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Lipoprotein Particle Remodelling Mediates the Association Between MASLD and Incident Atopic Dermatitis: A Dual-Cohort Study Running head: Lipoprotein remodelling in MASLD–AD association

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Research Article

Keywords: atopic dermatitis, metabolic dysfunction-associated steatotic liver disease, circulating lipoprotein, UK biobank, mediation analysis

Posted Date: November 12th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11441585/v1

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Additional Declarations: No competing interests reported.

Lipoprotein Particle Remodelling Mediates the Association Between MASLD and Incident Atopic Dermatitis: A Dual-Cohort Study

Running head: Lipoprotein remodelling in MASLD–AD association

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Manuscript word count

2918 (body text; excludes abstract, references, tables and figure legends)

Tables: 1

Figures: 3

Supporting information

Supplementary Methods; Tables S1-S8

Abstract

Background： Adult atopic dermatitis (AD) is increasingly recognised to coexist with systemic metabolic abnormalities, but the metabolic phenotype associated with AD remains unclear. Conventional lipid measures have shown inconsistent associations with AD and may not fully capture its metabolic heterogeneity. Metabolic dysfunction-associated steatotic liver disease (MASLD) represents a clinically recognisable systemic metabolic phenotype with hepatic lipid involvement, yet evidence for its association with incident AD remains limited and inconsistent. We therefore aimed to investigate the association between MASLD and incident adult AD and to explore circulating metabolic traits, with particular emphasis on lipoprotein particle characteristics.

Methods: We analysed 364,674 UK Biobank participants and 69,423 individuals from a real-world cohort at the Third Xiangya Hospital of Central South University. Cox proportional hazards models with sequential adjustment were used to evaluate the association between MASLD and AD. Exploratory mediation analyses were performed in the UK Biobank, and the hospital cohort was used to assess the reproducibility of the MASLD-AD association.

Result： In both cohorts, MASLD was associated with a higher risk of incident AD 2(HR=1.11, 95% CI: 1.03-1.21, P=0.009 in UKB cohort; HR=1.21, 95% CI: 1.07-1.35, P=0.002 in hospital cohort), but the association was attenuated after adjustment for BMI (HR=1.05, 95% CI: 0.94-1.17, P=0.418) (HR=1.06, 95% CI: 0.93-1.22, P=0.379). In the hospital cohort, only HDL-C was inversely associated with AD risk, whereas total cholesterol, triglycerides and LDL-C showed no significant associations. Exploratory mediation analyses in the UK Biobank identified multiple lipoprotein particle-related signals spanning particle size, particle concentration, lipid composition and apolipoprotein balance. Among these, LDL-size (30.75%), the ApoB/A1 (-22.13%) and xs-VLDL-P (-25.48%), showed particularly prominent indirect effects.

Conclusions: MASLD was associated with incident adult AD, although the association was substantially attenuated after adjustment for BMI. Particle-level lipoprotein traits revealed marked metabolic heterogeneity that were not reflected by a uniform lipid. These findings highlights the metabolic heterogeneity of adult AD and support further

investigation of circulating lipoprotein phenotypes in this context.

Keywords: atopic dermatitis; metabolic dysfunction-associated steatotic liver disease; circulating lipoprotein; UK biobank; mediation analysis

Introduction

Atopic dermatitis (AD) is one of the most common chronic inflammatory skin diseases worldwide and imposes a substantial disease burden[1-3]. AD is increasingly recognised as a systemic inflammatory disorder associated with metabolic comorbidities rather than as a skin-limited disease[4]. Accumulating evidence suggests that adult AD frequently coexists with systemic metabolic comorbidities, including obesity, dyslipidaemia, insulin resistance and metabolic syndrome[4-9]. However, available evidence does not support a uniform metabolic phenotype, and the strength of these associations varies across populations[10-12]. Consistent with this uncertainty, current American Academy of Dermatology (AAD) guidelines consider the association between AD and metabolic syndrome as a whole to be inconclusive and do not provide specific recommendations for metabolic screening[4]. Thus, an important clinical problem remains unresolved: although metabolic abnormalities are common in adults with AD, it remains unclear which features characterise the systemic metabolic phenotype associated with AD susceptibility.

Lipid metabolism plays a fundamental role in maintaining epidermal barrier integrity and regulating immune responses[13]. Circulating lipid abnormalities have been implicated in several inflammatory diseases, including psoriasis, inflammatory bowel disease, rheumatoid arthritis[14]. In AD, however, previous studies have predominantly focused on abnormalities in epidermal lipid composition, particularly alterations in ceramides, cholesterol, and free fatty acids[15, 16]. Studies based on conventional lipid measures have yielded inconsistent findings in AD. Higher total cholesterol and triglycerides and lower high-density lipoprotein cholesterol (HDL-C) have been reported in some obese or paediatric populations, whereas other studies found no significant associations or even inverse patterns in adults with AD[17-20]. These discrepancies may partly reflect the limited biological resolution of conventional lipid measures, which may not fully capture the complex systemic lipid phenotype of adult AD. More granular characterisation of circulating lipoprotein profiles may therefore provide further insight into the systemic metabolic heterogeneity of adult AD.

Against this background, metabolic dysfunction-associated steatotic liver disease (MASLD) provides a clinically recognisable phenotype of systemic metabolic

dysfunction with prominent hepatic lipid involvement[21]. MASLD is characterised by disturbance in lipid handling, including very-low-density lipoprotein (VLDL) secretion, apolipoprotein B (ApoB)-containing lipoprotein metabolism and alterations of circulating lipoprotein profiles[21, 22]. Therefore, it may provide a clinically meaningful entry point for evaluating systemic metabolic dysfunction in adult AD. However, epidemiological evidence linking fatty liver disease with incident AD remains limited and directionally inconsistent. Earlier studies reported a higher prevalence of fatty liver among patients with AD[23, 24], whereas a large population-based cohort from Taiwan found a modestly lower risk of incident AD among patients with non-alcoholic fatty liver disease[3]. Whether MASLD is associated with incident adult AD, and which circulating lipoprotein characteristics accompany this association, therefore remain unclear.

We therefore integrated data from the UK Biobank and a real-world clinical cohort from the Third Xiangya Hospital of Central South University. We first evaluated the association between MASLD and incident AD and then explored circulating metabolic traits potentially involved in this association, with particular emphasis on lipoprotein-related measures. Finally, we assessed whether the association showed a consistent pattern in the hospital cohort and examined the corresponding associations of routinely measured lipid parameters with incident AD. This study aimed to characterise the systemic lipid-metabolic phenotype of adult AD across complementary population settings.

Materials and Methods

Study design and participants

This dual-cohort study used data from the UK Biobank (UKB) and an external validation cohort from the Third Xiangya Hospital of Central South University, China. The UK Biobank (application No. 679050) recruited approximately 500,000 adults aged 40-70 years across the United Kingdom between 2006 and 2010. Participants of European ancestry with available baseline and follow-up data were eligible. Individuals with prevalent AD, other chronic liver diseases (seen in **Supplementary Table S1**), elevated alanine aminotransferase (ALT), or missing key variables were excluded. A

total of 364,674 participants were included. Follow-up continued until incident AD, death, loss to follow-up, or 31st December 2024, whichever occurred first.

External validation was performed using a real-world clinical cohort derived from the health examination system of the Third Xiangya Hospital between 1st January 2016 and 31st December 2023. After excluding duplicate records, prevalent AD and participants with missing key variables, 69,423 individuals were included. Detailed participant selection is shown in **Figure 1** and supplementary method. The study was approved by Ethics Committee of the Third Xiangya Hospital of Central South University, with the ethics approval number [fast 25065].

Assessment of Metabolic Dysfunction-Associated Steatotic Liver Disease

In the UK Biobank, hepatic steatosis was assessed using the Fatty Liver Index (FLI) (seen in **supplementary method**). Participants with FLI ≥60 were classified as steatotic liver disease, whereas those with FLI <60 and no other liver disease were eligible for non-SLD group. MASLD was defined as hepatic steatosis in the presence of at least one cardiometabolic risk factor and alcohol consumption below established MASLD thresholds **(shown in Figure 1)**. In the hospital cohort, MASLD was defined using imaging-confirmed hepatic steatosis, cardiometabolic criteria and the same alcohol-consumption thresholds. Detailed definitions, alcohol thresholds, chronic liver disease exclusions and missing-data imputation are provided in the **Supplementary Methods**.

Definition of Outcomes and Covariates

The primary outcome was incident AD. In the UKB cohort, AD was defined through self-reported medical condition, hospital inpatient records or death registry data using ICD-10 code L20. For patients with multiple AD records, the earliest recorded date was defined as the date of disease onset. In the hospital cohort, AD was defined from outpatient and inpatient diagnostic records **(Supplementary Table S2).** Potential confounders included age, sex, ethnicity, education, BMI, socioeconomic status, smoking status, alcohol intake etc. Detailed covariate definitions and categorizations are provided in **Supplementary Table S2**.

Mediation analysis and external validation

To explore potential metabolic pathways linking MASLD and incident AD, mediation analyses were performed using circulating metabolic biomarkers measured in the UKB, particularly lipoprotein-related traits **(Supplementary Table S4)**. Biomarkers associated with both MASLD and incident AD were selected as candidate mediators. Average causal mediation effects, average direct effects and mediation proportions were estimated.

External validation was performed in the Third Xiangya Hospital cohort to assess the consistency and clinical applicability of the findings. Since nuclear magnetic resonance (NMR)- derived lipoprotein particle measurements were unavailable in this cohort, analyses focused on routinely measured lipid biomarkers. The validation analyses were intended to assess directional consistency and clinical detectability rather than validate the underlying biological mechanisms.

Statistical analysis

All statistical analyses were performed using R software (version 4.5.2). Continuous variables are presented as mean (standard deviation) and categorical variables as number (%). Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the association between MASLD and incident AD. Model 1 was adjusted for age and sex. Model 2 was additionally adjusted for ethnicity, education, smoking status, pack years of smoking, alcohol intake frequency, daily alcohol intake and townsend deprivation index. Model 3 was further adjusted for BMI. Subgroup analyses were conducted according to age, sex and BMI categories. Interactions were evaluated by including multiplicative interaction terms in the models. All P values were two-sided, with $P < 0.05$ considered statistically significant.

Results

Baseline characteristics of the study populations

A total of 364,674 UK Biobank participants were included, of whom 2,756 developed AD during the follow-up period. The Third Xiangya hospital cohort included a total of

69,423 participants of whom 1,475 had AD and 67,948 did not. The demographic and baseline characteristics are shown in **Table 1**.

In the UKB cohort, participants who developed AD were slightly older[57.11 (7.90) years vs. 56.79 (8.05) years, P <0.05]. The proportion of females was higher in the AD group [59.4% vs. 57.4%, P < 0.05]. Significant differences were also observed in educational attainment and smoking-related variables (P<0.05), whereas ethnicity, waist circumference and alcohol-related variables did not differ significantly between groups.

In the hospital cohort, participants who developed AD had higher BMI [23.96 (3.27) kg/m² vs. 23.57 (3.22) kg/m², P < 0.001] and waist circumference than those without AD. Significant differences were also observed in sex distribution, educational attainment and smoking-related variables (P< 0.05), whereas alcohol-related variables did not differ significantly.

Association between MASLD and incident AD across the two cohorts

In the UKB cohort, MASLD was associated with an increased risk of incident AD in both Model 1 (HR=1.12, 95% CI: 1.03-1.21, P=0.005) and Model 2(HR=1.11, 95% CI: 1.03-1.21, P=0.009). However, when BMI was further adjusted in Model 3, the association weakened and lost statistical significance (HR=1.05, 95% CI: 0.94-1.17, P=0.418) **(Figure 2A)**.

A similar pattern was observed in the hospital cohort. In both Model 1 (HR=1.19, 95% CI: 1.06-1.34, P=0.003) and Model 2 (HR=1.21, 95% CI: 1.07-1.35, P=0.002), MASLD was associated with an increased risk of AD. When BMI was further adjusted in Model 3, the association weakened and was no longer statistically significant (HR=1.06, 95% CI: 0.93-1.22, P=0.379) **(Figure 2B)**.

In subgroup analysis, the association between MASLD and incident AD was generally consistent across age, sex and BMI subgroups, with no evidence of significant interaction (all P for interaction >0.05). **(Figure 2C, D)**.

Lipoprotein and metabolic characteristics related to the MASLD-AD association

After predefined screening, 12 metabolic traits were retained for exploratory

mediation analyses and were grouped into three biological categories: lipoprotein particle-related traits, inflammatory markers and energy metabolism-related metabolites **(Supplementary Table S4)**.Lipoprotein particle-related traits constituted the major component of the retained mediators and spanned multiple dimensions of lipoprotein metabolism, including particle size, particle concentration, lipid composition and apolipoprotein balance.

Average Diameter for Low-Density Lipoprotein Particles (LDL size) showed the largest positive mediation proportion(30.75%), Other positive mediators included total cholesterol and triglycerides to total lipids ratio in large very-low-density lipoprotein (TG/TL (L-VLDL)). Several lipoprotein-related traits showed directionally inconsistent mediation estimates, including concentration of very small VLDL particles (xs-VLDL-P) (-25.48%), apolipoprotein B/apolipoprotein A1 ratio (ApoB/A1) (-22.13%), concentration of LDL Particles (LDL-P) (-16.78%),total free cholesterol and LDL cholesterol.

Beyond lipoprotein-related traits, C-reactive protein (CRP)(17.07%) and citrate (10.82%) showed positive mediation proportions, while lactate (-15.58%) and pyruvate (-14.38%) exhibited indirect effects in the opposite direction to the overall MASLD-AD association. **(Figure 3A).**

In parallel with NMR-based analyses in the UK Biobank, routinely measured lipid parameters were examined in the hospital cohort to provide complementary clinical information on circulating lipid profile **(Figure 3B)**. In the adjusted model c, HDL-C was inversely associated with incident AD (HR 0.64, 95% CI 0.43–0.95), whereas total cholesterol (HR 1.25, 95% CI 0.89–1.76), triglycerides (HR 0.92, 95% CI 0.79–1.07) and LDL-C (HR 0.86, 95% CI 0.61–1.22) were not statistically significant **(Figure 3B; Table S7).**

Discussion

In this dual-cohort study, MASLD was associated with an increased risk of incident adult AD after adjustment for demographic, lifestyle and socioeconomic factors, although the association was attenuated after additional adjustment for BMI. Exploratory metabolic analyses identified multiple lipoprotein-related signals

involving particle size, particle concentration, lipid composition and apolipoprotein balance. In the hospital cohort, only HDL-C was associated with incident AD, whereas total cholesterol, triglycerides and LDL-C were not.

The association between adult AD and systemic metabolic dysfunction remains difficult to define. Current AAD guidelines consider the overall association between AD and metabolic syndrome to be inconclusive, while previous studies of conventional lipid measures have reported positive, null and inverse associations[4, 10, 11]. Epidemiological findings for fatty liver disease are similarly inconsistent. Earlier studies reported a higher prevalence of fatty liver among patients with AD[23, 25], whereas a cohort from Taiwan reported a modestly lower risk of incident AD among individuals with non-alcoholic fatty liver disease, with a stronger inverse association among those younger than 40 years[3]. Our findings may help contextualise these conflicting observations. Lipoprotein-related traits showed directionally discordant indirect effects. This pattern suggests that AD-associated metabolic abnormalities may not follow a simple unindirectional lipid pattern.

In both cohorts, the association between MASLD and incident AD was observed before additional adjustment for BMI but was markedly attenuated thereafter. MASLD commonly occurs within a broader metabolic context characterised by adiposity, insulin resistance, dysregulated lipid metabolism and chronic inflammation[26, 27]. This suggests that adiposity accounts for part of the observed MASLD-AD association, rather than MASLD representing an isolated hepatic effect. In the UKB cohort, interpretation of the BMI-adjusted model requires additional caution, because BMI and waist circumference are incorporated into the FLI used to define hepatic steatosis[28]. However, a similar attenuation was observed in the hospital cohort, where hepatic steatosis was defined by imaging. This suggests that this pattern cannot be attributed solely to the FLI-based definition. Therefore, these findings support interpreting MASLD as a clinically recognisable systemic metabolic phenotype with hepatic involvement, while indicating that its association with adult AD is closely intertwined with adiposity.

The particle-level analyses provide a more granular view of this metabolic heterogeneity. Conventional lipid measures and particle-level lipoprotein traits capture different aspects of lipid metabolism. LDL-C, for example, reflects the amount of

cholesterol carried within LDL particles but does not directly indicate how many LDL particles are present or how large those particles are. Because the cholesterol content of individual LDL particles varies substantially, similar LDL-C concentrations can coexist with markedly different LDL particle numbers and size distributions[29, 30]. NMR-based profiling further distinguishes several dimensions of lipoprotein metabolism, including particle concentration, particle size, subclass distribution and lipid composition. In our exploratory analyses, mean LDL particle diameter showed the largest positive indirect effect, whereas LDL particle concentration, very-small VLDL particle concentration, the ApoB/ApoA1 ratio and several cholesterol-related traits showed indirect effects in the opposite direction. These directionally discordant effects should not be interpreted as evidence that individual lipoprotein traits exert protective or harmful effects in isolation[31]. Lipoprotein subclasses are metabolically interconnected, and alterations in particle size, particle number and lipid composition do not necessarily occur in parallel[32-34]. This distinction may be particularly relevant to AD. HDL isolated from patients with AD has previously shown altered lipid and apolipoprotein composition together with impaired immunomodulatory function[35]. Overall, these findings suggest that the metabolic information relevant to AD may partly reside in how circulating lipids are organised across lipoprotein particles and subclasses, rather than simply in whether conventional lipid concentrations are increased or decreased. However, since conventional lipid measures and NMR-derived traits were assessed in different cohorts in our studies, we cannot determine whether particle-level profiling provides incremental clinical information beyond routine lipid testing.

The observed metabolic signals may provide a basis for several testable mechanistic hypotheses. Altered stratum corneum lipid composition, ceramide abnormalities and impaired barrier function are central pathological features of AD[15, 16]. Beyond their role in lipid transport, circulating lipoproteins also participate in immune activation, inflammatory signalling, oxidative stress responses and cholesterol homeostasis in lipid rafts[36, 37]. Systemic lipid disturbances may therefore influence AD-relevant pathways through both immune and epidermal barrier mechanisms[38-40], although these mechanisms have not been directly demonstrated in MASLD-associated AD. Our exploratory analyses also identified indirect effects involving CRP and metabolites

related to central energy metabolism: CRP and citrate showed positive indirect effects, whereas lactate and pyruvate showed effects in the opposite direction[41]. This mixed pattern argues against a single linear inflammatory or metabolic pathway and instead suggests a broader systemic metabolic milieu. We therefore propose that MASLD-associated alterations in circulating lipoprotein characteristics may interact with epidermal lipid homeostasis and cutaneous immune response. This framework remains hypothesis-generating and requires direct experimental validation.

The clinical implication of these findings is not that advanced lipoprotein profiling should replace routine metabolic assessment in adults with AD. MASLD in this setting should not be viewed as an adiposity-independent hepatic risk factor. Rather, it may identify patients with broader systemic metabolic burden in which hepatic steatosis, adiposity and lipid abnormalities coexists. Conventional lipid concentrations alone may not adequately represent the lipid-related metabolic heterogeneity associated with AD. These findings do not support additional lipid testing or routine lipoprotein profiling in clinical practice. Conversely, clinicians managing patients with MASLD should remain aware that chronic inflammatory skin diseases, including AD, may coexists within the same metabolic background. Overall, our findings support a more integrated view of adult AD that consider both cutaneous disease and systemic metabolic health.

This study has several strengths, including the use of two complementary cohorts, prospective assessment of incident AD, and detailed NMR-based profiling of circulating lipoprotein characteristics. By combining MASLD with particle-level lipid measures, this study provides a multilevel view of the metabolic heterogeneity associated with adult AD.

Several limitations should also be acknowledged. First, MASLD was defined slightly differently across the two cohorts. This may have introduced differential exposure misclassification and may limit direct comparison of effect estimates between cohorts. Second, because BMI is incorporated into the FLI, interpretation of the BMI-adjusted UKB model requires caution and should not be regarded as estimating a MASLD effect independent of adiposity. Third, AD ascertainment differed between cohorts. Mild or untreated AD may therefore have been underascertained. Finally, hospital cohort lacked NMR-derived lipoprotein particle data, preventing direct replication of the particle-

level findings and head-to-head comparison with conventional lipid measures.

Further studies should validate the MASLD-AD associations in independent populations and examine its generalisability across age, sex, ethnicity and adiposity subgroups. Experimental studies are still required to determine whether changes in MASLD-related lipoprotein particles directly affect the lipid homeostasis, barrier function, and inflammatory response of keratinocytes. Thereby, it can provide more direct biological evidence for the candidate mechanism of lipoprotein remodeling involved in AD susceptibility.

Conclusion

This study shows that MASLD is associated with an increased risk of incident AD, although this association was substantially attenuated after accounting for adiposity. Particle-level analyses revealed heterogeneous lipoprotein-related signals were not reflected by a uniform pattern of conventional lipid abnormalities. These findings suggest that the systemic metabolic phenotype associated with adult AD is more complex than conventional dyslipidaemia alone and may involve heterogeneity in circulating lipoprotein characteristics. Further studies are needed to validate these patterns and determine their biological and clinical relevance.

Abbreviations

AD: Atopic dermatitis

MASLD: Metabolic dysfunction-associated steatotic liver disease

ACME: Average causal mediation effect

ADE: Average direct effect

ALT: Alanine aminotransferase

ApoA1: Apolipoprotein A1

ApoB: Apolipoprotein B

ApoB/ApoA1: Ratio of apolipoprotein B to apolipoprotein A1

BMI: Body mass index

CHO: Total cholesterol

CI: Confidence interval

CRP: C-reactive protein

FLI: Fatty Liver Index

GGT: Gamma-glutamyl transferase

HDL: High-density lipoprotein

HDL-C: High-density lipoprotein cholesterol

HR: Hazard ratio

ICD-9: International Classification of Diseases, Ninth Revision

ICD-10: International Classification of Diseases, Tenth Revision

LDL: Low-density lipoprotein

LDL-C: Low-density lipoprotein cholesterol

LDL-P: Concentration of low-density lipoprotein particle

LDL size: Average diameter of low-density lipoprotein particles

NMR: Nuclear magnetic resonance

non-SLD: Participants without steatotic liver disease (reference group)

SD: Standard deviation

SLD: Steatotic liver disease

TG: Triglycerides

UKB: UK Biobank

VLDL: Very-low-density lipoprotein

WC: Waist circumference

LDL size: Average Diameter for LDL Particles

LDL-P: Concentration of LDL Particles

XS-VLDL-P: Concentration of very small very-low-density lipoprotein particles

TG/TL (L-VLDL): Triglycerides to total lipids ratio in large very-low-density lipoprotein

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki. All UK Biobank participants provided informed consent at enrolment. The UK Biobank study was approved by the North West Multi-centre Research Ethics Committee, and data access for the present study was granted under application number 679050. The

hospital-based component was a retrospective cohort study using routinely collected clinical data from the Third Xiangya Hospital of Central South University. The hospital-based study was approved by the Ethics Committee of the Third Xiangya Hospital of Central South University, with the ethics approval number [approval No. fast 25065]. Because the study involved secondary analysis of existing clinical data without additional intervention or participant contact, and used de-identified data for analysis, the requirement for individual informed consent was waived by the Ethics Committee of the Third Xiangya Hospital of Central South University.

Consent for publication

Not applicable.

Availability of data and materials

UK Biobank data are available to approved researchers through the UK Biobank data access process (application 679050). Individual-level data from the Third Xiangya Hospital are not publicly available because they contain de-identified health examination records and are subject to institutional ethics and privacy restrictions. Aggregated data supporting the findings of this study are included in this article and its supporting information.

Competing interests

The authors declare no competing interests.

Funding

This study was supported by the National Natural Science Foundation of China (Grant No.82674511), the Hunan Provincial Health Commission Health Research Key Project (Grant No. 20256627), Science and Technology Innovation Program of Hunan Province (Grant No. 2024RC3064), Wisdom Accumulation and Talent Cultivation Project of the Third Xiangya Hospital of Central South University (Grant No. YX202214).

Author's contribution

YX: Conceptualization, Visualization, Methodology, Writing - review & editing; **YZ:** Data curation, Formal analysis, Visualization, Writing – original draft; **ZF:** Data curation, Investigation, Methodology; **YY:** Data curation, Investigation, Methodology; **NW:** Investigation, Methodology; **FX:** Investigation, Methodology; **HL:** Resources, Data curation; **WF:** Data curation, Conceptualization, Project administration; **JZ:** Resources, Supervision, Funding acquisition, Project administration.

Acknowledgments

We sincerely appreciate the participants and staff of the UK Biobank and the Third Xiangya Hospital of Central South University for their invaluable contributions and for providing the data that made this study possible.

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

During the preparation of this manuscript, the authors used ChatGpt (OpenAI) solely to improve readability and language. All authors reviewed and edited the content as

needed and take full responsibility for the accuracy and integrity of the published article.

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573 **Table 1** Baseline demographic and clinical characteristics of participants in the UK
574 Biobank and Third Xiangya Hospital cohorts.

Variables	Non-Atopic Dermatitis N=361918	Atopic Dermatitis N=2756	P-value
UKB			
Age	56.79 (8.05)	57.11 (7.90)	<0.05
Sex			
Female	207578 (57.4)	1638 (59.4)	<0.05
Male	154340 (42.6)	1118 (40.6)	
Ethnic			
Any other white background	12895 (3.6)	106 (3.8)	0.637
British	339251 (93.7)	2567 (93.1)	
Irish	9414 (2.6)	80 (2.9)	
White	358 (0.1)	3 (0.1)	
Education			<0.05
A levels/AS levels or equivalent	19814 (5.5)	160 (5.8)	
College or University degree	119352 (33.0)	879 (31.9)	
CSEs or equivalent	13249 (3.7)	118 (4.3)	
None of the above	61583 (17.0)	508 (18.4)	
NVQ or HND or HNC or equivalent	45405 (12.5)	309 (11.2)	
O levels/GCSEs or equivalent	48011 (13.3)	396 (14.4)	
Other professional qualifications eg: nursing, teaching	54504 (15.1)	386 (14.0)	
Townsend Deprivation Index	-1.53 (2.95)	-1.58 (2.88)	0.442
BMI	27.32 (4.81)	27.59 (5.01)	<0.05
Waist Circumference	89.62 (13.47)	89.93 (13.59)	0.233
Smoking Status			<0.05
Current	32098 (8.9)	264 (9.6)	

Variables	Non-Atopic Dermatitis N=361918	Atopic Dermatitis N=2756	P-value
Never	206807 (57.1)	1476 (53.6)	
Prefer not to answer	1108 (0.3)	7 (0.3)	
Previous	121905 (33.7)	1009 (36.6)	
Pack Years of Smoking	19.88 (16.43)	20.54 (16.12)	<0.05
Alcohol Intake Frequency			0.99
Daily or almost daily	51496 (14.2)	398 (14.4)	
Never	27705 (7.7)	210 (7.6)	
Once or twice a week	105998 (29.3)	797 (28.9)	
One to three times a month	46770 (12.9)	359 (13.0)	
Special occasions only	44956 (12.4)	335 (12.2)	
Three or four times a week	84993 (23.5)	657 (23.8)	
Daily Alcohol Intake	7.64 (7.76)	7.60 (7.67)	0.814

Third Xiangya Hospital cohort (continued)

Variables	Non-Atopic Dermatitis N=67948	Atopic Dermatitis N=1475	P-value
The Third Xiangya Hospital			
Age	43.36 (13.06)	43.17 (11.81)	0.582
Sex			
Female	31166 (45.9)	614 (41.6)	0.001
Male	36782 (54.1)	861 (58.4)	
Education			<0.001
Elementary School or below	1428 (2.1)	6 (0.4)	
Junior High School	5134 (7.6)	43 (2.9)	
Senior High School or technical secondary school	10850 (16.0)	144 (9.8)	

Variables	Non-Atopic Dermatitis N=67948	Atopic Dermatitis N=1475	P-value
University or junior college	42036 (61.9)	969 (65.7)	
Graduate degree or above	8500 (12.5)	313 (21.2)	
BMI	23.57 (3.22)	23.96(3.27)	<0.001
Waist Circumference	80.67 (9.72)	81.84 (9.86)	<0.001
Smoking Status			0.002
Never	50383 (74.1)	1151 (78.0)	
Previous	2075 (3.1)	44 (3.0)	
Current	15490 (22.8)	280 (19.0)	
Alcohol Intake Frequency			0.062
Never	48205 (70.9)	1045 (70.8)	
Previous	899 (1.3)	18 (1.2)	
Once to twice times a week	15316 (22.5)	357 (24.2)	
Three to five times a week	2560 (3.8)	44 (3.0)	
Six to seven times a week	968 (1.4)	11 (0.7)	
Number of Cigarettes Daily	3.60 (7.67)	2.92 (6.93)	0.001
Daily Alcohol Intake	3.21 (8.90)	3.07 (8.15)	0.536

577 Data are presented as mean (standard deviation) or n (%). AD, atopic dermatitis; BMI,
578 body mass index; UKB, UK Biobank.

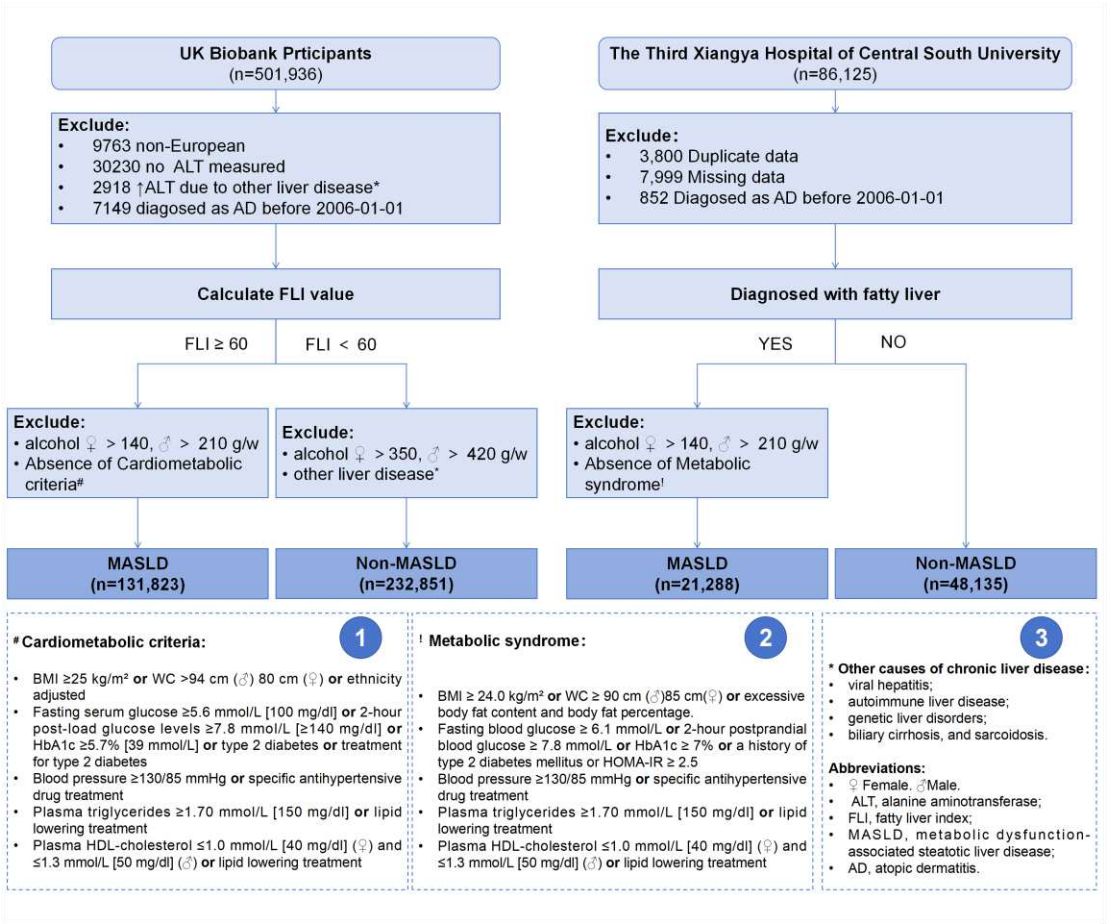


Figure 1. Study flow chart for the UK Biobank and Third Xiangya Hospital cohorts. The flow chart summarises participant selection, exposure classification and the final analytical cohorts. Detailed MASLD definitions, cardiometabolic criteria, alcohol thresholds and liver disease exclusions are provided in the Supplementary Methods.

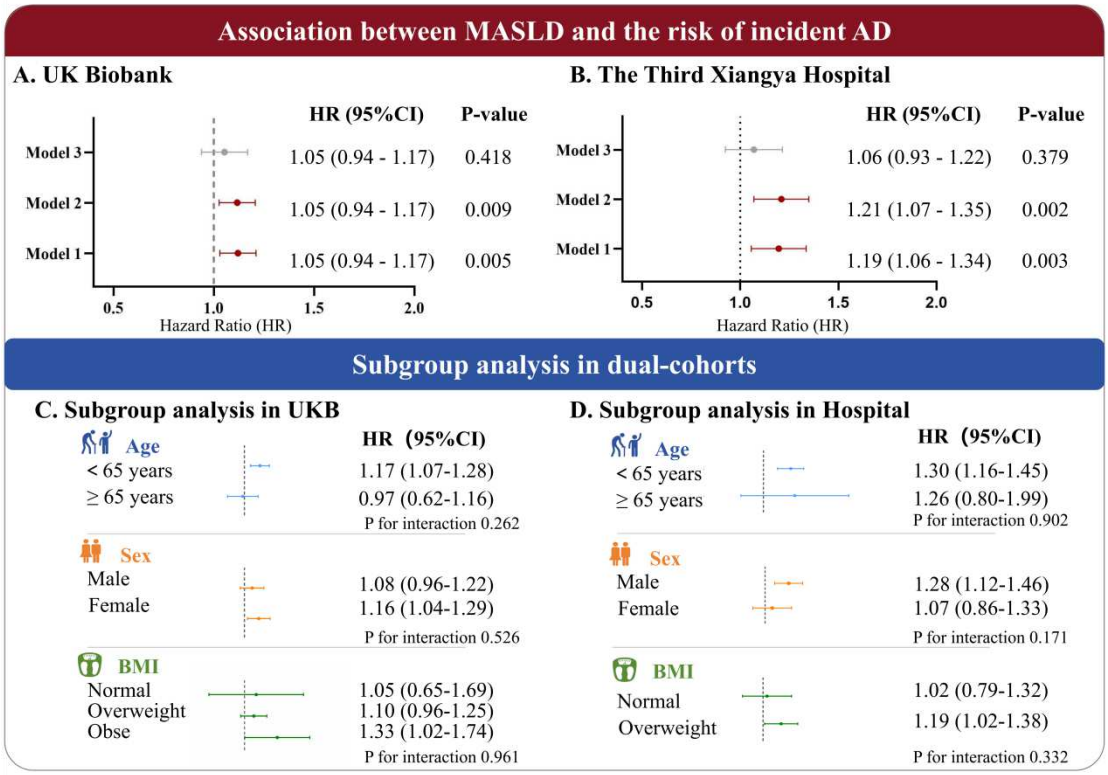


Figure 2. Association between MASLD and the risk of incident atopic dermatitis in the UKB and the Third Xiangya Hospital cohorts.

Note: Model 1: Adjusted for age and sex; Model 2: Adjusted for age, sex, ethnicity, education, smoking status, pack years of smoking, alcohol intake frequency, daily alcohol intake, and income; Model 3: Adjusted for all variables in Model 2 plus Body Mass Index (BMI). AD, atopic dermatitis; BMI, body mass index; CI, confidence interval; HR, hazard ratio; MASLD, metabolic dysfunction-associated steatotic liver disease.

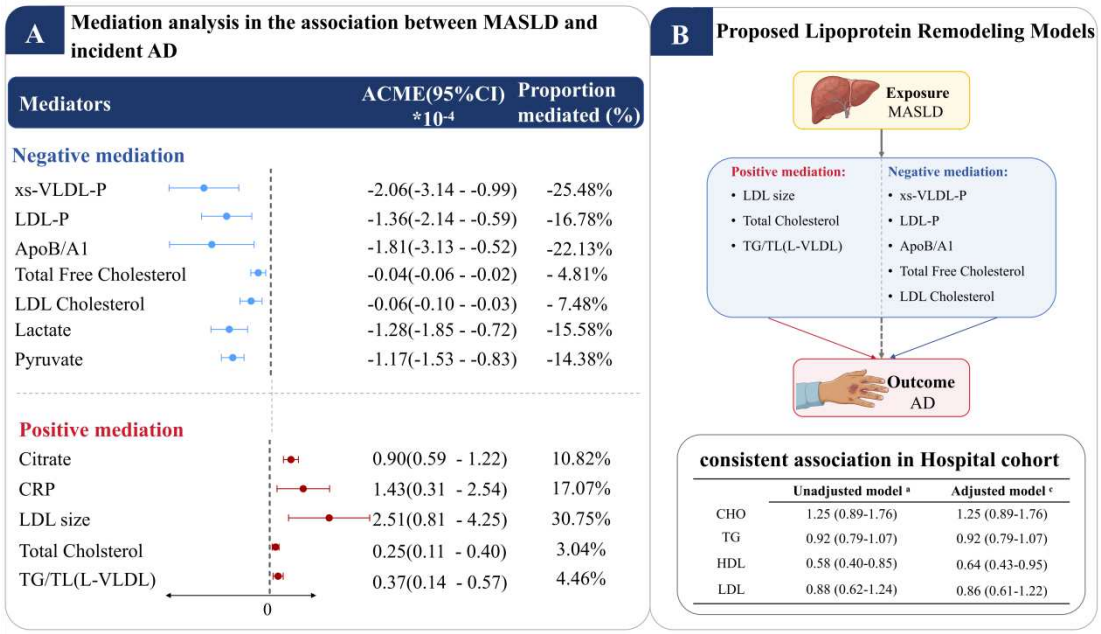


Figure 3. Lipoprotein remodeling metabolites in the association between MASLD and incident AD

Metabolic mediation signals and routine lipid biomarkers in the MASLD-AD association. (A) Average causal mediation effects (ACMEs) and 95% confidence intervals for 12 candidate metabolic mediators identified in the UK Biobank. (B) MASLD-associated lipoprotein particle remodelling may contribute to AD susceptibility through heterogeneous particle-level metabolic pathways. In the external hospital cohort, HDL-C was inversely associated with incident AD, whereas total cholesterol, triglycerides and LDL-C were not significantly associated with AD risk after adjustment. These findings suggest that routine lipid concentrations did not fully recapitulate the particle-level metabolic pattern identified by NMR profiling. Note: xs-VLDL-P, concentration of very small VLDL particles; LDL-P, concentration of LDL particles; ApoB/A1, apolipoprotein B to apolipoprotein A1 ration; LDL, low density lipoprotein; CRP, C-reactive protein; LDL size, average diameter for LDL particles; TG/TL(L-VLDL), Triglycerides to total lipids ratio in large very-low-density lipoprotein. unadjusted model: included no covariates.; Adjusted Modelc:adjusted for all covariates.

Supplementary Files

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