SYSTEMATIC REVIEW AND META-ANALYSIS

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Apolipoproteins Levels in Fatty Liver Disease: A Systematic Review and Meta-analysis

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ABSTRACT

Background & Aims: Fatty liver disease (FLD) is a prevalent condition linked to metabolic disorders and can progress to severe liver diseases. Alterations in apolipoprotein (Apo) levels may provide valuable insights for diagnosing and managing FLD. This systematic review and meta-analysis evaluates these changes across different FLD phenotypes to evaluate their potential as diagnostic biomarkers.

Methods: We evaluated studies from PubMed, EMBASE, and Scopus using a predefined search string. Predefined inclusion and exclusion criteria were applied, and the risk of bias was assessed using the Newcastle-Ottawa Scale (NOS). The main summary outcome was the mean difference (MD) in Apo levels.

Results: Out of 773 initial articles, 55 studies involving 432,328 individuals were included. In NAFLD patients vs. controls, ApoA levels showed a MD of -0.029 (95% CI: -0.133, 0.075), ApoA-I had a MD of -0.064 (95%CI: -0.107, -0.021), and ApoB levels had a MD of 0.098 (95%CI: 0.076, 0.120), while ApoB100 had an MD of 0.042 (95% CI: 0.008, 0.076). For NASH vs. controls, ApoA-I levels had a MD of -0.108 (95% CI: -0.125, -0.091) and ApoB levels had a MD of 0.123 (95% CI: 0.054, 0.193), while ApoB100 had a MD of 0.042 (95% CI: -0.051,0.136). In MAFLD vs. controls, ApoA-I levels had a MD of -0.068 (95% CI: -0.124, -0.012) and ApoB a MD of 0.099 (95% CI: 0.091, 0.107). For diabetic NAFLD vs. T2DM (type 2 diabetes mellitus) without NAFLD, ApoA levels had an MD of 0.028 (95% CI: -0.147, 0.204) and ApoB levels an MD of 0.081 (95% CI: 0.040, 0.122).

Conclusions: In NAFLD patients, ApoA-I levels were lower and ApoB and ApoB100 levels were higher compared to controls, with similar patterns seen in NASH patients, who also had higher ApoB levels than those with simple steatosis. MAFLD patients had elevated ApoB and ApoE levels, while overweight/obese NAFLD patients had higher ApoB levels than controls.

Key words: apolipoprotein – non-alcoholic fatty liver disease – NAFLD – non-alcoholic steatohepatitis – NASH – metabolic dysfunction-associated fatty liver disease – MAFLD - metabolic-dysfunction associated steatotic liver disease – MASLD – type 2 diabetes mellitus – biomarkers.

Abbreviations: Apo: apolipoprotein; CI: confidence interval; CT: computed tomography; FLD: fatty liver diseases; H-MRS: proton magnetic resonance spectroscopy; MAFLD: metabolic dysfunction-associated fatty liver disease; MASLD: metabolic-dysfunction associated steatotic liver disease; MD: mean difference; MRI: magnetic resonance; NAFLD: non-alcoholic fatty liver diseases NASH: non-alcoholic steatohepatitis; NOS: Newcastle-Ottawa Scale; SS: simple steatosis; US: ultrasound.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) represents a significant public health challenge worldwide. It encompasses a spectrum of liver conditions, ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), which can progress to fibrosis, cirrhosis, and hepatocellular carcinoma [1]. Epidemiological studies indicate that NAFLD affects approximately 25% of the global population, making it the most common chronic liver disease. The growing burden of NAFLD underscores the urgent need for improved diagnostic and therapeutic strategies to manage this complex condition effectively [2].

The pathogenesis of NAFLD is multifactorial, involving a combination of genetic, environmental, metabolic factors, and gut dysbiosis. At the same time, insulin resistance, adipose

tissue dysfunction, and inflammation play critical roles in the development and progression of NAFLD. The liver's inability to appropriately metabolize fats leads to hepatic steatosis, while oxidative stress and inflammatory cytokines contribute to hepatocyte injury and fibrosis in NASH [3].

Current treatment options for NAFLD are limited and primarily focus on lifestyle modifications, such as the use of the Mediterranean diet and physical exercise, to reduce liver fat and improve metabolic parameters. Pharmacological interventions are under investigation, but there remains a lack of approved medications specifically for NAFLD, highlighting the need for continued research into novel therapeutic targets [4]. Furthermore, in recent years the new nomenclatures metabolic dysfunction-associated fatty liver disease (MAFLD), followed by metabolic dysfunction-associated steatotic liver disease (MASLD) were proposed by scientific community due to the complex interplay between fatty liver disease (FLD) and dysmetabolic comorbidities [5].

Apolipoproteins (Apos) are components of lipoproteins, responsible for the transport and metabolism of lipids in the body. They play crucial roles in lipid binding, solubilization, and receptor-mediated uptake, influencing lipid homeostasis and cardiovascular health. Key Apos include ApoA-I, ApoB, and ApoE, each with distinct functions and associations with different lipoprotein particles [6]. Apolipoproteins also serve as biomarkers for various metabolic disorders, given their pivotal roles in lipid transport and metabolism [7]. In the context of FLD, alterations in Apo levels have been observed, suggesting their potential involvement in the disease's pathophysiology. For instance, reduced levels of ApoA-I have been associated with FLD, indicating impaired reverse cholesterol transport [8]. Conversely, elevated levels of ApoB may reflect increased hepatic lipid accumulation and very low-density lipoproteins secretion [9].

The interplay between different Apos and their impact on lipid metabolism in FLD provides valuable insights into the disease mechanisms and potential therapeutic targets [10]. Despite these observations, the precise role and clinical significance of Apos alterations in FLD remain to be fully elucidated. For this reason, this systematic review and meta-analysis aimed to comprehensively evaluate the levels of Apos in patients with FLD. By synthesizing data from multiple studies, we seek to clarify the associations between Apo levels and the presence and severity of FLD.

METHODS

This systematic review and meta-analysis was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist 2020 [11].

Data Sources and Search Strategy

Our aim was to review existing evidence by conducting a comprehensive search in PubMed, EMBASE, and Scopus databases, following the methodology described in Supplementary file. To ensure comprehensive coverage, we also manually checked the references of the included studies to avoid missing pertinent research. The search covered publications from the databases' inception up to March 18, 2024, without restrictions on timeframe or location. We initially screened titles and abstracts for relevance, followed by a detailed review of full texts based on predefined inclusion and exclusion criteria. Two authors (G.G.M.S. and R.A.) independently determined study eligibility and performed data extraction, while resolving any disagreements through consensus.

Eligibility criteria

Inclusion criteria of original articles were as follows: (1) full-text article studies of observational cohort population-based/ hospital-based, cross-sectional, or case-control designs that evaluated the association between Apos and FLD; (2) hepatic steatosis evaluated through biopsy, imaging techniques, scores, or biomarkers, while excluding secondary causes of hepatic steatosis or significant alcohol consumption; (3) clinical studies only; and (4) studies published in English, German, Italian, or Romanian languages.

Exclusion criteria were as follows: (1) significant consumption of alcohol, or presence of other secondary causes of hepatic steatosis; (2) pre-clinical studies; (3) genetic variant studies of Apos; (4) studies performed on pediatric population; (5) case reports, letters to the editor, commentaries, editorials, systematic reviews, practice guidelines, and abstracts published without an entire article.

Risk of Bias Assessment in Individual Studies

The Newcastle-Ottawa Scale (NOS) for assessing the quality of cross-sectional studies was utilized to evaluate the risk of bias in individual studies [12]. This tool was used to assess both the risk of bias and the internal validity of each study. The evaluations were independently conducted by two authors (G.G.M.S. and R.A.). Any discrepancies in their assessments were resolved through discussion to reach a consensus.

Summary Measures and Synthesis of Results

The primary summary outcome was the mean difference (MD) in Apo levels. We conducted the quantitative data analysis of the included studies using R with the Metafor package (OpenMeta [Analyst]) [13,14]. To assess between-study heterogeneity, we employed the χ^2-based Q-test and I^2 statistic. The overall effect size was estimated using a random-effects model and MD. For studies reporting medians and interquartile ranges, we calculated the mean and standard deviation, and for those with multiple subgroups of fatty liver disease patients or control subjects, we combined the groups according to Cochrane Handbook guidelines. Additionally, Apo levels reported in units other than g/L were converted to g/L to facilitate data pooling. Subgroup assessment was performed according to the different nomenclatures of FLD, and following the stratifications performed in the included articles. The data was reported as the estimated MD with 95% confidence interval (CI). A p value of <0.05 was considered statistically significant.

RESULTS

The initial search yielded 773 results (PubMed = 268 articles, EMBASE = 496 articles, Scopus = 8 articles, other

sources = 1 article) as illustrated in Fig. 1. After identifying and removing 123 duplicate articles, 650 records remained for screening based on eligibility criteria by evaluating the titles and abstracts. This screening process resulted in the following exclusions: 480 irrelevant articles, 3 letters and commentaries, 11 reviews, 23 articles involving pediatric patients, 4 case reports, and 7 articles without full text. Consequently, 528 articles were excluded during the initial assessment. The full texts of the remaining 122 articles were then thoroughly evaluated. Of these, 67 were excluded for the following reasons: 2 studies involved subjects not meeting the inclusion criteria, 9 articles lacked an FLD group, 18 articles had no control groups, 6 studies did not subdivide serum values into FLD vs. controls, 2 genetic studies, 29 studies lacked serum values, and 1 was a pre-clinical study, as reported in Supplementary file. Finally, 55 articles were included in our analysis [15-69].

Study Characteristics

The main study characteristics of the included articles were summarized as shown in Supplementary file. This systematic review and meta-analysis included 432,328 individuals. According to the geographical localization, eighteen studies took place in China [18, 19, 21, 31, 32, 33, 36, 37, 45, 53, 62-69], 9 in the United States [16, 17, 22, 30, 35, 40, 49, , 57], 3 in Turkey [23, 46, 47], 3 in Korea [20, 48, 55], 2 in France, Greece, Italy, Argentina, Serbia, and Netherlands, respectively [24,26, 29, 38, 41, 42, 44, , 50, 51, 52, 59, 61], while only 1 study in Egypt, Japan, United Kingdom, India, Iran, Australia, Poland, Spain, Romania, and Sweden, respectively [15, 25, 27, 28, 34, 43, 54, 56, 58, 60].

Definition of Hepatic Steatosis

Hepatic steatosis was evaluated through liver ultrasound (US) in in 26 studies [,19, 20, 23, 24, 25, 27, 28, , 31-33, 36-38, 41-45, 51, 53, 55, 60, 63,67,68 69,], while 14 studies used liver biopsy [17, 18, 22, 29,30, , 35,39, 40, 47, 49, 50, 52, 54, 57], and 2 studies used diagnostic biomarkers or scores [46, 61]. Furthermore, two studies used US in combination with diagnostic biomarkers and scores [34, 48], while one used either imaging or liver biopsy [66]. Another 3 studies used US and liver biopsy [21, 56, 62], while the remaining 7 studies used computed tomography (CT), magnetic resonance imaging (MRI), CT and liver biopsy, US and MRI, proton magnetic resonance spectroscopy (H-MRS) and liver biopsy, and MRI plus US and diagnostic scores [15, 16, 26, 58, 59, 64, 65].

Serum Apolipoproteins Levels in NAFLD vs. Controls

The combined studies for the analysis evaluating serum ApoA levels in NAFLD vs. controls showed an overall MD of -0.029 (95%CI: -0.133, 0.075), while the heterogeneity was significant (I^2=95.23% and p<0.001) (Fig. 2A), ApoA-I levels in NAFLD patients vs. controls showed an overall MD of -0.064 (95%CI: -0.107, -0.021), while the heterogeneity was significant (I^2=99.42% and p<0.001), as showed in Fig. 2B. Regarding ApoB, the combined studies showed an overall MD of 0.098 (95% CI: 0.076, 0.120), with a significant heterogeneity

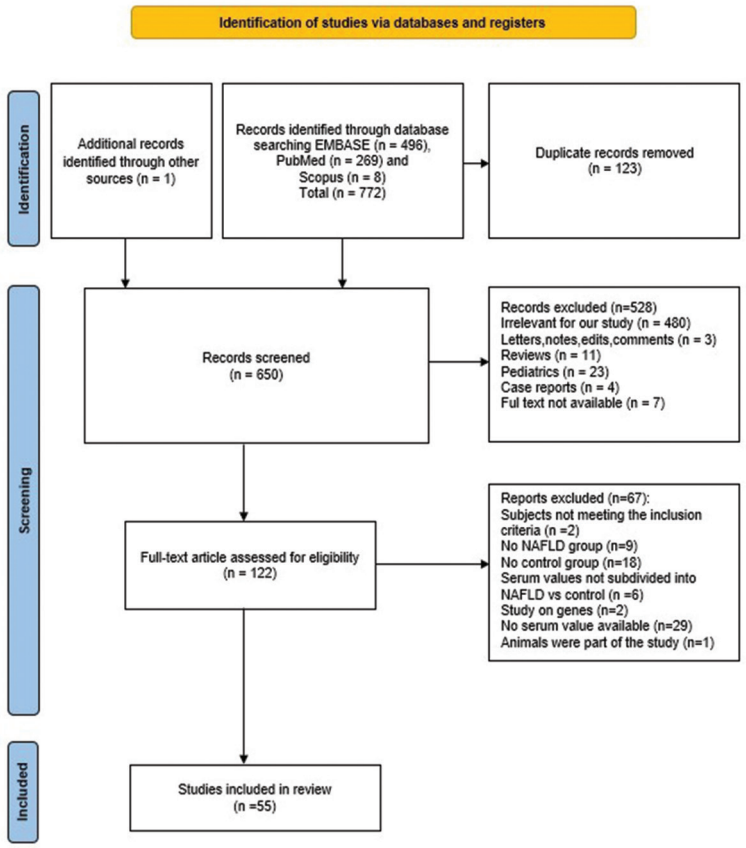

Fig. 1. Summary of the identification, screening, and inclusion phases of our systematic review and meta-analysis according to the PRISMA flow diagram.

(I^2=98.13% and p<0.001), as outlined in Fig. 2C. ApoB100 combined analysis showed an overall MD of 0.042 (95%CI: 0.008, 0.076) and a substantial heterogeneity (I^2=62.18% and p=0.012), as showed in Fig. 2D. Meanwhile the analysis for the combined studies regarding ApoC3 levels showed an overall MD of 0.008 (-0.024, 0.040), with a substantial heterogeneity (I^2=51.81% and p=0.150*)* and (Fig. 2E). At the same time, the cumulative analysis for ApoA-I/ApoB ratio showed an overall MD of 0.180 (95%CI: 0.100, 0.261) and a significant heterogeneity (I^2=99.35% and p<0.001), as shown in Figure 2F. Finally, the combined analysis for ApoE levels evaluation showed an overall MD of 0.019 (95%CI: 0.002, 0.036) with a significant heterogeneity of results (I^2=92.59% and p<0.001), as shown in Fig. 2G.

Serum Apolipoproteins Levels in NASH vs. Controls

The combined studies for the analysis evaluating serum ApoA-I levels in NASH patients vs. controls showed an overall MD of -0.108 (95%CI:-0.125, -0.091), without a significant heterogeneity (I^2=0% and p=0.440), as showed in Fig. 3A. Regarding ApoB, the overall MD was 0.123 (95%CI: 0.054, 0.193) with a substantial heterogeneity (I^2=71.78% and p<0.001), as outlined in Fig. 3B. ApoB100 analysis showed an overall MD of 0.042 (95%CI: -0.051, 0.136) and a significant heterogeneity (I^2=82.01% and p=0.005), as shown in Fig. 3C.

Serum Apolipoproteins Levels in MAFLD vs. Controls

The combined studies for the analysis evaluating serum ApoA-I levels in MAFLD patients vs. controls showed an overall MD of -0.068 (95%CI: -0.124, -0.012), with a significant heterogeneity (I^2=99.12% and p<0.001), as showed in Fig. 4A. At the same time, the overall MD for ApoB levels was 0.099 (95%CI: 0.091, 0.107) with a moderate heterogeneity (I^2=41.08 and p=0.034), as outlined in Fig. 4B. Finally, ApoE levels evaluation showed an overall MD of 0.004 (95%CI: 0.002, 0.007) and a significant heterogeneity (I^2=81.84 and p=0.002), as shown in Fig. 4C.

Serum Apolipoprotein Level in Simple Steatosis vs Control

The combined studies for the analysis evaluating serum ApoA-I levels in simple steatosis (SS) vs. control showed an overall MD of -0.089 (95%CI: -0.172, -0.006), without significant heterogeneity (I^2=0% and p=0.786), as shown in Fig. 5A. At the same time, ApoB levels showed an overall MD of 0.116 (95%CI: 0.067, 0.164), without a significant heterogeneity (I^2=0% and p=0.438), as reported in Fig. 5B.

Serum Apolipoprotein Levels in NASH vs. Simple Steatosis

The combined studies for the analysis evaluating serum ApoA levels in NASH vs. SS showed an overall MD of 0.027 (95%CI: -0.041, 0.095), without significant heterogeneity (I^2=0% and p=0.973), as shown in Fig. 6A. At the same time, ApoA-I levels showed an overall MD of -0.036 (95%CI: -0.101,0.028), without a significant heterogeneity (I^2=0% and p=0.516), as reported in Fig. 6B. Meanwhile ApoB analysis showed an overall MD of 0.096 (95%CI:0.007,0.186) with a

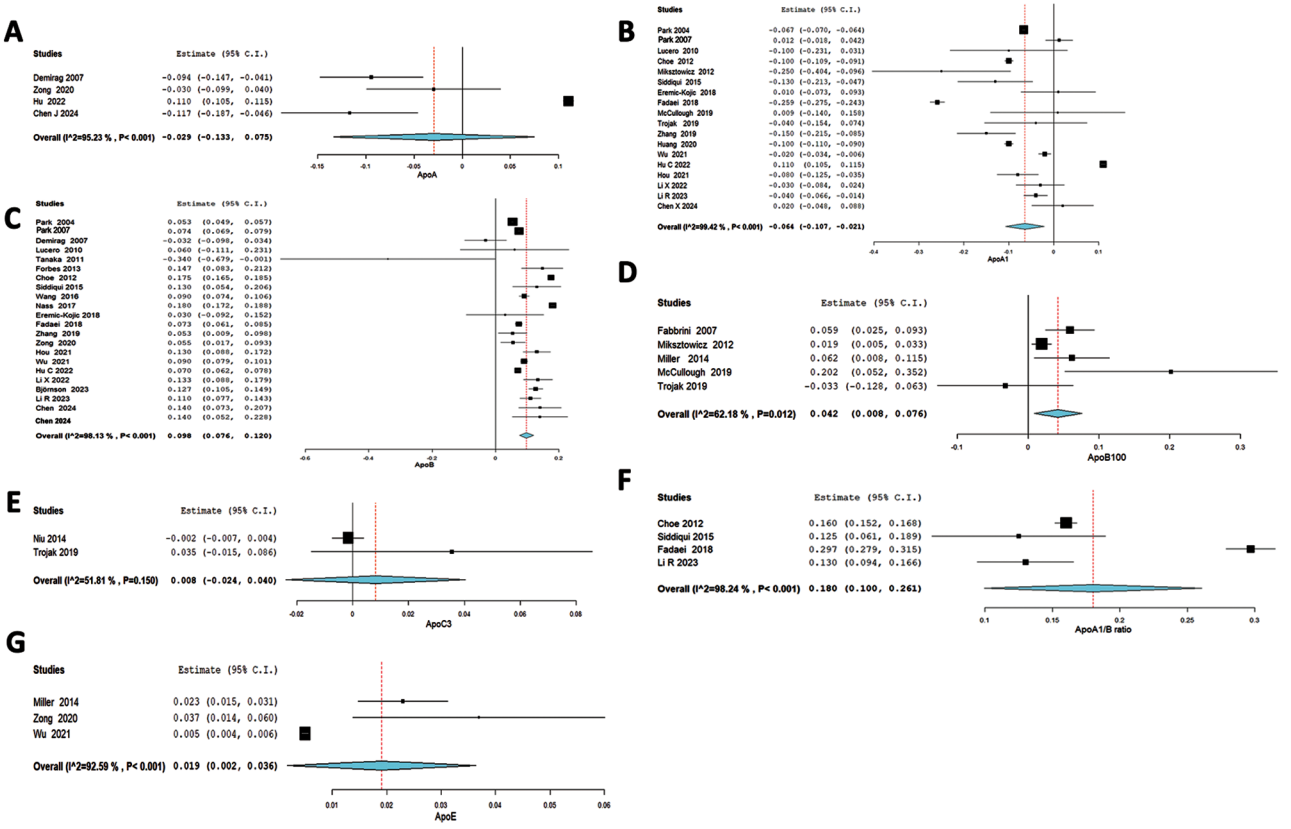

Fig. 2. Studies evaluating serum ApoA (A), ApoA-I (B) ApoB (C), ApoB100 (D), ApoC3 (E), ApoA-I/ApoB ratio (F), and ApoE (G) levels in NAFLD patients vs. controls.

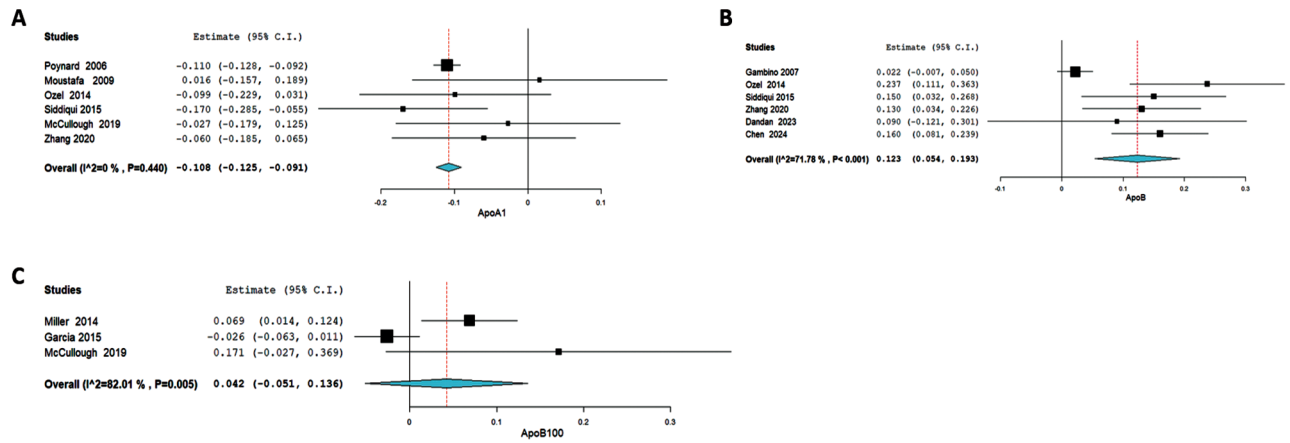

Fig. 3. Studies evaluating serum ApoA-I (A), ApoB (B) and ApoB100 (C) levels in NASH patients vs. controls.

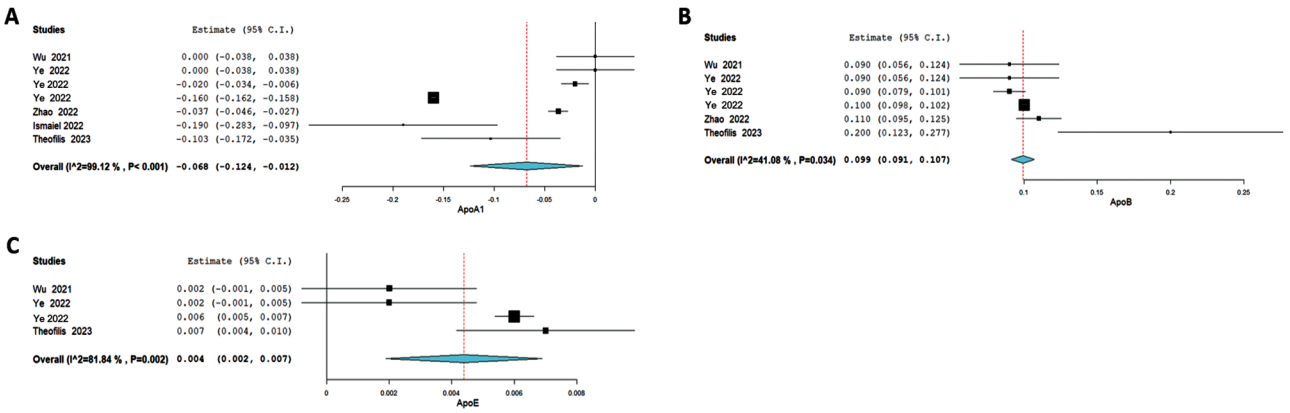

Fig. 4. Studies evaluating serum ApoA-I (A), ApoB (B), and ApoE (C) levels in MAFLD patients vs. controls.

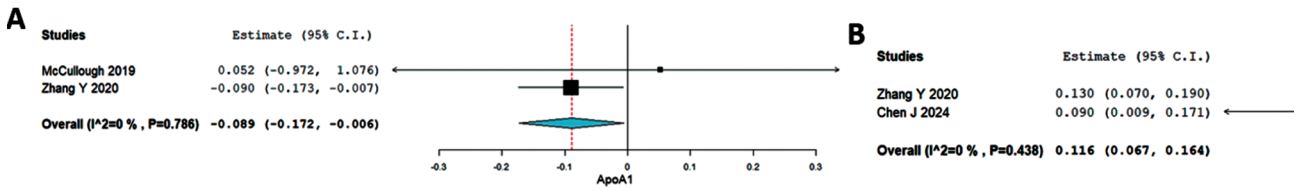

Fig. 5. Studies evaluating serum ApoA-I (A) and ApoB (B) levels in SS patients vs. controls.

moderate heterogeneity (I^2=70.78 and p=0.028), as outlined in Fig. 6C. Finally, ApoB100 showed an overall MD of -0.073 (95%CI: -0.220,0.074) and a significant heterogeneity (I^2=79.74 and p=0.002), as reported in Fig. 6D.

Serum Apolipoproteins Levels in Overweight/obese NAFLD vs. Controls

The combined studies for the analysis evaluating serum ApoA-I levels in overweight/obese NAFLD vs. controls showed an overall MD of 0.006 (95%CI: 0.001, 0.011), without a significant heterogeneity (I^2=0% and p=0.925), as shown in Fig. 7A. At the same time, this evaluation reported for ApoB levels showed an overall MD of 0.074 (95%CI: 0.069, 0.079), without significant heterogeneity (I^2=0% and p=0.479), as shown in Fig. 7B.

Serum Apolipoproteins Levels in Diabetic NAFLD vs. Non-diabetic NAFLD

The combined studies for the analysis evaluating serum ApoA levels in diabetic NAFLD vs. non-diabetic NAFLD showed an overall MD of -0.000 (95%CI: -0.007, 0.007), without significant heterogeneity (I^2=0% and p=0.694), as shown in Fig. 8A. At the same time, ApoB levels showed an overall MD of 0.022 (95%CI: -0.086, 0.129) and a significant heterogeneity (I^2=94.25% and p<0.001), as reported in Fig. 8B.

Serum Apolipoproteins Levels in Diabetic NAFLD vs. Diabetic Patients without NAFLD

The combined studies for the analysis evaluating serum ApoA- levels in diabetic NAFLD vs. diabetic patients without NAFLD showed an overall MD of 0.028 (95%CI: -0.147, 0.204),

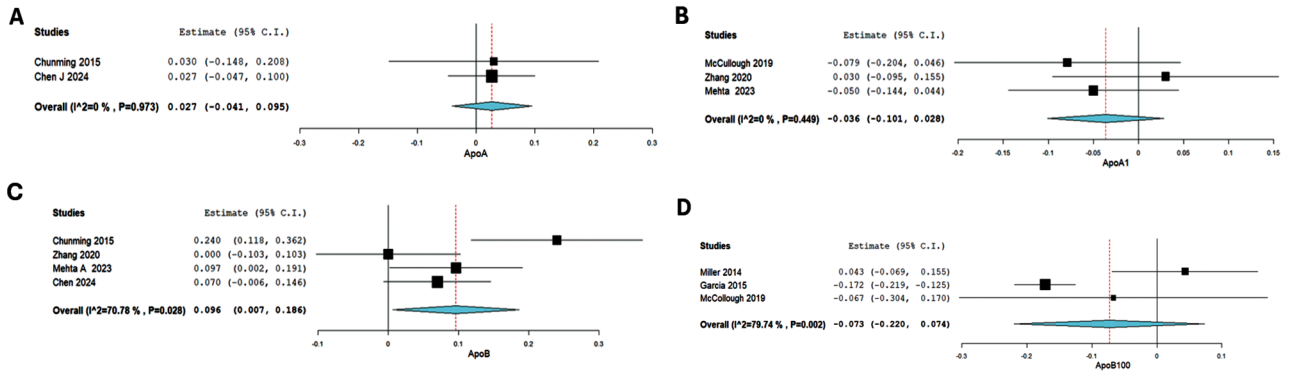

Fig. 6. Studies evaluating serum ApoA(A), ApoA-I (B), ApoB (C) and ApoB100 (D) levels in NASH patients vs. patients with SS.

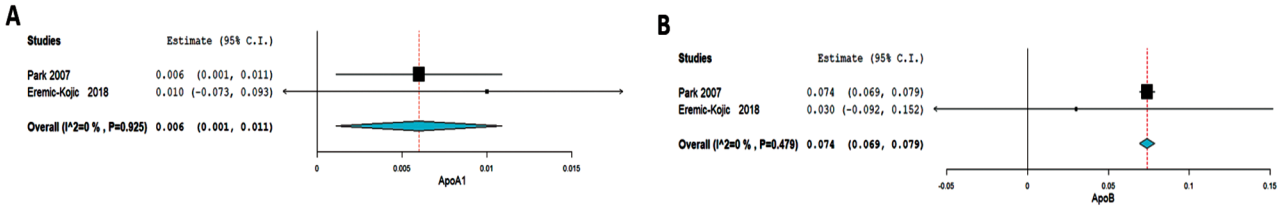

Fig. 7. Studies evaluating serum ApoA-I (A), and ApoB (B) levels in overweight/obese NAFLD patients vs. controls.

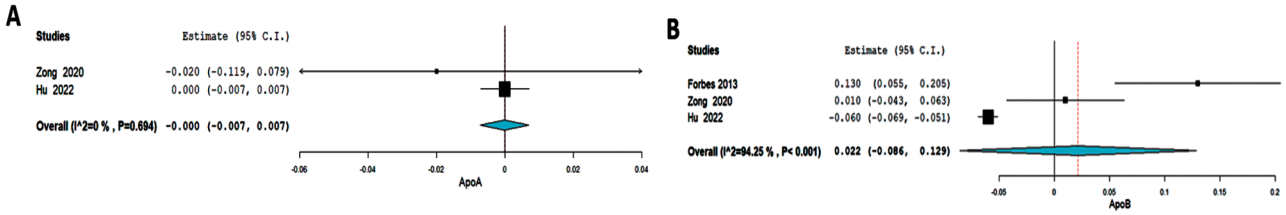

Fig. 8. Studies evaluating serum ApoA (A), and ApoB (B) levels in diabetic NAFLD patients vs. non-diabetic NAFLD patients.

with a significant heterogeneity (I^2=90.8% and p<0.001), as shown in Fig. 9A. The ApoA1 levels in the same group showed an overall MD of -0.040 (95%CI: -0.065, -0.015), with insignificant heterogeneity (I^2=0% and p=0.996). Furthermore, the same analysis performed for the evaluation of ApoB levels showed an overall MD of 0.081 (95%CI: 0.040, 0.122) and a significant heterogeneity of results (I^2=83.04% and p<0.001), as highlighted in Fig. 9B.

Liver Fibrosis F0-F1 vs. F2-F4 in NAFLD

The combined studies for the analysis evaluating serum ApoA-I levels in F0/F1 NAFLD vs. F2/F4 NAFLD showed an overall MD of 0.109 (95%CI: 0.019, 0.199, with a significant heterogeneity (I^2=92.98% and p<0.001), as shown in Fig. 10.

Liver Fibrosis F0-F2 vs. F3-F4 in NAFLD

The combined studies for the analysis evaluating serum ApoA-II levels in F0-F2 NAFLD vs. F3-F4 NAFLD showed an overall MD of -0.041 (95%CI: -0.589, 0.508), with a significant heterogeneity (I^2=89.05% and p=0.003), as shown in Fig. 11.

FLI >60 vs. FLI <60

The combined studies for the analysis evaluating serum ApoA-I levels in patients with fatty liver index (FLI) >60 vs. patients with a FLI<60 showed an overall MD of -0.107 (95%CI: -0.153, -0.061), with a significant heterogeneity (I^2=96.28% and p<0.001), as shown in Fig. 12A. Regarding the same evaluation performed for the ApoB serum levels, the overall MD was 0.172 (95%CI: 0.122, 0.222) and a significant heterogeneity (I^2=96.61% and p<0.001), as reported in Fig. 12B.

Mild NAFLD vs. Moderate/severe NAFLD

The combined studies for the analysis evaluating serum ApoA-I levels in patients with mild NAFLD vs. patients with moderate/severe NAFLD showed an overall MD of 0.038 (95%CI: -0.014, 0.090), with an insignificant heterogeneity (I^2=0% and p=0.546), as shown in Fig. 13A. At the same time, ApoB levels analysis showed an overall MD of -0.111 (95%CI: -0.179, -0.044) and an insignificant heterogeneity (I^2=9.15% and p=0.294), as outlined in Fig. 13B.

Cirrhotic NAFLD vs. Non cirrhotic NAFLD

The combined studies for the analysis evaluating serum ApoA-I levels in cirrhotic NAFLD vs. non cirrhotic NAFLD patients showed an overall MD of -0.042 (95%CI: -0.184, 0.099), with substantial heterogeneity (I^2=72.67% and p=0.019), as shown in Fig. 14A. At the same time, ApoB serum levels analysis reported an overall MD of -0.135 (95%CI: -0.290,

0.021) and a significant heterogeneity of results (I^2=76.25% and p=0.001), as shown in Fig. 14B.

Quality Assessment

The quality of the studies included in this systematic review and meta-analysis was rigorously assessed to ensure the reliability of the findings. Among the 55 studies evaluated, only 2 studies reported an overall of 5 stars [50, 59], while 11 studies 6 stars [18, 21, 29, 31, 36, 40, 43, 52, 57, 60, 61], 31 studies 7 stars [15,16, 19, 20, 23-28, 30, 32-35, 37-39, 41, 42, 44, 45, 48, 49, 51, 53, 55, 56, 64, 65, 68], and 11 studies 8 stars [17,, 46, 47, 54, 58, 62, 63, 66, 67, 69, 70], as reported in Supplementary file.

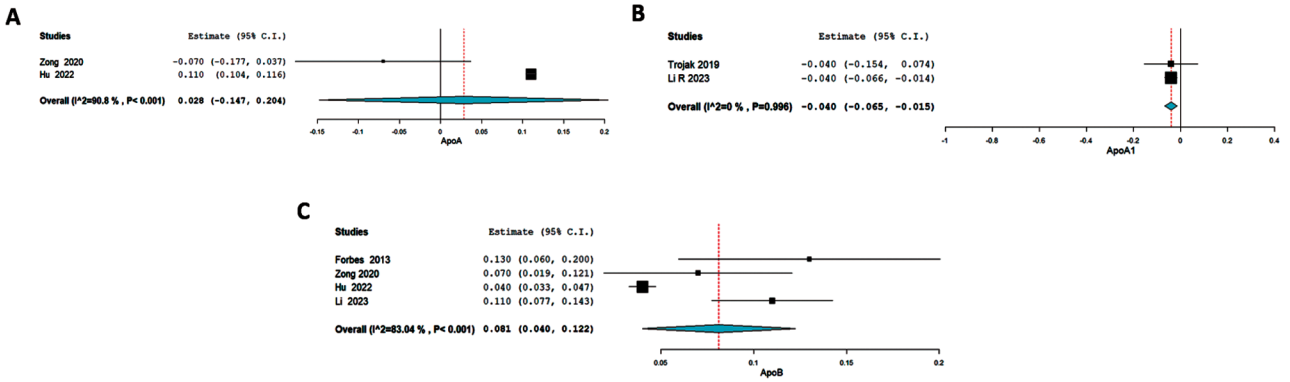

Fig. 9. Studies evaluating serum ApoA (A), ApoA-I (B) and ApoB (C) levels in diabetic NAFLD patients vs. diabetic patients without NAFLD.

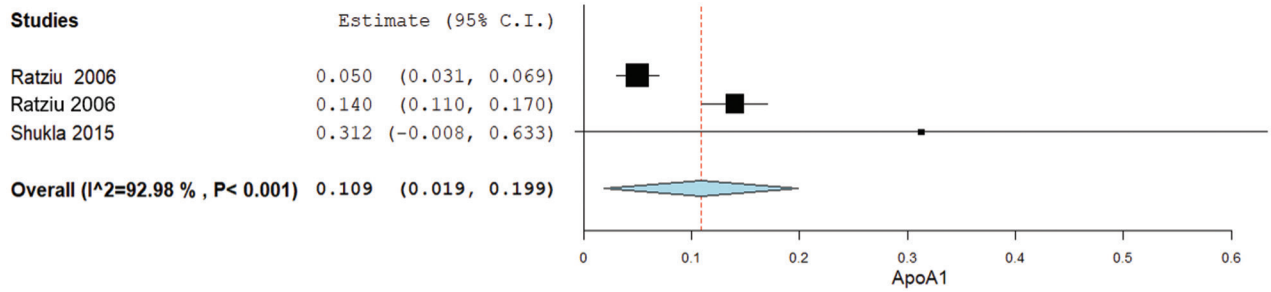

Fig. 10. Studies evaluating serum ApoA-I levels in F0/F1 NAFLD patients vs. F2/F4 NAFLD patients.

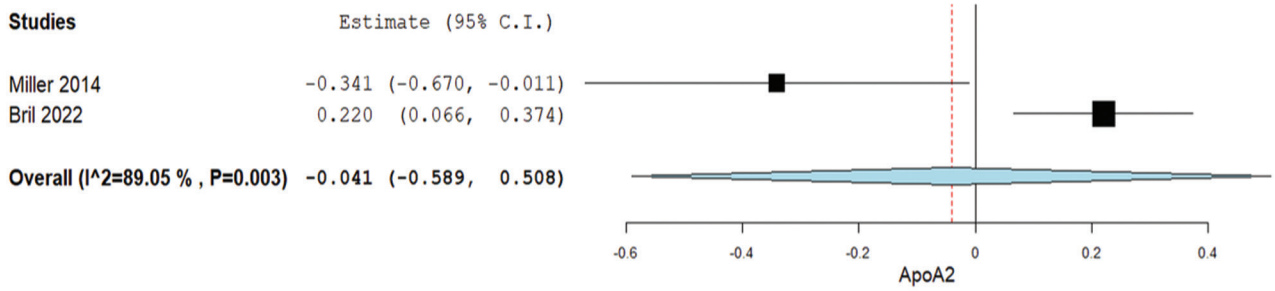

Fig. 11. Studies evaluating serum ApoA-II levels in F0/F2 NAFLD patients vs. F3/F4 NAFLD patients.

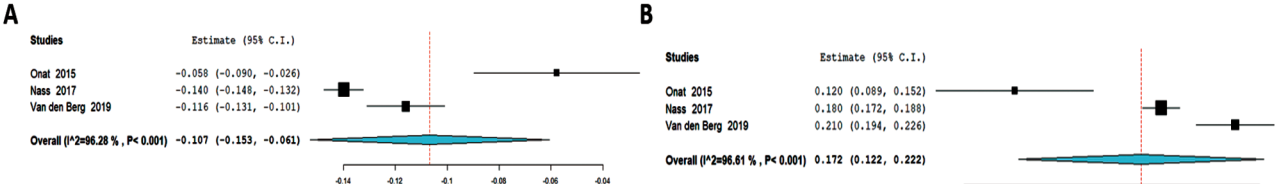

Fig. 12. Studies evaluating serum ApoA-I (A), and ApoB (B) levels in patients with FLI>60 vs. patients with a FLI<60.

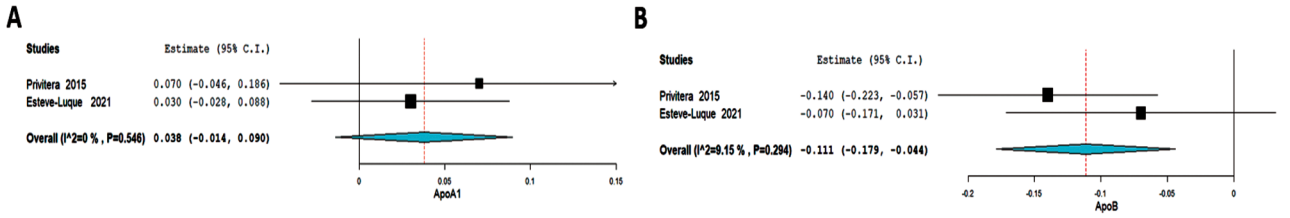

Fig. 13. Studies evaluating serum ApoA-I (A), and ApoB (B) levels in patients with mild NAFLD vs. patients with moderate/severe NAFLD.

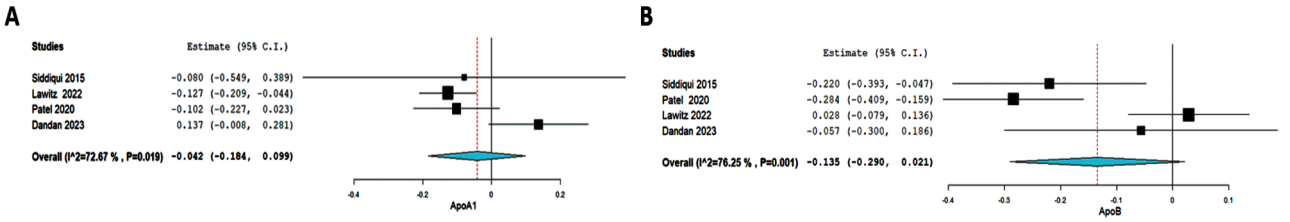

Fig. 14. Studies evaluating serum ApoA-I (A), and ApoB (B) levels in patients with cirrhotic NAFLD vs. patients with non-cirrhotic NAFLD.

DISCUSSION

This systematic review and meta-analysis synthesized data from 55 studies, encompassing a total of 432,328 individuals, to elucidate the relationship between serum apolipoproteins levels and various stages and subtypes of FLD. In NAFLD patients compared to controls, ApoA levels did not show a significant difference, while ApoA-I levels were lower and ApoB, ApoB100 and ApoE levels were higher. NASH patients had lower ApoA-I and higher ApoB levels than controls, with no significant difference in ApoB100. MAFLD patients showed higher ApoB and ApoE levels and lower levels of ApoA-I. NASH had higher ApoB levels than SS, with no difference in ApoA, ApoA-I and ApoB100. Overweight/obese NAFLD had higher ApoA-I and ApoB levels compared to controls. Also, the diabetic NAFLD group had higher ApoB levels, lower ApoA-I levels and no difference seen in ApoA levels when compared to the diabetic non-NAFLD group. Between different FLI scores ApoA-I levels were found to be lower in FLI<60 compared to FLI<60, while for ApoB levels they were higher. Between mild and severe NAFLD there was no significant change in ApoA-I levels, while ApoB levels were lower in mild NAFLD compared to severe NAFLD. ApoA-I and ApoB levels were not significantly different between cirrhotic and non-cirrhotic NAFLD.

In this meta-analysis, we found that NAFLD patients exhibited lower ApoA-I levels and higher ApoB, ApoB100 and ApoE levels compared to controls. These findings are consistent with previous studies that highlight the characteristic dyslipidemia in NAFLD, including reduced HDL cholesterol and elevated LDL and VLDL cholesterol levels [70]. The reduction in ApoA-I, a major component of HDL, suggests impaired reverse cholesterol transport, which is essential for the removal of excess cholesterol from peripheral tissues and its delivery to the liver [71]. Elevated ApoB and ApoB100 levels indicate an increase in atherogenic lipoproteins, which can exacerbate hepatic lipid accumulation and contribute to cardiovascular risk [72]. The lack of significant change in ApoE levels might be due to its varied roles in lipid metabolism and different expression patterns across individuals with NAFLD.

In NASH patients, our analysis demonstrated lower ApoA-I and higher ApoB levels compared to controls, while ApoB100 levels did not show a significant difference. This pattern is indicative of the more severe metabolic disturbances in NASH, the progressive form of NAFLD characterized by inflammation and fibrosis [73]. The lower ApoA-I levels reflect a greater impairment in HDL function and cholesterol clearance, while the higher ApoB levels suggest an increased burden of atherogenic lipoproteins contributing to hepatic inflammation and damage [74, 75]. The non-significant change in ApoB100 might be attributed to variations in study populations or differences in the stages of NASH among the included studies.

The same was observed in MAFLD patients, where we observed higher ApoB and ApoE levels,with lower levels in ApoA-I levels compared to controls. The increase in ApoB levels is consistent with the elevated cardiovascular risk and lipid abnormalities in MAFLD as well as the significant rise in ApoE levels, which might be related to its role in lipid transport and metabolism, reflecting the complex interplay of metabolic dysfunctions in MAFLD [76].

Comparing NASH to SS, we found higher ApoB levels in NASH, with no significant difference in ApoA-I levels. This result aligns with the understanding that NASH, marked by inflammation and fibrosis, is associated with more pronounced dyslipidemia than SS [77]. The elevated ApoB levels in NASH underscore the heightened atherogenic lipoprotein burden, which may contribute to the progression from SS to NASH [78].

Diabetic NAFLD patients showed higher ApoB levels and lower ApoA-I compared to diabetic patients without NAFLD, while ApoA levels were not significantly different. This observation supports the link between NAFLD and increased cardiovascular risk in diabetic individuals [79]. The elevated ApoB levels in diabetic NAFLD suggest a greater prevalence of atherogenic lipoproteins, which may be exacerbated by the insulin resistance and metabolic disturbances common in diabetes [80].

No significant changes in ApoA-I levels were found between, between mild and severe NAFLD. Additionally, ApoA1 levels were not significantly different between cirrhotic and non-cirrhotic NAFLD. These non-significant findings may be attributed to the heterogeneity in the study populations, differences in diagnostic criteria, and the varying stages of disease progression across the included studies. The lack of significant differences in these subgroups suggests that while Apo levels are useful biomarkers for distinguishing NAFLD from controls, their utility in differentiating between stages of NAFLD or between related conditions may be limited [81].

Overall, these findings contribute to a nuanced understanding of lipid abnormalities in NAFLD and its subtypes, highlighting the potential of apolipoprotein profiling in clinical practice for diagnosis and risk stratification. However, further research is needed to elucidate the underlying mechanisms and to refine the diagnostic criteria for these biomarkers.

This systematic review and meta-analysis have several limitations that should be considered when interpreting the findings. Firstly, the substantial heterogeneity observed across studies, particularly in apolipoprotein measurements, may affect the generalizability of the results. Differences in study populations, diagnostic criteria for NAFLD and its subtypes, and variations in laboratory methods for Apo quantification contribute to this heterogeneity. Secondly, the cross-sectional nature of most included studies limits the ability to infer causality between Apo levels and NAFLD progression. Additionally, the inclusion of studies with varying quality may introduce bias. Finally, the relatively small number of studies examining certain Apos, such as ApoE, reduces the statistical power to detect significant differences and limits the robustness of conclusions for these biomarkers.

Despite these limitations, this study has several strengths. We conducted a comprehensive literature search across three electronic databases, ensuring a broad inclusion of relevant studies. A large number of studies, with a broad geographical distribution, and a very large, pooled sample size, contribute to the generalizability and precision of the results. Our analysis included several key apolipoproteins, providing a detailed assessment of lipid metabolism in NAFLD and its subtypes. The inclusion of both NAFLD and MAFLD terms allowed us to account for the evolving definitions and diagnostic criteria in the literature. Additionally, we performed several subgroup analyses to evaluate the impact of disease severity, presence of NASH, and degree of liver fibrosis on apolipoprotein levels. This comprehensive approach enhances the understanding of the role of Apos in different stages and phenotypes of fatty liver disease, offering valuable insights for clinical practice and future research.

CONCLUSIONS

NAFLD patients exhibited lower ApoA-I and higher ApoB and ApoB100 levels compared to controls. NASH patients also had lower ApoA-I and higher ApoB levels compared to controls. In MAFLD, ApoB and ApoE levels were significantly higher compared to controls. Additionally, NASH patients had higher ApoB levels compared to those with SS, and diabetic NAFLD patients showed higher ApoB levels compared to diabetic patients without NAFLD.

This systematic review and meta-analysis provides comprehensive evidence of altered serum Apo levels in FLD and its subtypes, highlighting their potential as biomarkers for disease diagnosis and monitoring. The findings emphasize the need for further research to explore the mechanistic pathways linking lipid metabolism and FLD. Finally, integrating serum Apo levels into clinical practice could enhance the early detection and management of FLD, improving patient outcomes.

Conflicts of interest: None to declare.

Authors' contribution: A.I. had the idea of the manuscript. R.A. and G.G.M.S. independently applied the search strategy and performed the study selection. R.A., G.G.M.S., and M.G. performed risk of bias assessment. R.A. and G.G.M.S. performed the data extraction. R.A., G.G.M.S., A.I. and D.C.L. conducted the statistical analysis. R.A., G.G.M.S., and M.G. drafted the manuscript. A.I., D.C.L, S.L.P, L.A., and D.L.D. contributed to the writing of the manuscript. A.I., D.C.L., L.A., and D.L.D. made substantial contributions to the conception and critically revised the manuscript for important intellectual content. All authors revised the final manuscript and approved the final version.

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