

Scientific Letter

Association of Plasma Metabolic Profiling With Asthma Phenotypes and Exacerbation

Asthma, a heterogeneous chronic airway inflammatory disease, accounted for 21.6 million disability-adjusted life years (DALYs) worldwide in 2019 [1]. Eosinophilic asthma represents a prominent phenotype characterized by more severe exacerbations, more comorbidities, and worse lung function [2]. Metabolites including lipids, amino acids, and glucose-related metabolites are essential in inflammation and immune regulation [3–5]. Recent metabolomics research has indicated possible associations between metabolic profiles and asthma severity and phenotypic discrimination [6,7]. Considering the intricate relationship among lipid metabolism, obesity, and asthma pathophysiology, lipidomics may provide new insights. However, few studies have examined plasma metabolites within asthmatic populations, particularly in relation to eosinophilic phenotype and exacerbation. To address this gap, we conducted a metabolomic analysis among individuals with asthma, using data from a large population-based cohort. We examined associations between a broad panel of plasma metabolites, primarily related to lipid metabolism, and asthma-related traits, including eosinophilic phenotypes, lung function, current wheeze, and hospitalization.

We conducted a cross-sectional analysis within the UK Biobank cohort, including 24,925 participants aged 37–73 with available plasma metabolomics and outcome-related data (Supplemental Figure 1). Metabolites were quantified using proton nuclear magnetic resonance (H-NMR) spectroscopy by Nightingale Health's laboratories in Finland. The profiling covered 168 biomarkers, primarily related to lipid metabolism, including lipids, 14 lipoprotein subclasses, and fatty acids, as well as several amino acids and other metabolites. All metabolite concentrations were standardized before analysis. Outcomes included eosinophilic asthma (blood eosinophils $\geq 0.30 \times 10^9/L$), lung function parameters (FEV₁, FVC, FEV₁/FVC), current wheeze, and asthma hospitalization. Multivariable logistic regression was used to examine associations between plasma metabolite levels and the odds of eosinophilic asthma, current wheeze, and hospitalization, while linear regression assessed their relationships with lung function measures. Models were adjusted for potential confounders including age, sex, race, education level, Townsend deprivation index, body mass index (BMI), smoking status, pack-years of smoking, alcohol status, diet quality, physical activity, hypertension, diabetes and high cholesterol. Analyses were performed using R software (version 4.3.0), and two-sided *P*-values <0.05 were considered statistically significant. Detailed definition of the outcomes and covariates can be found in the Supplementary Methods.

We included 24,925 asthma patients without concomitant COPD, with a median age of 56.0 years; 57.9% of which were female and 94.7% were white (Supplemental Table 1). Among them, 26.5% had eosinophilic asthma, 60.8% reported current wheeze, and 56.6% had a history of asthma-related hospitalization. The median FEV₁/FVC ratio was 73.5%. We first examined the associations between lipid metabolites and asthma phenotype and exacerbation, followed by other metabolic classes including fatty acids, amino acids, and glucose-related metabolites (Fig. 1 and Supplemental Table 3). Among lipid metabolites, plasma concentrations of triglyceride (TG) in lipoproteins of different densities exhibited overall consistent associations with adverse asthma profiles – namely, higher odds of eosinophilic asthma and current wheeze, and reduced β value for FEV₁ and FVC. In contrast, certain lipid constituents, including phospholipids, cholesteryl esters, and cholesterol were mostly protective when carried by HDL or LDL, only cholesteryl esters exhibited risk-decreasing patterns when present in VLDL. Further analysis of 14 lipoprotein subclasses revealed that larger VLDL particles (XXL-VLDL, XL-VLDL, and L-VLDL) were markedly associated with elevated odds of eosinophilic asthma and current wheeze, as well as impaired lung function (Fig. 2 and Supplemental Table 4). However, smaller lipoproteins ranging from M-VLDL to S-LDL were predominantly related to favorable asthma profiles. Notably, total lipoprotein particle concentration were generally negatively associated with adverse asthma profiles and reduced lung function, underscoring the importance of lipoprotein carrier context in lipid-asthma relationships (Fig. 1 and Supplemental Table 3).

In addition to lipids, multiple other metabolite classes were also associated with eosinophilic phenotype and exacerbation (Fig. 1 and Supplemental Table 3). Overall, higher plasma levels of total fatty acids were associated with lower lung function and higher odds of current wheeze. However, a progressive shift toward protective associations was observed with increasing degrees of unsaturation, with polyunsaturated fatty acids (PUFAs), including omega-3, omega-6, and linoleic acid, demonstrating the most favorable profiles. Among amino acids, higher glutamine, alanine, valine and histidine levels were associated with a more severe asthma phenotype, whereas elevated levels of phenylalanine and tyrosine were linked to milder asthma presentations. Plasma glucose levels showed inverse associations with the odds of eosinophilic asthma and current wheeze, but were also correlated with lower β values of FVC. Lactate and glycoprotein acetylation were positively associated with exacerbation odds and poor lung function, while plasma citrate and albumin levels correlated with better asthma control and improved spirometry measures.

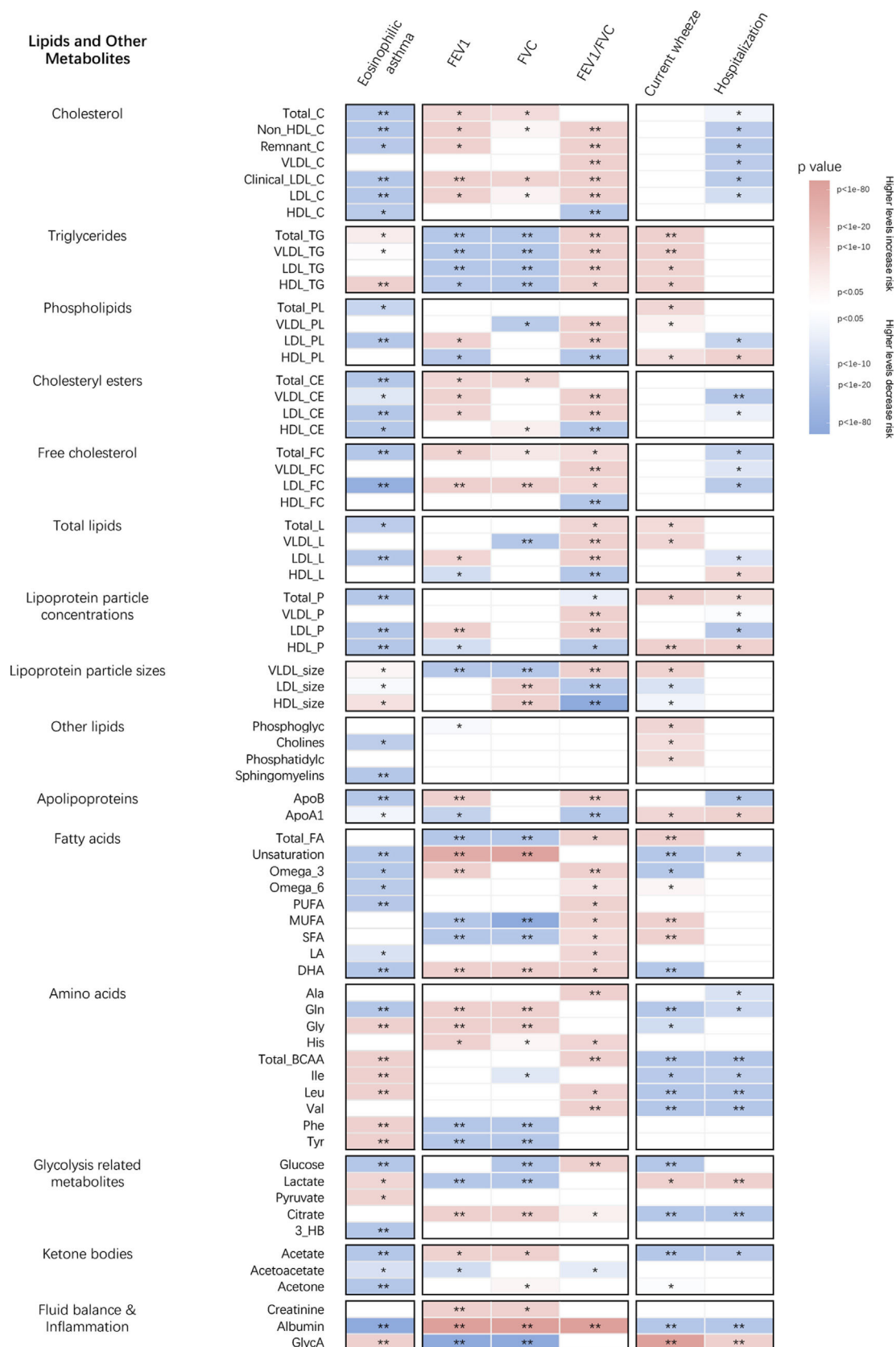


Fig. 1. Lipids and other metabolites associated with asthma phenotypes, lung function and clinical characteristics. Colors indicate the direction and magnitude of the associations between lipids and other metabolites and asthma phenotypes and exacerbation. Red denotes positive associations, blue denotes negative associations, and color intensity reflects the significance level ($-\log_{10}[P]$). Asterisks indicate significance: * P -value <0.05 ; ** P -value <0.001 . The model was adjusted for age, sex, race, education level, Townsend deprivation index, body mass index (BMI), smoking status, alcohol status, diet quality, physical activity, hypertension, diabetes and high cholesterol.

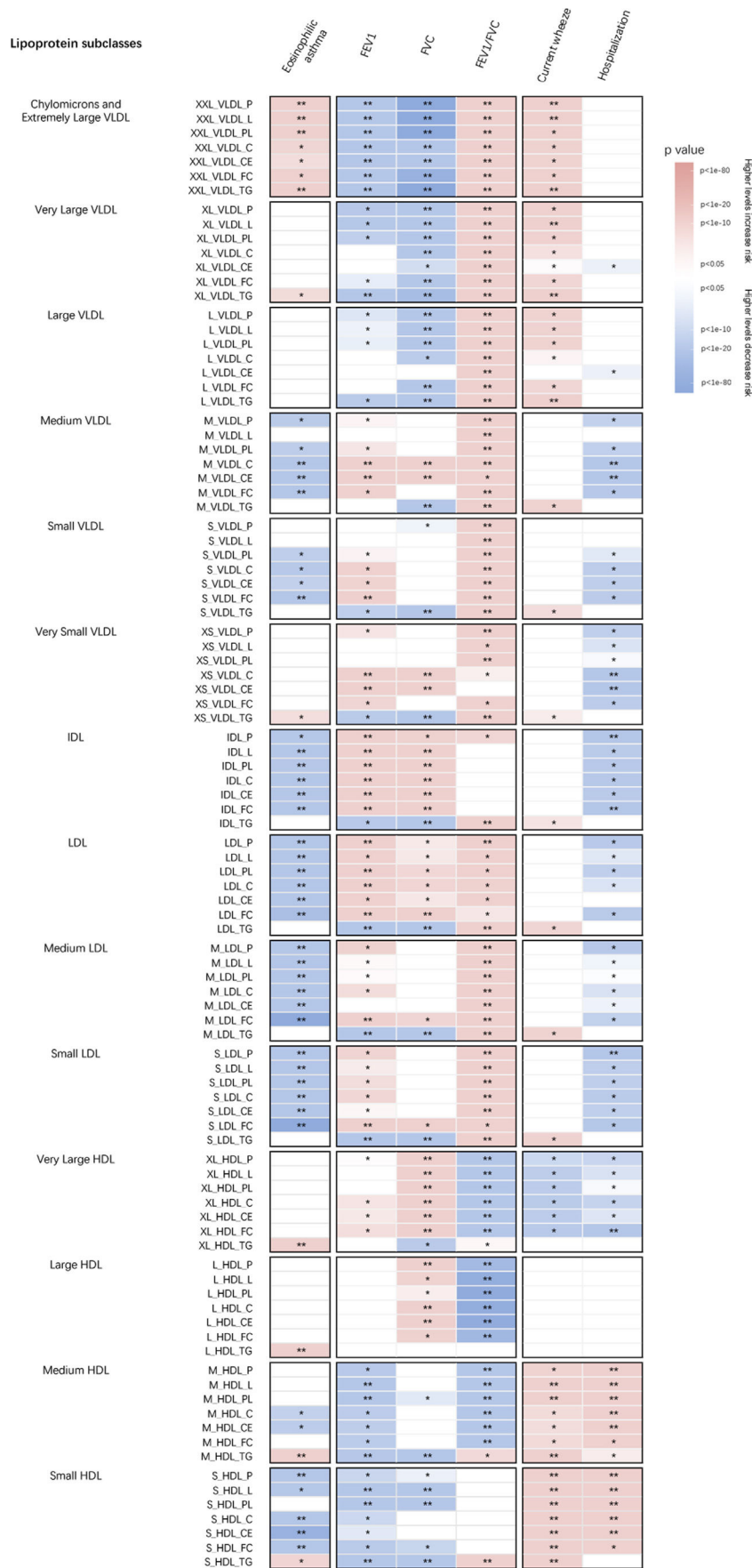


Fig. 2. Lipoprotein subclasses associated with asthma phenotypes, lung function and clinical characteristics. Colors indicate the direction and magnitude of the associations between lipoprotein subclasses and asthma phenotypes and exacerbation. Red denotes positive associations, blue denotes negative associations, and color intensity reflects the significance level ($-\log_{10}[P]$). Asterisks indicate significance: * P -value <0.05 ; ** P -value <0.001 . The model was adjusted for age, sex, race, education level, Townsend deprivation index, body mass index (BMI), smoking status, alcohol status, diet quality, physical activity, hypertension, diabetes and high cholesterol.

Our findings highlight distinct associations between plasma metabolic profiles and asthma phenotypes, suggesting underlying metabolic heterogeneity among asthmatic individuals. Notably, higher triglyceride concentrations and increased particle size of VLDL subclasses were consistently related to eosinophilic asthma, current wheeze, and impaired lung function, whereas smaller, denser lipoproteins such as LDL and HDL (excluding TG) demonstrated predominantly protective associations. These patterns suggest a density- and composition-dependent role of lipoproteins in asthma pathophysiology. In addition, a higher degree of fatty acid unsaturation was associated with favorable asthma profiles, supporting the potential anti-inflammatory properties of omega-3 and omega-6 fatty acids. Furthermore, amino acids showed variable associations with asthma outcomes, reflecting their complex involvement in metabolic and immune regulation.

Previous studies reported that total cholesterol, triglycerides, and LDL-cholesterol levels were positively associated with the risk of incident asthma, while HDL-cholesterol was shown to have converse association [8–10]. Our findings align partially with these observations, revealing subclass-specific trends in HDL and LDL components, which may reflect differing roles in immune modulation. Although HDL was often associated with favorable health outcomes, we discovered that certain HDL subclasses, specifically M-HDL and S-HDL, were associated with lower odds of eosinophilic asthma, yet also correlated with impaired lung function and increased risk of current wheeze. These seemingly paradoxical findings may partly explain the inconsistent associations reported in previous studies. For example, a cross-sectional analysis from the NHANES cohort ($n=7005$) found no significant relationship between HDL-C and current wheeze [11]. While several national studies reported that higher HDL-C levels were associated with increased FVC and FEV1 [12], a cohort study from China ($n=3978$) revealed the opposite trend, with elevated HDL-C related to accelerated lung function decline [13]. These discrepancies may stem from differences in study populations, asthma status, or unmeasured metabolic heterogeneity.

The mechanisms underlying these associations may involve complex immunometabolic interactions. Lipids such as LDL exert divergent effects on asthma pathophysiology. LDL has been shown to alleviate eosinophilic airway inflammation induced by house dust mites via receptor-mediated inhibition of dendritic cell-driven adaptive immune responses [14]. However, elevated LDL levels can disrupt the structure and function of pulmonary surfactant films [15] and are closely associated with obesity-related asthma [16]. These opposing effects suggest that distinct LDL-related components may act through different pathways, contributing to inconsistent findings in previous studies. To better understand these complex associations, our study separately evaluated the relationships between metabolites and inflammatory markers, lung function, and asthma exacerbations.

This study has several limitations. First, as metabolite levels were measured only once, without longitudinal tracking, potential dynamic changes over time remain unaccounted for. Second, blood samples were collected in non-fasting conditions and stored for extended periods prior to metabolomic profiling, which may introduce potentially inevitable bias. Third, the diagnosis of asthma was partly based on self-reported, perhaps leading to recall bias. Fourth, the UK Biobank cohort is predominantly composed of white British adults, which may limit the generalizability of our findings to more diverse populations. Finally, although smoking status and pack-years of smoking were included as covariates, the potential influence of smoking on asthma-related outcomes such as wheezing and hospitalization cannot be fully excluded. Despite these limitations, our study represents one of the largest and most comprehensive metabolomic investigations in asthma to date, characterizing phenotypic heterogeneity through multiple

outcomes. The findings highlight potential metabolic signatures of asthma subtypes and underscore the value of detailed lipoprotein subclass and multiple metabolites profiling in understanding disease mechanisms. Further prospective and experimental studies are warranted to validate these associations and clarify underlying pathways.

In conclusion, we discovered that a wide range of plasma metabolites, including lipids, fatty acids, amino acids, and glucose-related metabolites, were significantly associated with asthma phenotypes and exacerbation. These findings suggest potential biomarkers for asthma severity and offer new insights into the metabolic underpinnings of asthma pathogenesis.

CRediT authorship contribution statement

Qinyu Chang and Yiqun Zhu are joint first authors. Yan Zhang and Pinhua Pan obtained funding. Yan Zhang and Yiqun Zhu designed the study. YZhu and Yan Zhang collected the data. Huaying Liang and Zhuanxing Zhu performed data cleaning and verification. Dianwu Li and Ben Liu analyzed the data. Qinyu Chang, and Yan Zhang drafted the manuscript. Fengyu Lin and Ben Liu contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content and approved the final version of the manuscript. All authors have read and approved the final manuscript. Yan Zhang is the study guarantor.

Declaration of generative AI and AI-assisted technologies in the writing process

No artificial intelligence was involved in the study.

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Conflict of interest

The authors declare no conflict of interest.

Data availability

We thank the UK Biobank Access Management Team members for helping with data preparation.

E-data supporting the findings of this study are available from the UK Biobank; however, restrictions apply to the availability of

these data, which were used under license for the current study and are not publicly available (Reference No. 84979).

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version available at <https://doi.org/10.1016/j.arbres.2025.07.016>.

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