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Ceramide and sphingolipids are elevated across sample types in Crohn's Disease compared to controls: A Systematic Review

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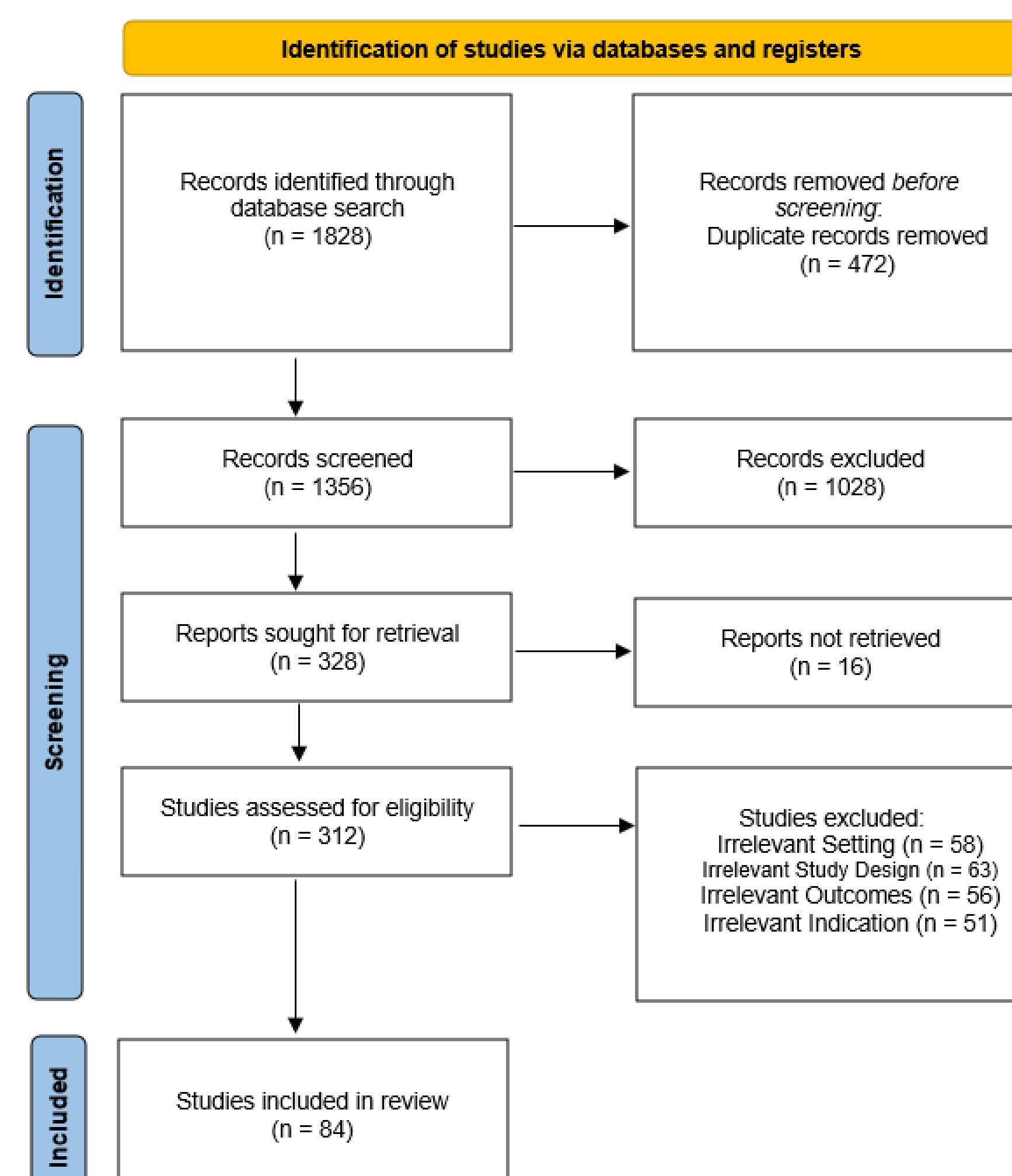


Introduction

- Metabolomics refers to the analysis of patterns of small molecular metabolites in biological samples.
- Given the systemic effects of Crohn's Disease (CD) on metabolite production, immune mediation, and microbiota growth, metabolomic studies undoubtedly provide clarity into disease course and prognosis.
- We performed a comprehensive systematic review of human studies to identify common metabolite signatures in human CD.

Design / Sample

- Two independent reviewers searched Medline and Embase databases to identify human CD studies from inception to June 2022 that measured metabolites.
- Inclusion criteria encompassed studies with human subjects, utilization of high-throughput screening methods, and identification of individual metabolites.
- Exclusion criteria were studies not assessing CD patients, not comparing CD patients to healthy controls (HCs), and those with <10 CD subjects.
- Metabolites identified in 2 or more studies were recorded and compared between CD patients and HCs.



Results

Type of Sample and Relative Level in Crohn's Disease Compared to Controls					
Lipids (number of studies identifying each metabolite)	Colonic Tissue	Stool	Serum	Urine	Breath
Acetic Acid (5)		↓		↓	↑↑↑
Acetate (5)		↑/↓	↑↑		↑
Arachidonic Acid (9)	↑	↑↑	↑↑↑/↓↓↓		
Butyrate (4)		↑/↓↓	↑		
Butyric Acid (9)		↓↓↓↓↓	↑/↓	↑↑/↓	
Ceramides (6)	↑↑	↑	↑↑↑↑	↑	
Docosahexaenoic Acid (5)			↓↓↓↓↓		
Docosapentaenoic Acid (2)			↑/↓		
Eicosapentaenoic Acid (2)			↑/↓		
Eicosatrienoic Acid (5)		↑	↑↑↑/↓		
Linoleic Acid (5)	↓	↑	↓↓↓		
Lysophosphatidylcholine (3)	↑		↑/↓		
Monoacylglycerol (3)	↑↑/↓				
Palmitic Acid (3)		↑	↑↑		
Palmitoleic Acid (2)			↑↑		
Pentanoic Acid (4)		↑/↓	↓		↑
Phosphatidylcholine (4)	↑↑	↑	↑		
Phosphatidylethanolamine (3)	↑↑		↑		
Phosphatidylglycerol (2)	↑↑				
Phosphatidylinositol (4)	↑↑↑		↑		
Phosphatidylserine (4)	↑↑		↑/↓		
Propionate (3)		↓	↑		↑
Propionic Acid (2)		↓	↓		
Sphingolipids (8)	↑↑↑	↑↑	↑↑↑	↑	
Triacylglycerol (3)	↑	↓	↑		

Type of Sample and Relative Level in Crohn's Disease Compared to Healthy Controls (number of studies reporting altered levels in each sample type)					
Other Primary Metabolites	Colonic Tissue	Stool	Serum	Urine	Breath
Alpha-ketoglutarate (2)			↓↓		
Benzene (4)		↑↑	↓	↓↓	
Citrate/Citric Acid (5)			↑/↓↓	↓↓↓	
Ethanol (2)			↑		↑↑
Formic Acid/Formate (4)			↓↓	↑↑↑	
Galactose (2)			↑	↑	
Hippuric acid (7)		↓	↑↑/↓	↑/↓↓↓	
Quinolinic Acid (2)			↑↑		
Succinate (4)			↑↑/↓	↑↑/↓	
Sulfur (2)	↑↑				
Xylose (2)			↑	↑	

Type of Sample and Relative Level in Crohn's Disease Compared to Healthy Controls					
Biogenic Amines and Proteins (number of studies identifying each metabolite)	Colonic Tissue	Stool	Serum	Urine	Breath
Alanine (7)		↑↑↑	↑/↓	↑/↓	↓
Arginine (6)	↑↑	↑	↓	↓	
Aspartic Acid (3)			↑/↓	↓	
Carnitine (6)	↑↑↑		↑/↓		
Creatine (2)			↑		
Creatinine (3)	↓		↓	↑	
Cysteine (2)			↓		
Ethanolamine (7)	↑↑↑↑		↑↑/↓		
Fibrinogen Alpha Chain (3)	↑		↑↑		
Fibrinogen Beta Chain (2)	↑↑				
Glutamine (4)	↑		↓		
Glutathione (3)	↑↑		↑		
Glycine (3)		↑	↑/↓		
Hemoglobin Subunit Epsilon (2)	↑↑				
Histidine (5)		↑	↑/↓	↓	
Homocysteine (2)			↑↑		
Indole (2)	↑	↑			
Isoleucine (5)		↑	↑↑↑/↓	↑	
Kynurenine (5)		↑↑	↑↑↑↑		
Leucine (6)		↑↑	↑/↓	↑↑↑	
Lysine (7)	↑↑	↑↑	↓		↓
Methionine (5)	↑↑		↑↑↑		
Ornithine (2)		↑/↓			
Phenylalanine (7)	↑↑	↑	↑↑	↑↑	
Proline (4)	↑↑		↑/↓		
Radixin (2)	↑↑				
Serine (3)	↑		↑/↓	↑	
Taurine (4)		↑	↑/↓	↓	
Thioredoxin (2)	↑↑				
Threonine (2)	↑↑				
Tryptophan (4)			↑↑	↓	
Tyrosine (6)	↑↑	↑↑/↓	↑		
Valine (7)		↑↑	↑	↓	

Type of Sample and Relative Level in Crohn's Disease Compared to Healthy Controls (number of studies reporting altered levels in each sample type)				
Bile Acids	Colonic Tissue	Stool	Serum	Urine
Chenodeoxycholic Acid (3)	↓	↑↑	↑/↓↓	↑
Cholic Acid (3)	↓	↑↑	↑/↓	
Taurocholic Acid (2)		↑↑	↑	
Glycocholic acid (2)		↑↑	↑	
Tauro-chenodeoxycholic acid (3)		↑↑	↑/↓	
Lithocholic Acid (3)		↑↑	↑↑	↑
Tauro-beta-muricholic acid (3)	↓↓	↑↑	↑	
Hyochoic acid (3)	↓↓	↑↑	↑	
Taurolithocholic acid (3)	↓↓	↑↑	↑	
Deoxycholic Acid (3)	↓	↑↑	↑	
Trihydroxy-6beta-cholic acid (3)	↓	↑↑	↑	
Taurodeoxycholic acid (3)	↓	↑↑	↑	
Glyco-lithocholic acid (3)	↓	↑↑	↑	
Glycodeoxycholic acid (3)	↓	↑↑	↑	

↑: each arrow represents a single study, directionality of the arrow denotes that the relative level of each metabolite was either elevated or decreased in CD patients compared to controls. Studies with this arrow either had a combination of CD patients with and without active disease or the presence of active disease was not properly defined.
 ↑: a red arrow represents a study where all CD participants were denoted to have active disease and colonic tissue biopsies were taken from areas of active inflammation.
 /: In the case that one study found a metabolite elevated in a given biosample but another found it decreased, the arrows with differing directionality are separated by a slash

Summary

- Our review showed that short-chain and long-chain fatty acids, sphingolipids, and ceramides were dysregulated in CD patients compared to HCs.
- Sphingolipids and ceramides levels were elevated across colonic tissue, stool, urine and serum in CD patients.
- Arachidonic acid was elevated in both stool and colonic tissue samples of CD patients.
- Biogenic amines, amino acids and their metabolites were elevated in the colonic tissue of CD patients
- Similar to arachidonic acid, levels of amino acids were elevated both in colonic tissue and stool samples.
- Whether elevated or decreased, levels of biogenic amines in CD were concordant between urine and serum samples.
- Both primary and secondary bile acids were found elevated in serum samples of CD patients.
- Levels of primary metabolites, including hippuric acid, acetic acid, ethanol, and sulfur were relatively low in the serum and urine samples of CD patients.
- Contrary to the elevated levels of arachidonic acid and amino acids in stool and colonic tissue samples, hippuric acid was decreased in both analytes in CD patients.

Conclusions / Further Study

- CD patients had similar dysregulated metabolites in the colonic tissue and stool samples.
- Levels of ceramides and sphingolipids were elevated in CD patients compared to healthy controls (HCs) across various sample types vs levels of other metabolites varied by sample type and provide insight into the pathophysiology of CD.
- Our study suggests that type of sample followed by the class of metabolites are critical in biomarker development in CD.

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