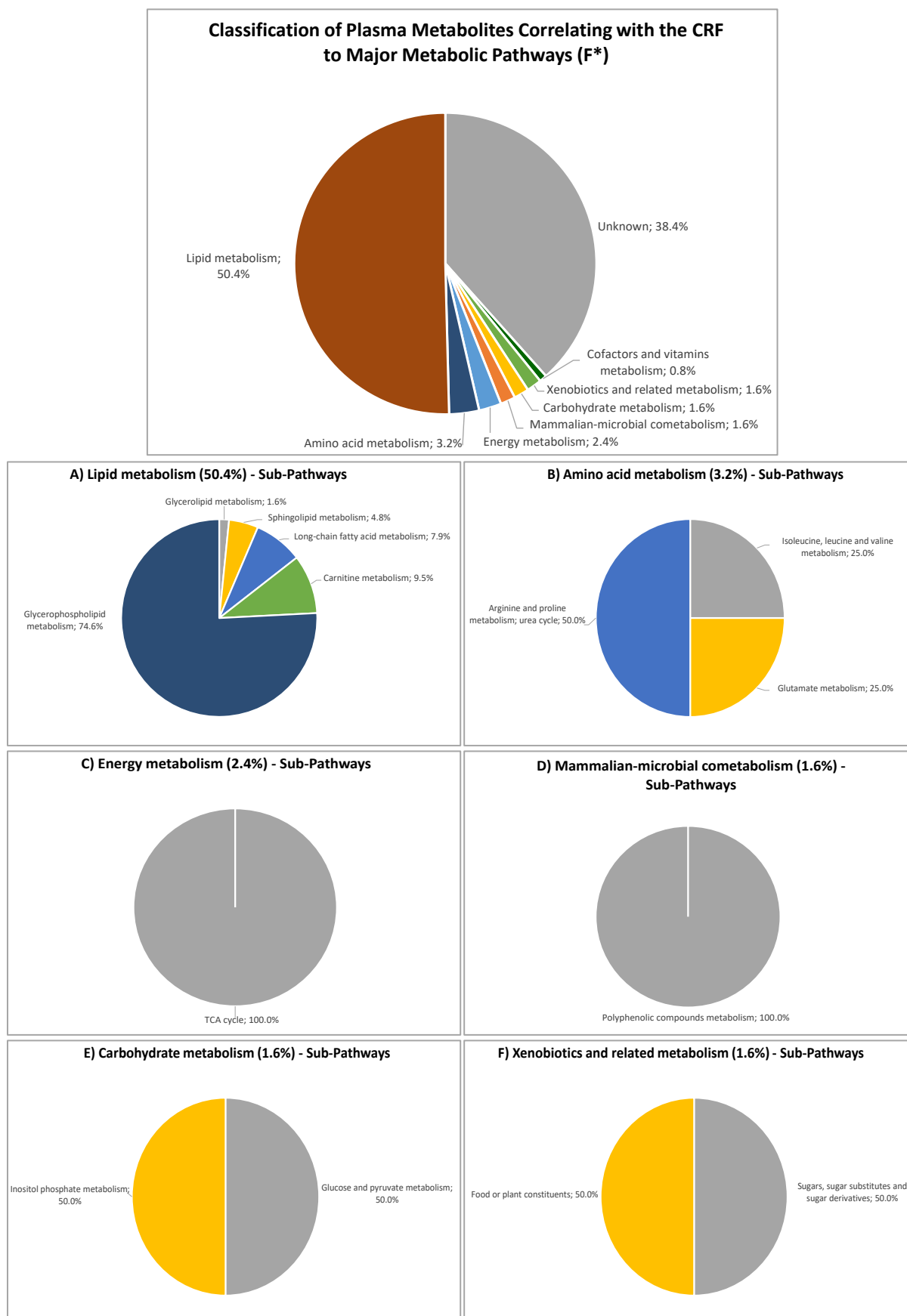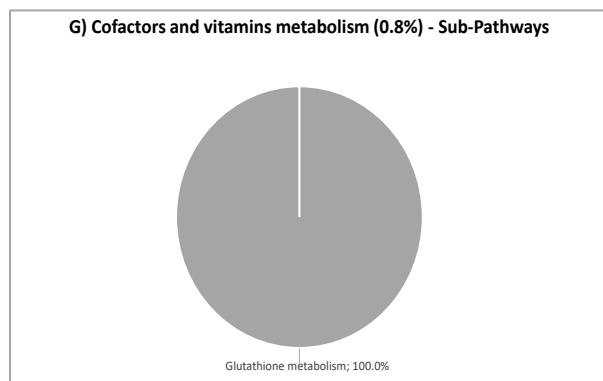# File S3: Classification of metabolites with significant bivariate correlations to metabolic pathways

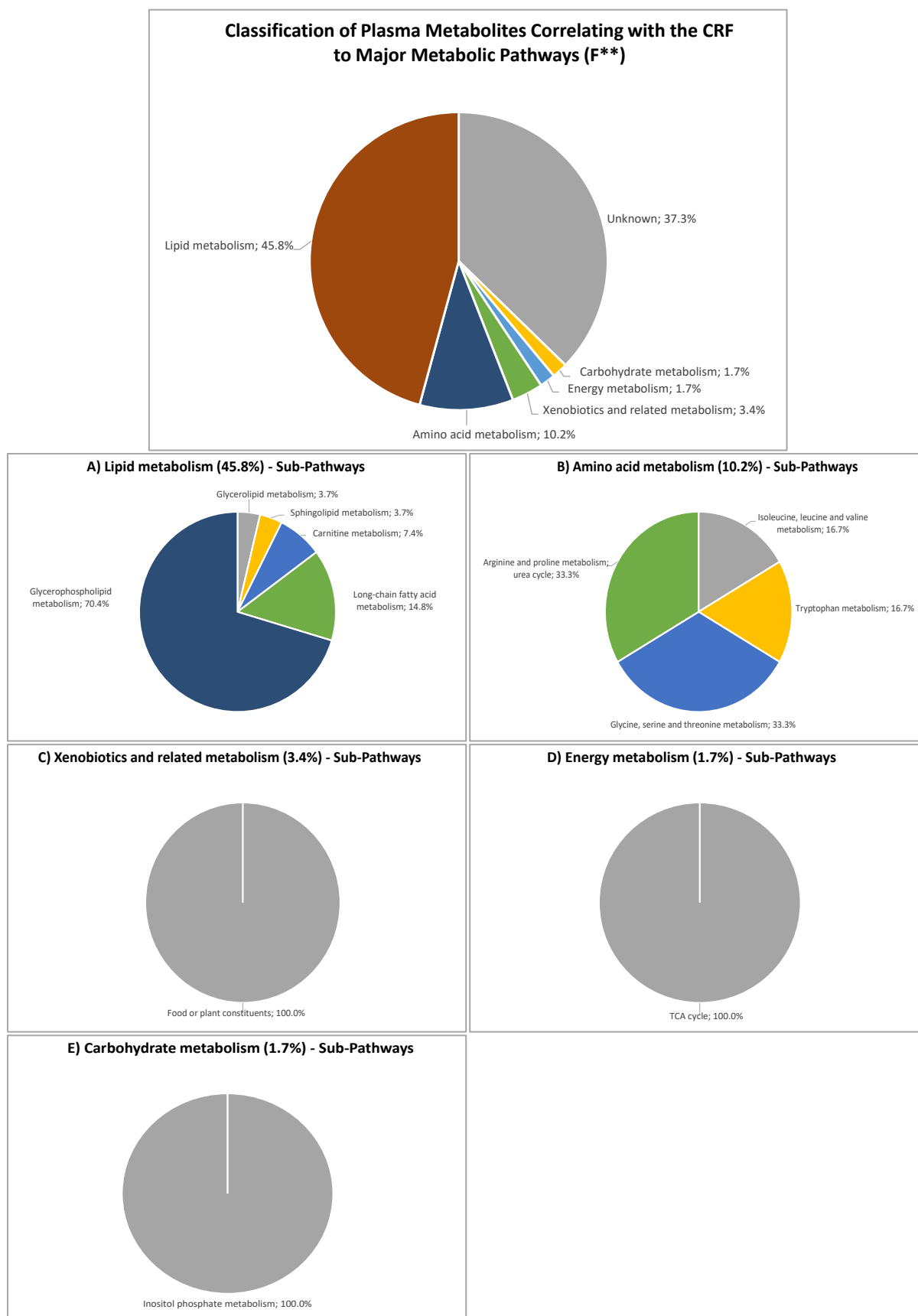## 1. Confounder-adjusted correlations in females (F*)

Classification of Plasma Metabolites Correlating with the CRF to Major Metabolic Pathways (F*)

- Lipid metabolism; 50.4%
- Unknown; 38.4%
- Amino acid metabolism; 3.2%
- Energy metabolism; 2.4%
- Mammalian-microbial cometabolism; 1.6%
- Carbohydrate metabolism; 1.6%
- Xenobiotics and related metabolism; 1.6%
- Cofactors and vitamins metabolism; 0.8%

A) Lipid metabolism (50.4%) - Sub-Pathways

- Glycerophospholipid metabolism; 74.6%
- Carnitine metabolism; 9.5%
- Long-chain fatty acid metabolism; 7.9%
- Sphingolipid metabolism; 4.8%
- Glycerolipid metabolism; 1.6%

B) Amino acid metabolism (3.2%) - Sub-Pathways

- Arginine and proline metabolism; urea cycle; 50.0%
- Isoleucine, leucine and valine metabolism; 25.0%
- Glutamate metabolism; 25.0%

C) Energy metabolism (2.4%) - Sub-Pathways

- TCA cycle; 100.0%

D) Mammalian-microbial cometabolism (1.6%) - Sub-Pathways

- Polyphenolic compounds metabolism; 100.0%

E) Carbohydrate metabolism (1.6%) - Sub-Pathways

- Inositol phosphate metabolism; 50.0%
- Glucose and pyruvate metabolism; 50.0%

F) Xenobiotics and related metabolism (1.6%) - Sub-Pathways

- Food or plant constituents; 50.0%
- Sugars, sugar substitutes and sugar derivatives; 50.0%

G) Cofactors and vitamins metabolism (0.8%) - Sub-Pathways

Glutathione metabolism; 100.0%

Figure 1. Classification of CRF-correlated metabolites to major metabolic pathways and sub-pathways (females).
125 plasma metabolites showed signficant bivariate correlations with the CRF in females (after adjusting for confounders). Most of them belong to lipid metabolism (63/125) and amino acid metabolism (4/125), followed by energy metabolism (3/125) and mammalian-microbial, carbohydrate or xenobiotics-related metabolism (each 2/125) and cofactors and vitamins metabolism (1/125). 48 plasma analytes were unknown.
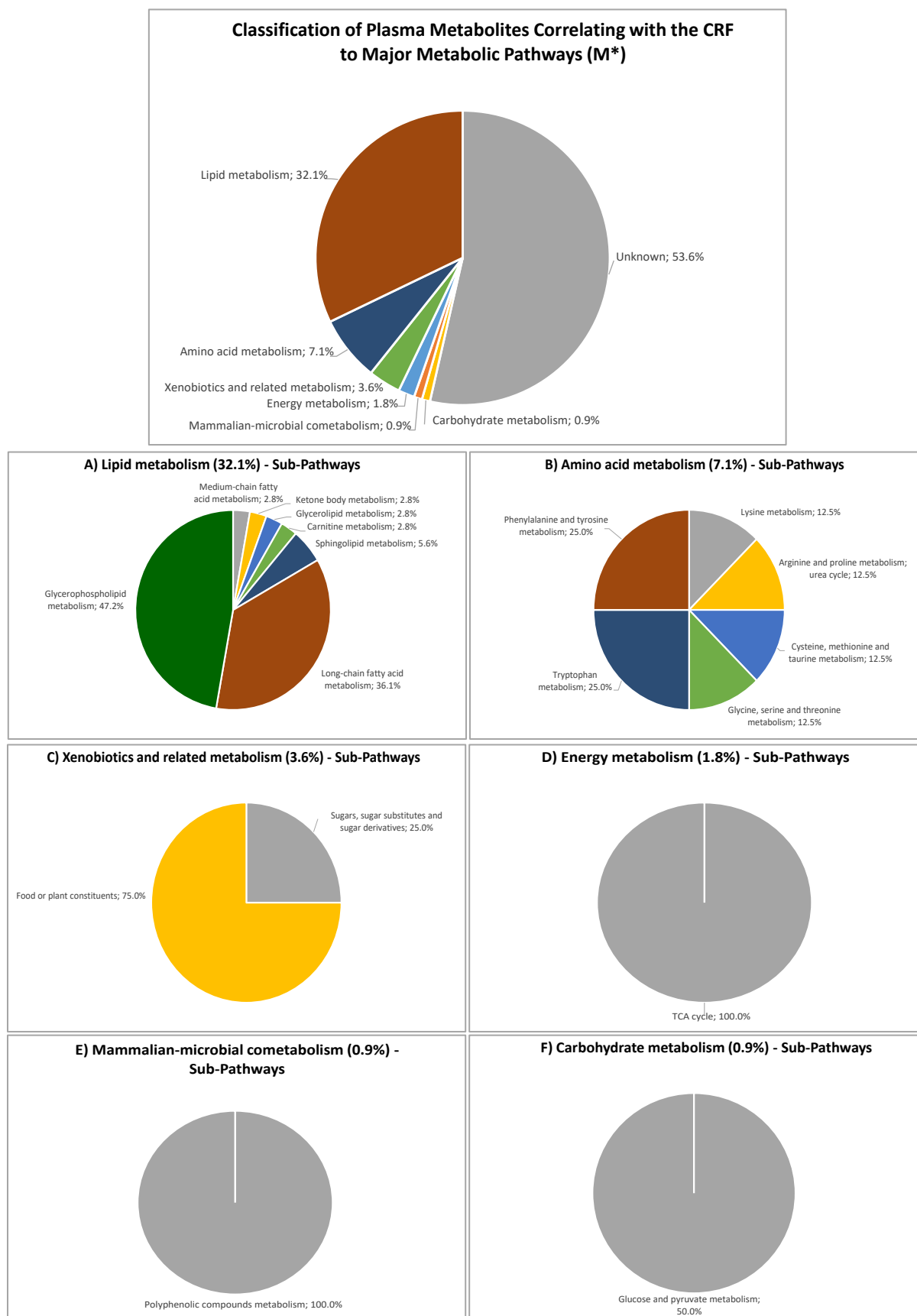
2. Confounder- and clinical/phenotypical variables-adjusted correlations in females (F**)

Classification of Plasma Metabolites Correlating with the CRF to Major Metabolic Pathways (F**)

Unknown; 37.3%

Lipid metabolism; 45.8%

Carbohydrate metabolism; 1.7%

Energy metabolism; 1.7%

Xenobiotics and related metabolism; 3.4%

Amino acid metabolism; 10.2%

A) Lipid metabolism (45.8%) - Sub-Pathways

Glycerolipid metabolism; 3.7%

Sphingolipid metabolism; 3.7%

Carnitine metabolism; 7.4%

Glycerophospholipid metabolism; 70.4%

Long-chain fatty acid metabolism; 14.8%

B) Amino acid metabolism (10.2%) - Sub-Pathways

Isoleucine, leucine and valine metabolism; 16.7%

Arginine and proline metabolism; urea cycle; 33.3%

Tryptophan metabolism; 16.7%

Glycine, serine and threonine metabolism; 33.3%

C) Xenobiotics and related metabolism (3.4%) - Sub-Pathways

Food or plant constituents; 100.0%

D) Energy metabolism (1.7%) - Sub-Pathways

TCA cycle; 100.0%

E) Carbohydrate metabolism (1.7%) - Sub-Pathways

Inositol phosphate metabolism; 100.0%

Figure 2. Classification of CRF-correlated metabolites to major metabolic pathways and sub-pathways (females).
59 plasma metabolites showed significant bivariate correlations with the CRF in females (after adjusting for confounders and phenotypical/clinical variables). Most of them belong to lipid metabolism (27/59) and amino acid metabolism (6/59), followed by xenobiotics and related metabolism (2/59), energy or carbohydrate metabolism (each 1/59). 22 plasma analytes were unknown.
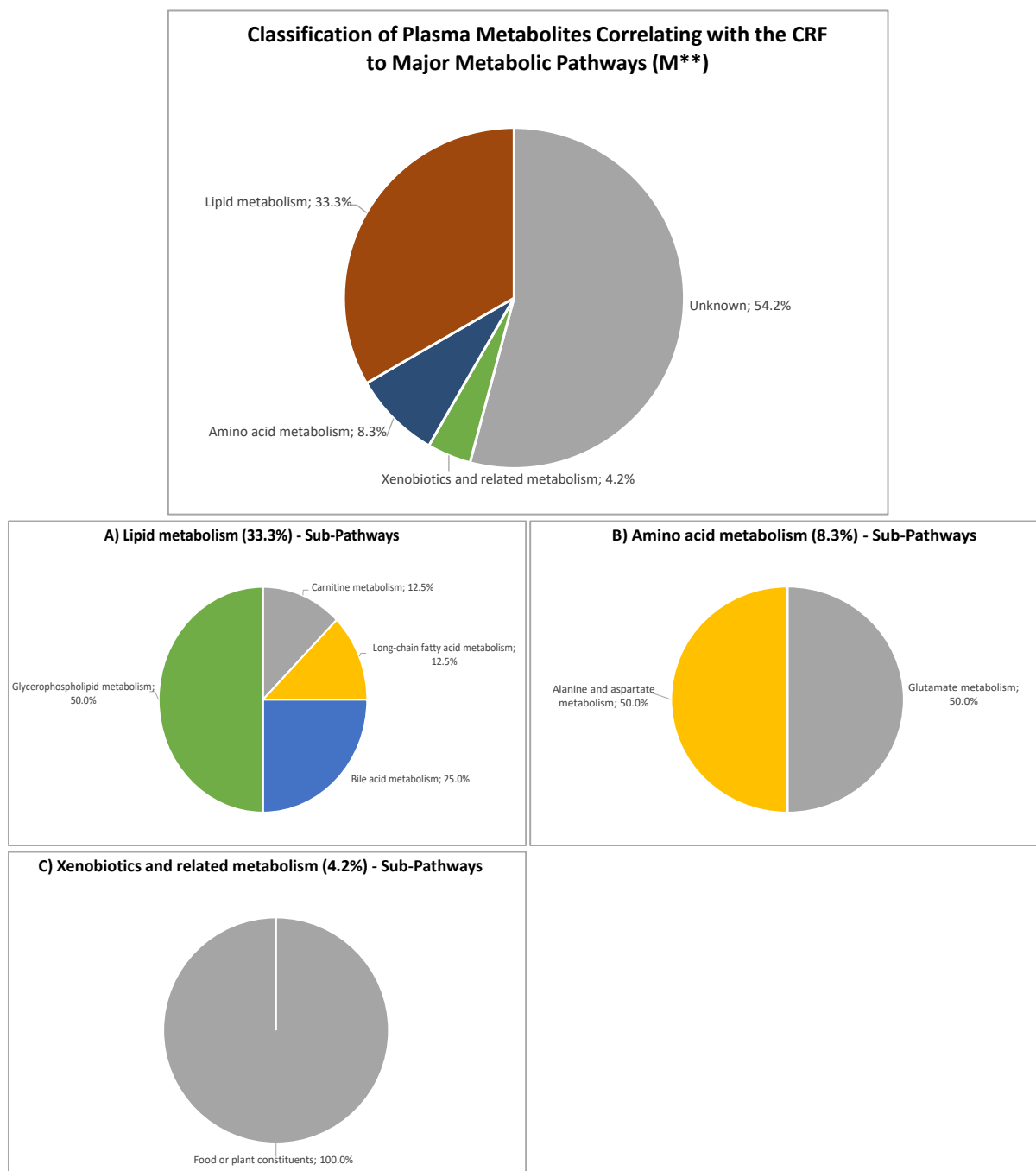
3. Confounder-adjusted correlations in males (M*)

Figure 3. Classification of CRF-correlated metabolites to major metabolic pathways and sub-pathways (males).
112 plasma metabolites showed significant bivariate correlations with the CRF in males (after adjusting for confounders). Most of them belong to lipid metabolism (36/112) and amino acid metabolism (8/112), followed by xenobiotics and related metabolism (4/112), energy metabolism (2/112) and carbohydrate or mammalian-microbial (co-)metabolism (each 1/112). 60 plasma analytes were unknown.

4. Confounder- and clinical/phenotypical variables-adjusted correlations in males (M**)

Classification of Plasma Metabolites Correlating with the CRF to Major Metabolic Pathways (M)**

- Lipid metabolism; 33.3%
- Unknown; 54.2%
- Amino acid metabolism; 8.3%
- Xenobiotics and related metabolism; 4.2%

A) Lipid metabolism (33.3%) - Sub-Pathways

- Carnitine metabolism; 12.5%
- Long-chain fatty acid metabolism; 12.5%
- Glycerophospholipid metabolism; 50.0%
- Bile acid metabolism; 25.0%

B) Amino acid metabolism (8.3%) - Sub-Pathways

- Alanine and aspartate metabolism; 50.0%
- Glutamate metabolism; 50.0%

C) Xenobiotics and related metabolism (4.2%) - Sub-Pathways

- Food or plant constituents; 100.0%

Figure 4. Classification of CRF-correlated metabolites to major metabolic pathways and sub-pathways (males).
24 plasma metabolites showed significant bivariate correlations with the CRF in males (after adjusting for confounders and phenotypical/clinical variables). Most of them belong to lipid metabolism (8/24) and amino acid metabolism (2/24), followed by xenobiotics and related metabolism (1/24). 13 plasma analytes were unknown.