





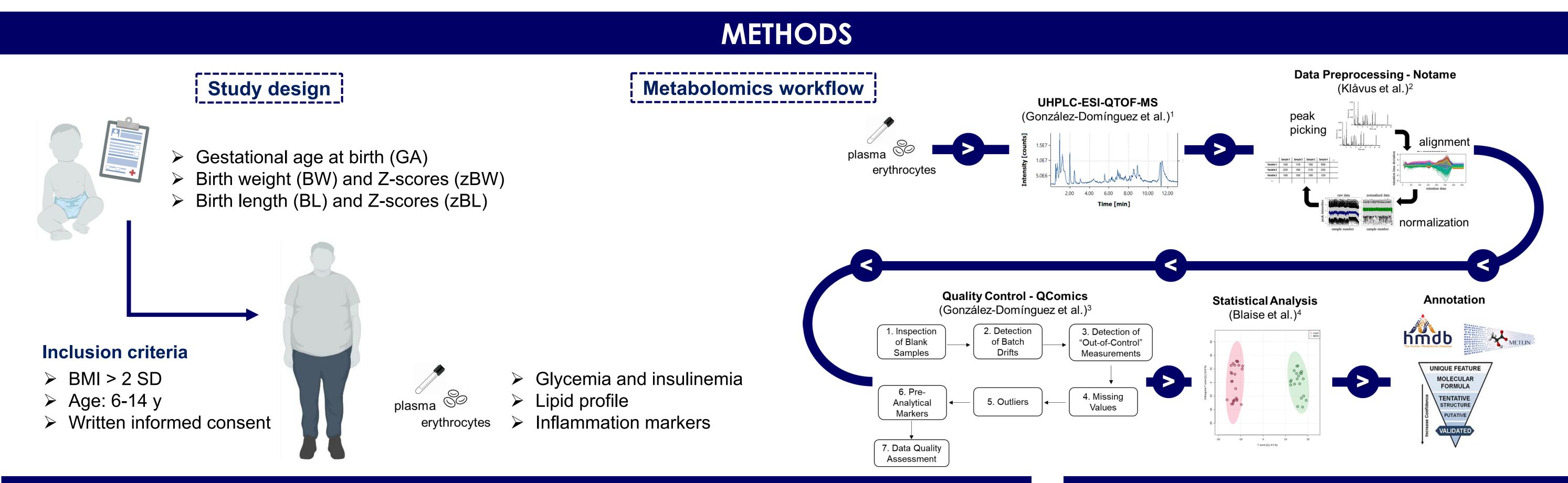


# Adverse neonatal outcomes predispose to exacerbated metabolic disturbances in childhood obesity

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The occurrence of adverse neonatal outcomes (i.e., prematurity, small for gestational age) is a significant contributing factor to the development of metabolic perturbations, which can persist throughout the lifespan and potentially lead to the onset of childhood obesity. Metabolomics has been employed in the past to investigate the pathophysiological mechanisms underlying those neonatal conditions. However, longitudinal studies elucidating the impact of neonatal determinants (i.e., gestational age, birth weight, birth length) on later metabolic health in general populations are scarce, and the molecular mechanisms underpinning their influence in the predisposition to obesity in children remain to be elucidated.



### RESULTS Association study between neonatal and clinical variables **Neonatal variables Anthropometry** GA (weeks) $39.3 \pm 1.9$ Weight (kg) 67.7 ± 19.7 BW (kg) $3.2 \pm 0.5$ Weight Z-score $4.9 \pm 2.1$ BMI $(kg/m^2)$ $0.5 \pm 4.6$ $30.0 \pm 5.2$ BL (cm) $50.4 \pm 2.6$ BMI Z-score $4.4 \pm 2.0$ $0.5 \pm 1.4$ WC (cm) 96.7 ± 12.9 zBLAssociation study between neonatal variables and metabolomics data Synthesis of Bile Acids polysaccharides ----- Glucose Taurine<sub>.</sub> Fructose 6-phosphate glucosamine 6-phosphate 6-phosphate Pentose Phosphate Fructose 1,6-Cholesterol → Pregnenolone → Progesterone Pathway bisphosphate N-Acetyl-Amino sugar Carnosine ← Histidine → metabolism ⊕ zBW Oxysterols 6-sulfate Glyceraldehyde 3 Ribose 5 Xanthosine 5'-phosphate 3-Phosphoglycerate phosphate Phosphocreatine 5'-phosphate 2-Phosphoglycerate Ceramides ⊖GA/BW/BL phospholipids ⊕ BW/zBW/B Uric acid 5-Hydroxyisouric Oxaloacetate VLCFA ⊕ zBW / zBL ⊕ BW / zBW Biosynthesis Θ GA / BW / zBW cis-Aconitate 2-sulfate Malate \ ⊝ zBW Krebs Cycle Fumarate 2-Carboxy-L-threo-Monodehydro Hydroxy | SFA ⊝ BW / zBW fatty acids VLCFA ⊕ zBW / zBL MCFA ⊕GA Trimethyllysine ← Lysine Glutathione-Dicarboxylic ⊕ GA Dehydro Ascorbate Cycle Lysine acids Ascorbate Metabolism \_\_\_\_ 5-Amino-⊕ BW / zBW / BL / zBL 5-Amino-Glutathione Oxidized Metabolism of Glutathione pentanamide pentanoate Biosynthesis Glutathione Lipid ω-Branched Chain Oxidation Amino Acids NADP+ NADPH Peroxidation Glutamyl Aldehydes (MDA) ⊙ BL / zB Isovaleryl Leucine oxovaleric acid cysteine ΘBL Oxylipins (HODE, HETE, HDoHE, etc.) © GA/BW/zBW 3-Hydroxy-3-methylbutyric 3-Methyl-2-Isoleucine -**Dipeptides** oxovaleric acid | butyryl-CoA ⊝ BL / zBL 2-Ketobutyric acid ----- 2-Hydroxybutyric acid Proteolysis ⊕ GA / BW / zBW N-Acetylamino acids 、 Propionyl-Isobutyryloxobutyric acid ⊕ BW / zBW / BL / zBL CoA $\Theta$ BW O-Acetyl-serine ← Serine ⊕ BL / zBL Sulfur Amino Metabolism Acid Metabolism Dityrosine **O-Sulfotyrosine** of Tryptophan Tryptophan -Ornithine **Phenylalanine** sulfate ⊝ zBL ⊜ BW ⊕ BW / zBW Glutamine ⊝ GA / BW Metabolism of ⊕ GA / BL Indole-3-Phenylalanine ⊕ GA lactate 4-Hydroxyphenyl-Cycle 2-Oxoarginin 4-Hydroxyphenyland Tyrosine Kynurenine Indole Indole-3zBW Aspartic acid Hydroxyphenylacrylate Homogentisic ⊙ BL / zBL Hydroquinone Indoxyl acetic acid Kynurenic sulfate sulfate acid ⊕ BL / zBL Indole-3-⊕ BW / zBW Positive association between neonatal variables and propionate **Phenylacetylglutamine** plasma metabolites ⊕ BW / zBW / zBL Negative association between neonatal variables and plasma metabolites 2-Hydroxybenzoic acid ⊙ Bl Xanthine alkaloids Positive association between neonatal variables and Diet-Related 3-Hydroxybenzoic acid ⊕ GA Theophylline ⊕BW/zBW Endocrine Diethyl phosphate ⊙ BL / zBL erythroid metabolites Napthtyl sulfate ⊖ BL / zBL 4-Hydroxybenzoic acid GA Metabolites Theobromine ⊕ BL / zBL Negative association between neonatal variables and **2-Hydroxyhippuric acid** ⊙ BL / zBL 7-Methylxanthine BL/zBL ervthroid metabolites

# CONCLUSIONS

- ✓ Adverse neonatal outcomes (i.e., low gestational age, weight, and length at birth) may predispose to an unhealthier metabolic status, as reflected in negative associations with anthropometric parameters (e.g., waist circumference) and biochemical markers of insulin resistance (e.g., HOMA-IR) and inflammation (e.g., CRP, inflammatory indices).
- ✓ This was accompanied by exacerbations in a multitude of central metabolic pathways which play a crucial role in obesity pathophysiology, such as energy metabolism, homeostasis of branched chain and aromatic amino acids, regulation of oxidative stress, and biosynthesis of steroid hormones and bile acids.
- ✓ Accordingly, we hypothesize that even minor variations in neonatal conditions may provoke deleterious molecular programming mechanisms with strong impact on later metabolic risk.

## References

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