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ORIGINAL RESEARCH

# Causal Effects of Lipids-Related Metabolites on Androgenic Alopecia: A Mendelian Randomization Study

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**Purpose:** To investigate whether increased levels of lipids-related metabolites (LRMs) result in androgenic alopecia (AGA).

**Patients and Methods:** A two-sample Mendelian randomization (MR) study was designed, and single nucleotide polymorphisms (SNPs) respectively related to nine LRMs were selected from the genome-wide association study (GWAS) dataset. An MR analysis was performed to assess the causal association between LRMs and AGA.

**Results:** Through the fixed-effect inverse variance weighting (IVW) method, MR analysis indicated that Apolipoprotein B (ApoB), low-density lipoprotein (LDL), and very-low-density lipoprotein (VLDL) had a causal relationship with AGA. No obvious heterogeneity or pleiotropy was observed.

**Conclusion:** The risk of AGA increases significantly when the serum levels of ApoB, LDL, and VLDL increase. This causal relationship is solid and free of interference from confounding factors.

**Keywords:** androgenic alopecia, apolipoprotein B, VLDL, LDL

## Introduction

Non-cicatricial alopecia is one of the most common diseases in daily dermatology practice and can lead to a number of psychological disorders such as anxiety, depression, and distress.[1,2] Androgenic alopecia (AGA) is the most prevalent type of non-cicatricial alopecia. AGA manifests as gradually progressive hair loss in the front hairline or vertex area, which is believed to result from the excessive sensitivity of hair follicles (HFs) to androgen or elevated androgen levels.[3] Minimization of HF and increased proportion of vellus hair are the two main features of AGA.

Interestingly, several studies have reported abnormal levels of multiple lipids in AGA patients.[4] AGA is also considered an indicator of a higher risk of cardiovascular disease, the occurrence of which is closely related to lipid profile levels in blood.[5,6] Although the correlation between AGA and lipid profiles has been investigated and discussed, the exact causal relationship between AGA and abnormal levels of lipids-related metabolites (LRMs) such as Apolipoprotein B (ApoB), low-density lipoprotein (LDL), and very-low-density lipoprotein (VLDL) remains unclear or controversial. Let alone it is inconsistent that AGA patients have a higher serum lipid profile, whereas androgen, which is a major cause of AGA, is negatively regulated by lipids.[7,8]

To test whether the elevated levels of LRMs results in or from AGA, we applied the Mendelian randomization method, which is believed to be one of the most convincing analytical methods for evaluating causal relationships.

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# Materials and Methods

## Study Design of Mendelian Randomization

The MR analysis is a method for assessing causal relationships that are free of bias due to confounding variables.[9] According to MR theory, a qualified instrumental variable (IV) should meet the following three assumptions:1) IVs are closely related to relevant exposure factors; 2) IVs follow random allocation rules without being affected by confounding factors; and 3) IV does not directly affect outcomes but through the potential causal effect of the selected exposure. A detailed flow chart and hypotheses of this MR study are presented in Figure 1. In our study, we used GWAS summary data downloaded from the open-access database to select the single nucleotide polymorphisms (SNPs) closely related to the nine types of exposure as IVs and assessed the potential causal relationship of LRMs with the outcome of AGA.

## Selecting Instrument Tools

Datasets of exposures, except serum total cholesterol, were obtained from a GWAS of circulating metabolites containing 249 blood metabolites that were completed and published previously by Nightingale Health in collaboration with the UK Biobank, whereas the exposure data on the serum total cholesterol was from the dataset published by Kettunen in GWAS because no data on cholesterol was found in the dataset published by Nightingale Health.[10] All datasets were downloaded from the open GWAS project website (https://gwas.mrcieu.ac.uk/).

The criteria were initially set as $p < 5\times10^{-8}$ and $r^2 < 0.01$ for the selection of SNPs with genome-wide significance. However, the number of SNPs was too small to be used for MR analysis. Finally, SNPs were chosen as IVs for LRMs with the criterion $p < 5\times10^{-6}$. A threshold setting of $r^2 < 0.01$ and a window size of 10000 KB were used in linkage disequilibrium (LD) to determine if there was a genetic link between SNPs. Based on the genotype and phenotype correlation of the open database Pheno Scanner V2 (http://www.phenoscanner.medschl.cam.ac.uk/), SNPs connected with the confounding factors of AGA were excluded from the MR analysis. SNPs with inconsistent alleles or palindromic variation were also excluded.

## Data Sources for AGA

GWAS summary data for AGA were obtained from Finn Gen Biobank in the IEU open-access GWAS website (https://gwas.mrcieu.ac.uk/), separate from the UK Biobank database for the sources of exposure. There were 119,185 participants from the Finn Gen Biobank, with a mean age of onset of 47.7 years. The databases of exposure and outcome were both from the GWAS in the European population, which minimized the possible bias due to population heterogeneity.

## Statistical Analysis of MR Studies

Inverse variance weighting (IVW), Mendelian randomization-Egger method (MR-Egger), Weighted Median, and Weighted Mode were used to evaluate the causal association between exposure and AGA. Among these, IVW was adopted as the main analysis method in this study.

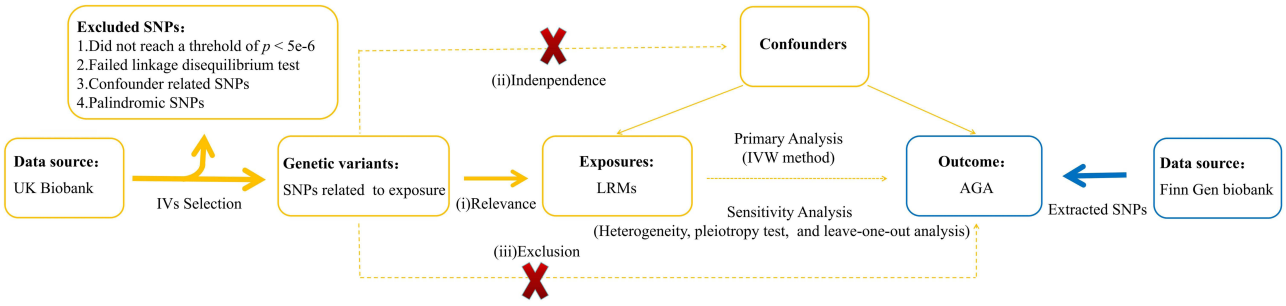


**Figure 1** The flow chart shows the assumption and details of the current Mendelian Randomization, including the data source, the exposure, the outcome and the analysis methods.

Additional ancillary methods were used to verify the consistency and efficiency of the MR analysis. The MR-Egger regression is most commonly used for evaluating horizontal pleiotropy, providing causality estimates where the IV is weak.[11] In addition, the results of MR analysis were visualized using forest, funnel, and scatter plots.

### Sensitivity Analysis

The sensitivity analyses included heterogeneity, pleiotropy, and leave-one-out tests. In the IVW approach, the heterogeneity of the IVs was statistically significant when $p < 0.05$, as determined using Cochran's Q test. MR-Egger and MR-PRESSO evaluated the pleiotropy of the IVs; when $p > 0.05$, the pleiotropy was ignored.[12] The robustness of the results was evaluated by eliminating SNPs individually in the leave-one-out test. The causality was stable and reliable when no significant changes were observed after eliminating the remaining results. All analyses were conducted using the two-sample Mendelian randomization package in R version 4.3.0.

## Results

### MR Analysis Revealed the Causal Effects of the ApoB, LDL and VLDL on the AGA

In a two-sample MR analysis, SNPs with incompatible alleles, alleles with intermediate allele frequencies, and SNPs related to confounding factors were excluded. The final MR analysis included 139 SNPs that were eligible for association with ApoB, 138 SNPs with the concentration of LDL particles, and 173 eligible SNPs associated with VLDL particle concentrations. Information about the SNPs of these three exposures, as well as the remaining exposures, is contained in Supplementary Tables 1–9.

The results of MR analysis of the nine LRMs are shown in Figure 2. Under the IVW method, MR analysis indicated that Apo B, LDL, and VLDL particle concentrations in the serum have a causal relationship with AGA. Other exposures, including HDL, ApoA1, and total cholesterol in serum, as well as polyunsaturated fatty acid (PUFA), Omega3 fatty acid and Omega6 fatty acid, were found not causally related to AGA (Figure 2). When the gene-predicted ApoB levels increased, the risk of AGA also increased (odds ratio (OR) = 2.288, 95% confidence interval (CI) = 1.197–4.373, p = 0.012). The OR represents the change in AGA risk when the concentration of each corresponding LRM increases by one standard deviation (SD). This causal association was supported by the weighted median method (OR = 4.388, 95% CI = 1.636–11.771, p = 0.003) and the weighted mode (OR = 3.116, 95% CI = 1.261–7.702, p = 0.015).

The risk of AGA was found to increase when the concentration of LDL particles increases using IVW method (OR = 2.490, 95% CI = 1.319–4.699, p = 0.005), Weighted Median method (OR =4.253, 95% CI = 1.583–11.428, p = 0.004) and Weighted Mode (OR = 2.891, 95% CI = 1.191–7.017, p = 0.020).

An increase in VLDL particle concentration also led to a higher risk of AGA according to the IVW method (OR = 1.942, 95% CI = 1.038–3.632, p = 0.038).

Other methods suggested a similar trend in the causal effect of LRMs mentioned on AGA above although some of the results were not statistically significant.

The scatter diagrams show the effects of SNPs on different LRMs as well as AGA (Figure 3A–C). The balance of the effect distribution for each SNP is displayed in funnel plots. (Figure 4A–C).

### Sensitivity Analysis

Cochran's Q test revealed no significant heterogeneity in the effect of exposure-related SNPs on AGA (Table 1). The MR-Egger intercept analysis (intercept =−0.06, SE=0.03, p=0.049) and MR-PRESSO also showed no horizontal pleiotropy (Table 2). Additionally, no potential confounding factor was believed to interfere with the causality of LRMs in AGA.

Leave-one-out tests showed similar results to the main MR results, indicating that no single SNP significantly affected the MR analysis results and that the MR analysis was robust (Figure 5).

| Exposure | Outcome | Method | SNPs | OR (95%CI) | Pval |
|---|---|---|---|---|---|
| ApoA1 | Androgenic alopecia | MR Egger | 189 | 0.858 ( 0.274 , 2.687 ) | 0.792 |
| | | Weighted median | 189 | 0.445 ( 0.138 , 1.431 ) | 0.174 |
| | | Inverse variance weighted | 189 | 0.572 ( 0.292 , 1.117 ) | 0.102 |
| | | Weighted mode | 189 | 0.604 ( 0.211 , 1.731 ) | 0.349 |
| ApoB | Androgenic alopecia | MR Egger | 139 | 2.668 ( 0.986 , 7.217 ) | 0.055 |
| | | Weighted median | 139 | 4.388 ( 1.597 , 12.060 ) | 0.004 |
| | | Inverse variance weighted | 139 | 2.288 ( 1.197 , 4.373 ) | 0.012 |
| | | Weighted mode | 139 | 3.116 ( 1.208 , 8.037 ) | 0.020 |
| HDL_P | Androgenic alopecia | MR Egger | 171 | 0.769 ( 0.219 , 2.692 ) | 0.681 |
| | | Weighted median | 171 | 0.568 ( 0.169 , 1.902 ) | 0.359 |
| | | Inverse variance weighted | 171 | 0.712 ( 0.352 , 1.442 ) | 0.346 |
| | | Weighted mode | 171 | 0.655 ( 0.177 , 2.431 ) | 0.528 |
| LDL_P | Androgenic alopecia | MR Egger | 138 | 2.774 ( 1.047 , 7.351 ) | 0.042 |
| | | Weighted median | 138 | 4.253 ( 1.569 , 11.530 ) | 0.004 |
| | | Inverse variance weighted | 138 | 2.490 ( 1.319 , 4.699 ) | 0.005 |
| | | Weighted mode | 138 | 2.891 ( 1.138 , 7.344 ) | 0.027 |
| VLDL_P | Androgenic alopecia | MR Egger | 173 | 1.081 ( 0.364 , 3.210 ) | 0.888 |
| | | Weighted median | 173 | 2.325 ( 0.803 , 6.727 ) | 0.120 |
| | | Inverse variance weighted | 173 | 1.945 ( 1.040 , 3.639 ) | 0.037 |
| | | Weighted mode | 173 | 2.085 ( 0.599 , 7.256 ) | 0.250 |
| Omega_6 | Androgenic alopecia | MR Egger | 143 | 2.084 ( 0.524 , 8.296 ) | 0.299 |
| | | Weighted median | 143 | 1.850 ( 0.585 , 5.856 ) | 0.295 |
| | | Inverse variance weighted | 143 | 1.215 ( 0.572 , 2.579 ) | 0.612 |
| | | Weighted mode | 143 | 1.484 ( 0.348 , 6.326 ) | 0.594 |
| Omega_3 | Androgenic alopecia | MR Egger | 149 | 1.159 ( 0.531 , 2.530 ) | 0.711 |
| | | Weighted median | 149 | 0.832 ( 0.330 , 2.100 ) | 0.698 |
| | | Inverse variance weighted | 149 | 1.074 ( 0.620 , 1.860 ) | 0.799 |
| | | Weighted mode | 149 | 1.067 ( 0.497 , 2.291 ) | 0.868 |
| PUFA | Androgenic alopecia | MR Egger | 166 | 1.100 ( 0.342 , 3.536 ) | 0.873 |
| | | Weighted median | 166 | 1.745 ( 0.587 , 5.187 ) | 0.316 |
| | | Inverse variance weighted | 166 | 1.190 ( 0.612 , 2.315 ) | 0.608 |
| | | Weighted mode | 166 | 1.270 ( 0.413 , 3.901 ) | 0.677 |
| Serum total cholesterol | Androgenic alopecia | MR Egger | 60 | 1.564 ( 0.644 , 3.795 ) | 0.327 |
| | | Weighted median | 60 | 1.365 ( 0.665 , 2.804 ) | 0.396 |
| | | Inverse variance weighted | 60 | 1.358 ( 0.832 , 2.214 ) | 0.220 |
| | | Weighted mode | 60 | 1.738 ( 0.682 , 4.430 ) | 0.252 |


**Figure 2** The forest plots of MR analysis of the causal associations between each exposure with AGA.

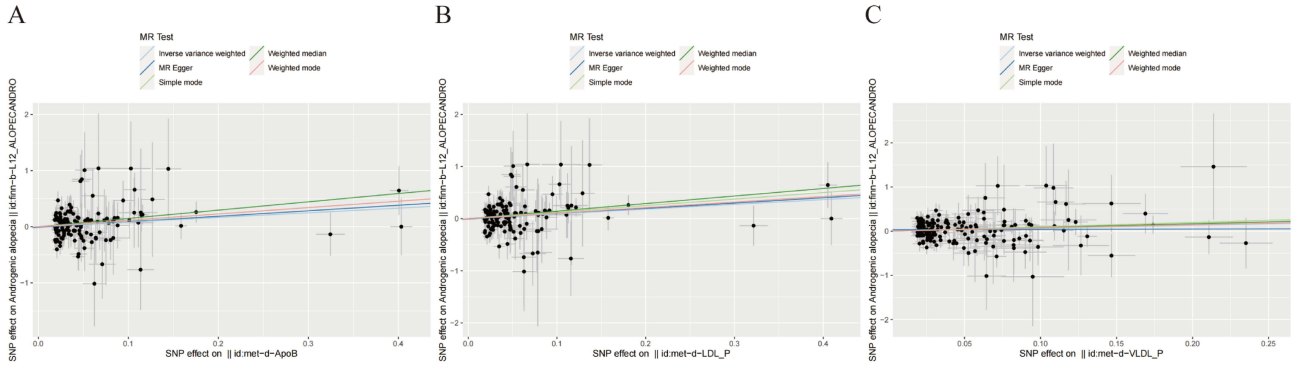


**Figure 3** The scatter plots show the effects of single-nucleotide polymorphisms (SNPs) on different types of exposures and AGA (**A**–**C**). The x-axis represents the effect of each genetic variant on Apo B (**A**), LDL (**B**) and VLDL (**C**), respectively. The y-axis represents the effect of each genetic variant on AGA (**A–C**).

## Discussion

AGA is a non-cicatricial alopecia characterized by gradual hair shedding. Among all types of non-cicatricial alopecia, AGA is the most common worldwide, affecting at least 50% of both males and females by the age of 60.[13,14] It manifests differently in male and female patients. In males, the shedding area is mostly in the frontal and vertex parts, whereas in females, the hair is thin in the diffusing pattern at the central scalp and the frontal hairline remains.[15,16]

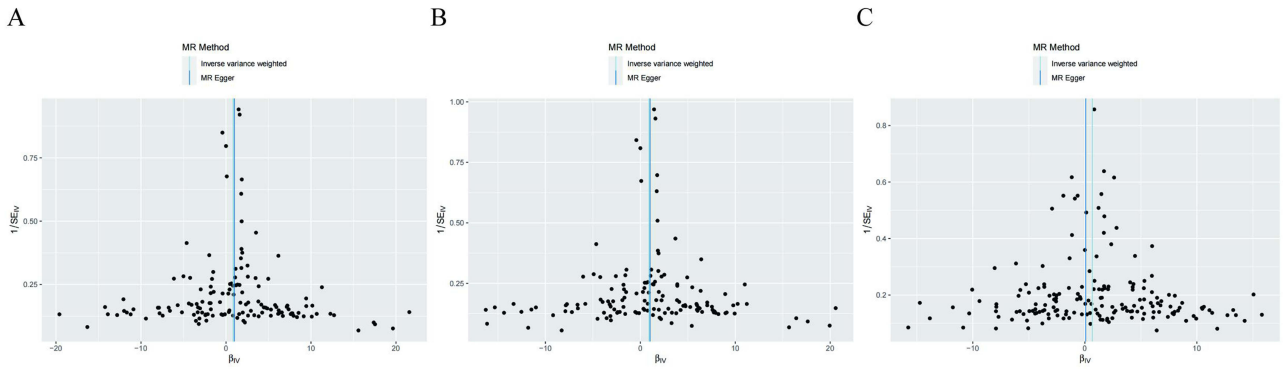


**Figure 4** The funnel plots display the the heterogeneity of SNPs in the MR analysis that evaluates causal effects of Apo B (**A**), LDL (**B**) and VLDL (**C**) on AGA.

Many theories have been proposed to explain the AGA pathogenesis. Among them, excessive androgen levels and hypersensitivity to androgen in HF are believed to be the most important.[17,18] However, testosterone has long been considered a negative regulator of LDL levels in males, whereas high levels of LDL reduces testosterone production in mice by undermining the function of Leydig cells.[19] These findings contrast with the ones that reported higher cardiovascular risks in patients with AGA due to increased levels of triglyceride (TG), LDL, and other LRMs. In our study, clear and convincing causal effects of LDL, VLDL, and ApoB levels were found on AGA.

Several previous studies have confirmed that both male and female patients with AGA show elevated levels of TG, total cholesterol, and LDL-C, which is consistent with the findings of our study.[4,20] The abnormally high levels of LRMs is not merely related to a high Body Mass Index (BMI).[21] The risk of cardiovascular disease has also been reported to be increased in AGA patients.[22] However, whether there is a causal relationship between LRMs and AGA remains uncertain because observational studies fail to control or measure potential confounding factors and determine causality.

Firstly, LDL and ApoB regulate androgen production. The synthesis of androgens is stimulated by insulin, which happens to be the result of high LDL levels.[23,24] Elevated ApoB levels have also been reported to correlate with higher levels of testosterone.[25] Moreover, increased LDL and ApoB often indicate high TG levels in the blood, which are related to the overproduction of testosterone.[26] However, the effects of VLDL on androgens require further investigation.

**Table 1** The Table of Results of Heterogeneity Analysis

| Exposure | Outcomes | MR Methods | Statistic | Q-dif | p-value |
|---|---|---|---|---|---|
| Apo B | Androgenic alopecia | MR Egger | 143.8697 | 137 | 0.3269 |
| | | IVW | 144.0374 | 138 | 0.3453 |
| LDL | | MR Egger | 134.3824 | 136 | 0.5231 |
| | | IVW | 134.4643 | 137 | 0.5453 |
| VLDL | | MR Egger | 162.2218 | 171 | 0.6725 |
| | | IVW | 163.8974 | 172 | 0.6583 |

**Table 2** The Table of Results of Pleiotropy Analysis

| Exposure | Outcomes | Egger Intercept | SE | p-value | MR-PRESSO |
|---|---|---|---|---|---|
| Apo B | Androgenic alopecia | −0.010 | 0.025 | 0.690 | 0.272 |
| LDL | | −0.007 | 0.026 | 0.775 | 0.337 |
| VLDL | | 0.032 | 0.025 | 0.197 | 0.660 |

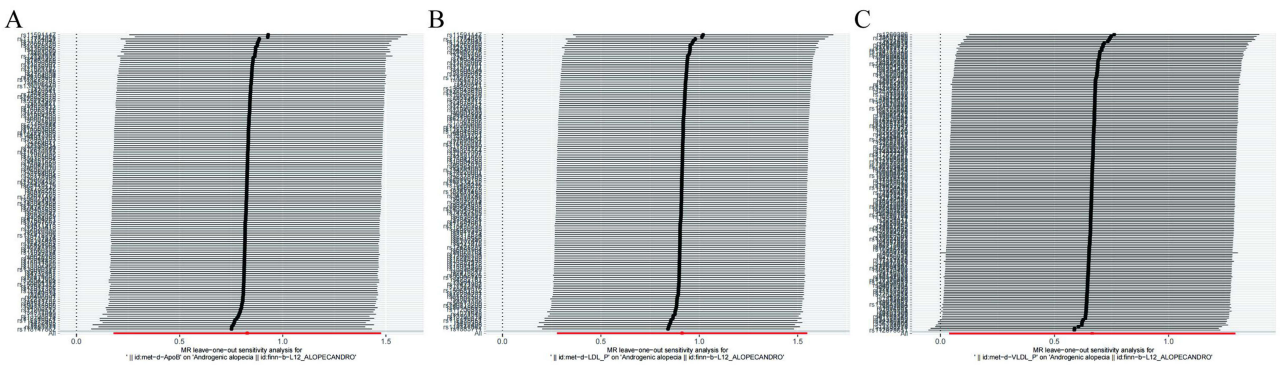


**Figure 5** The leave-one-out plots visualized the sensitivity analysis of causal effects of Apo B (**A**), LDL (**B**) and VLDL (**C**) on AGA. The x-axis of leave-one-out plots shows the effect on MR analysis results due to each excluding SNP; the y-axis represents the excluded SNP.

Secondly, LDL contributes to androgen activity. A reduction in insulin-like growth factor-1 (IGF-1) levels can result in the development of AGA.[27] However, the apheresis of serum LDL upregulates IGF-1 levels in blood, indicating that the high LDL levels may accelerate the process of AGA.[28]

Finally, LDL and ApoB can inhibit the conversion of androgen to estrogen.[29,30] They regulate the production of other sex hormones and the estrogen/androgen ratio through decreased aromatase activity, leading to androgen accumulation and estrogen deficiency. As a result, an imbalance in the estrogen/androgen ratio contributes to alopecia.

Apart from their impact on androgens, LRMs can regulate hair growth in other ways. For example, excessive secretion of sebum from the scalp is a classic symptom of AGA. Multiple clinical studies have reported an increase in scalp lipid secretion in both male and female AGA patients.[31,32] Lipids including TG, fatty acids, cholesterol, esters, and squalene, are secreted from the sebaceous glands.[33] Besides, excessive sebaceous secretion occurs more often in the vertex area than in the occipital area, which is consistent with the hair loss pattern.[34] The HF in this area is also more sensitive to androgens. Excessive lipids in the scalp will increase the risk of seborrheic dermatitis and worsen the microenvironment of HF, accelerating the alopecia process in the end.[35]

To our knowledge, this study makes the first attempt to use MR analysis to investigate the causal association between LRMs and AGA. In addition to eliminating vertical pleiotropy, the MR evaluated independent causal effects on AGA of each exposure. Additionally, the results remained stable in each sensitivity test, indicating the validity and robustness of the causal relationship.

However, our study still had some limitations. First of all, we were unable to further investigate which parts of AGA pathogenesis are regulated by LRMs, because of the lack of data about testosterone, DHT, or 5a-reductase activity in the existing GWAS database. Secondly, whether LRMs are related to other types of alopecia, such as alopecia areata, telogen effluvium, and cicatricial alopecia, remains unknown.

In summary, our study revealed the causal effects of LDL, VLDL and ApoB on AGA using MR analysis. The findings of our study are solid, considering the results of sensitivity analyses. Thus, it is important to control the serum lipid profiles in treating AGA. The potential of other metabolites in the pathogenesis is worthy of further investigation to improve the overall therapeutic effect of AGA.

## Conclusion

ApoB, LDL, and VLDL levels are causally associated with the incidence of AGA. The risk of AGA increases significantly when the serum levels of ApoB, LDL, and VLDL increase. The causal relationships are solid and free of interference from confounding factors.

## Data Sharing Statement

All datasets mentioned in this manuscript can be downloaded online. Details of the analysis are available upon reasonable request to the first author (Lingbo Bi, Email address: b1359028021@163.com).

## Ethics Approval and Consent to Participate

This study has been approved by the IRB of Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital (Approval number: 2023-SR-354).

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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