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Association between ApoA1, ApoB, and the ApoB/ApoA1 ratio with the risk of diabetic neuropathy: A systematic review and meta-analysis

Ervina Gosal,[1] Tena Djuartina,[2*] Alfred Sutrisno,[3] Iskandar R. Budianto[4]

[1]Biomedicine Magister Program, School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, Jakarta, Indonesia
[2]Department of Anatomy, School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, Jakarta, Indonesia
[3]Department of Surgery, Faculty of Medicine, Tarumanegara University, Jakarta, Indonesia
[4]Department of Surgery, School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, Jakarta, Indonesia

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***Corresponding author:**
tena.djuartina@atmajaya.ac.id

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Systematic Review

ABSTRACT

Diabetic neuropathy is a common complication of diabetes mellitus and a major contributing factor to the development of diabetic foot ulcers (DFU). Apolipoproteins A1 (ApoA1) and B (ApoB), as well as the ApoB/ApoA1 ratio, play a crucial role in lipid metabolism and are believed to be involved in the development of neuropathic damage in individuals with diabetes. This study highlights the association between ApoA1, ApoB, and the ApoB/ApoA1 ratio with the risk of developing diabetic neuropathy. A systematic review was conducted following the PRISMA guidelines. An extensive literature search was conducted on December 7, 2024, using multiple databases, including PubMed, ProQuest, EBSCOhost, and Medline. There were no language or publication date restrictions. This synthesis relied solely on odds ratios (ORs) with 95% confidence intervals (CIs) as effect sizes. Included studies were observational in design, examining the association between ApoA1, ApoB, or the ApoB/ApoA1 ratio with diabetic neuropathy in an adult population. Of the 320 studies identified, 5 met the criteria for inclusion in the qualitative synthesis and meta-analysis, involving 2,756 diabetic patients. Findings showed higher ApoB levels and lower ApoA1 levels in patients with diabetic neuropathy compared with controls. However, no significant association was found between ApoB, ApoA1, or the ApoB/ApoA1 ratio with diabetic neuropathy or DFU risk. This review found no significant association between ApoB, ApoA1, or the ApoB/ApoA1 ratio with diabetic neuropathy or DFU. Further research is needed to explore their potential role in DM complications.

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disease characterised by elevated blood glucose due to inadequate insulin production or action. Its global burden is rising rapidly.[1] In 2021, an estimated 537 million adults (10.5% of the global adult population) had DM, with a significant proportion being older adults.[2] Indonesia ranks fifth globally, with 19.47 million people affected, a number projected to rise to 30 million by 2030.[3,4]

One of the most debilitating complications of DM is diabetic neuropathy, affecting sensory, motor, and autonomic nerves.[5] Prolonged hyperglycemia leads to nerve damage, manifesting as pain, numbness, and loss of function, and in severe cases, progressing to diabetic foot ulcers (DFUs).[6–8] Approximately 20% of DFU patients require lower-extremity amputation, either minor or major, with a one-year mortality rate of 10% following the initial diagnosis.[8,9]

Beyond hyperglycemia, recent studies emphasise the role of lipid metabolism, particularly apolipoproteins, in DM progression and complications.[10] Apolipoprotein A1 (ApoA1), associated

with HDL, exerts protective effects through antioxidant and anti-inflammatory mechanisms and enhances insulin sensitivity.[11] In contrast, Apolipoprotein B (ApoB), a key component of LDL and VLDL, contributes to atherogenesis, inflammation, and insulin resistance.[12] Evidence from in vitro and animal studies suggests that ApoA1 and ApoB influence fasting blood glucose levels by modulating the function of pancreatic beta-cells and insulin secretion.[13,14] In addition, epidemiological and clinical studies have examined the relationships between circulating levels of ApoA1, ApoB, and the ApoB/A1 ratio with fasting glucose levels and type 2 DM (T2DM).[15] These studies generally indicate an inverse or non-significant association between ApoA1 and fasting glucose, while ApoB and the ApoB/A1 ratio show positive correlations with elevated fasting glucose levels and a higher risk of T2DM. The inconsistent findings related to ApoA1 and T2DM indicate that these associations could be affected by demographic characteristics, genetic predispositions, and metabolic conditions.[10] Nevertheless, existing evidence consistently highlights the involvement of ApoB and the ApoB/A1 ratio in promoting insulin resistance, disrupting normal glucose metabolism.

The underlying mechanisms linking ApoB to insulin resistance and hyperglycemia include its role in promoting chronic inflammation and oxidative stress. Meanwhile, ApoA1 appears to enhance antioxidant enzyme activity and support beta-cell function, thereby maintaining glucose homeostasis.[10,12,13] The ApoB/ApoA1 ratio, widely recognised as a predictor of cardiovascular risk, has also been implicated in DM-related complications.[16,17] In patients with DM, an imbalance between ApoA1 and ApoB is believed to exacerbate inflammatory processes and nerve damage, potentially contributing to the progression of diabetic neuropathy.[18,19]

Despite growing evidence of these associations, no systematic review has been conducted, to our knowledge, that thoroughly examines the relationship between ApoA1, ApoB, and the ApoB/ApoA1 ratio with the risk of developing diabetic neuropathy. Therefore, this study reviewed and consolidated current evidence on these associations. Gaining deeper insight into apolipoproteins role in diabetic neuropathy initiation may provide new insights for risk stratification, prevention strategies, and more targeted management of DM complications.

METHODS

This research was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework and followed the methodological standards outlined in the Cochrane Handbook for Systematic Reviews.

Search strategy and databases

A systematic literature search was conducted on December 7, 2024, utilising multiple electronic databases, including PubMed, ProQuest, EBSCOhost, and Medline. To ensure the quality and rigour of the search process, the Peer Review of Electronic Search Strategies (PRESS) Checklist was used as a guideline for developing and refining the strategy. The search was conducted without restrictions on publication date or language, allowing for the inclusion of all potentially relevant studies. Articles published in languages other than English were translated using Google Translate or other reliable tools to ensure no valuable data was overlooked.

The keyword combination strategy incorporated both Medical Subject Headings (MeSH) and free-text terms, combined using Boolean operators (AND, OR). In PubMed, the search string included terms such as: ("Diabetic Neuropathies"[Mesh] OR "diabetic neuropathy" OR "peripheral neuropathy" OR "neuropathic complications") AND ("Apolipoproteins A"[Mesh] OR "Apolipoprotein A1" OR "ApoA1") AND ("Apolipoproteins B"[Mesh] OR "Apolipoprotein B" OR "ApoB") AND ("Apolipoprotein B/A1 Ratio" OR "ApoB/ApoA1" OR "ApoB:ApoA1"). Similar terms were used in ProQuest, EBSCOhost, and Medline, with syntax adjusted according to each platform's requirements. Across all platforms, the searches were limited to human studies involving adult populations aged 18 years and above.

In addition to database searches, the reference lists of all included studies were manually screened to identify any further relevant publications. Searches of grey literature and preprint platforms were also conducted to capture the most recent and unpublished studies. This

comprehensive, multi-step approach was designed to minimise the risk of omitting eligible studies and to enhance the overall robustness of the systematic review.

Study inclusion and data extraction

Studies considered eligible for inclusion in this review were those with observational designs, specifically cross-sectional, cohort, or case-control studies, which investigated ApoB, ApoA1, and the ApoB/ApoA1 ratio relationship with diabetic neuropathy occurrence or risk in adult populations. Studies that did not meet these criteria—such as duplicates, interventional, reviews, case reports, and conference abstracts—were excluded. Interventional studies were excluded to ensure methodological consistency and focus on observational evidence in humans. Although such studies, including those in animals, may offer mechanistic insights, their controlled settings and limited generalisability do not align with the real-world clinical focus of this review.

Duplicate records were removed using reference management software. Two independent reviewers screened titles and abstracts using predefined inclusion and exclusion criteria. Discrepancies were resolved through discussion or adjudicated by a third reviewer. Full texts of potentially relevant articles were assessed to confirm eligibility.

Data were extracted into Microsoft Excel, including publication year, country, study design, sample size, participant age, apolipoprotein markers evaluated (ApoA1, ApoB, ApoB/A1 ratio), and outcomes related to diabetic neuropathy. This standardised process ensured consistent and accurate data capture across studies.

Risk of bias and publication bias

The risk of bias assessment was conducted independently by multiple researchers to ensure objectivity and minimise reviewer bias. For studies with cohort and case-control designs, the Newcastle–Ottawa Scale (NOS) was employed as the primary assessment tool. This scale evaluates studies based on three key domains: selection of study groups, comparability of groups, and ascertainment of the outcome and exposure of interest. Each study could receive a maximum of nine stars, with higher scores indicating greater quality of methodology. For studies utilising a cross-sectional design, an adapted NOS version specifically tailored for cross-sectional studies (NOS-CS) was applied. This tool uses similar criteria but is modified to suit the characteristics of cross-sectional research, evaluating aspects such as sample representativeness, measurement of exposure and outcome, and control for confounding factors.

In both types of assessments, studies that received a score of seven stars or more were categorised as having a low risk of bias, while those scoring fewer than seven stars were assessed to be high risk of bias, indicating potential concerns regarding methodological rigour or study validity. Differences in scoring between reviewers were addressed through discussion to reach a consensus. Furthermore, funnel plots were created and examined visually to assess potential publication bias among the included studies. Asymmetry in the funnel plots was interpreted as a potential indication of publication bias.

Synthesis methods

All statistical analyses were performed using STATA version 15. The primary outcome measure was the odds ratio (OR) with 95% confidence intervals (CIs). If studies reported alternative effect sizes such as hazard ratios (HRs), relative risks (RRs), or standardised mean differences (SMDs), these were converted to ORs using validated statistical methods.[20]

For continuous data reported as medians and interquartile ranges (IQRs), values were converted to means and standard deviations (SDs) using established formulas.[21] When necessary, SMDs were transformed to log ORs (lnORs) and corresponding standard errors to facilitate meta-analysis pooling.[22]

Heterogeneity was assessed using the I^2 statistic with 95% uncertainty intervals, and tau^2 (τ^2) was reported as a variance estimate. An $I^2 \geq 60\%$ was interpreted as substantial heterogeneity, warranting the use of a random-effects model (DerSimonian & Laird method). Fixed-effects models were applied for $I^2 < 60\%$. Sensitivity analyses were conducted by excluding

studies identified as high risk of bias to assess the robustness of the pooled estimates.

Methodological limitations

Key methodological limitations were also acknowledged. First, potential misclassification bias may arise due to variation in the diagnostic criteria for diabetic neuropathy across included studies, which could affect outcome consistency. Second, the effect of converting diverse effect sizes, such as HR, SMD, and RR, into OR was carefully considered. Although these transformations enabled statistical pooling, they may introduce interpretational challenges and reduce comparability across studies. This is particularly relevant when original effect sizes represent time-to-event outcomes (as with HRs) or continuous outcomes (as with SMDs), which are simplified into binary associations when expressed as ORs.

RESULTS

Study selection

A total of 320 records were identified through systematic searches conducted across multiple databases (Figure 1). These records were first subjected to a duplicate screening process, during which 137 duplicate entries were removed to ensure data accuracy and eliminate redundancy. Following the removal of duplicates, 183 unique records remained for further screening based on titles and abstracts. At this stage, each record was carefully reviewed to assess its relevance according to predefined inclusion and exclusion criteria. As a result, 162 articles were excluded, either due to the irrelevance of the study focus or because they failed to address the outcomes of interest. The remaining 21 articles underwent full-text assessment for eligibility. During this thorough evaluation, each study was carefully inspected to decide its appropriateness for review inclusion. Out of these, 16 studies were excluded. The reasons for exclusion were carefully documented: 14 studies were excluded because the outcomes reported were not relevant to the objectives of this review, and 2 studies were removed because they lacked sufficient quantitative data required for meta-analysis. Ultimately, 5 studies met all eligibility criteria and were included in the qualitative and quantitative analysis.

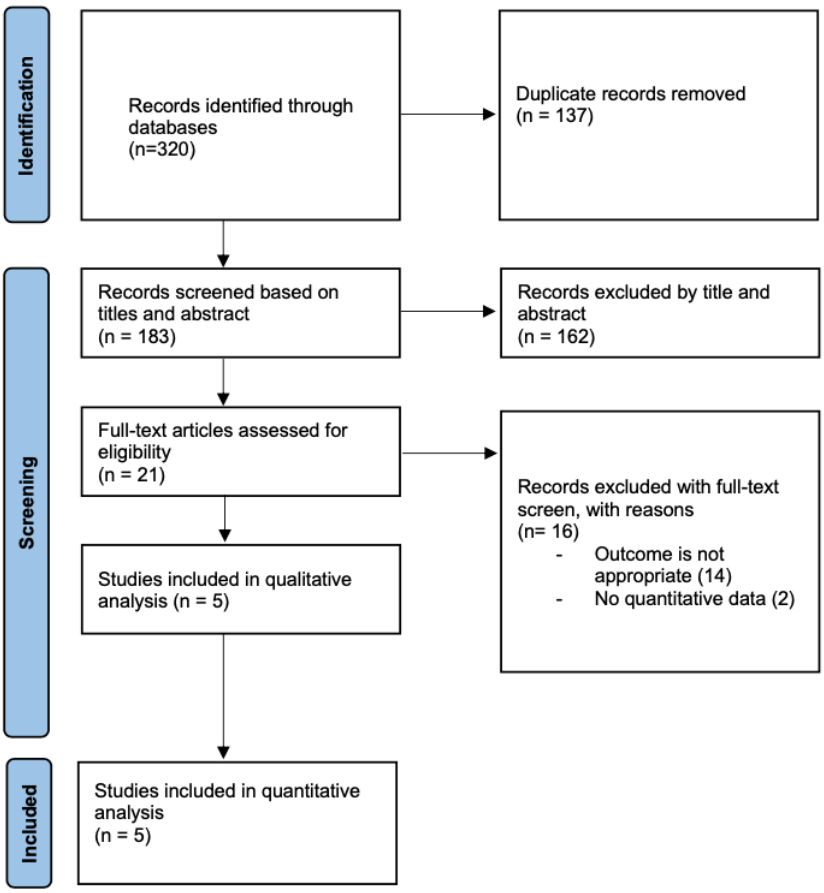

Figure 1. Study Selection Process

Study characteristics

Five studies from different countries were included in this review, all of which examined the role of apolipoprotein markers in patients with diabetes experiencing neuropathic complications, including DFU. These studies were published between 2010 and 2022 and encompassed a variety of research designs: two were case-control studies, one was a case-cohort study, one employed a cohort design, and one was a cross-sectional study. Across these studies, the total sample size consisted of 2,756 participants, with individual study sample sizes ranging from 152 to 1,057 diabetic patients. The types of neuropathies evaluated varied, including both generalised diabetic neuropathy and diabetic foot-specific neuropathy.

The studies assessed three key apolipoprotein indicators: ApoB (analysed in four studies), ApoA1 (in three studies), and the ApoB/ApoA1 ratio (in two studies). A detailed summary of each study's characteristics can be found in Table 1. Overall, the findings consistently showed that ApoB levels were elevated in diabetic patients with neuropathy when compared to those without neuropathic complications. Conversely, ApoA1 levels were generally lower in neuropathic patients, with the study by Nanda et al. particularly highlighting this trend. The ApoB/ApoA1 ratio showed relatively minor differences between neuropathy patients and control groups; however, certain studies reported a modest increase in this ratio among diabetic individuals with neuropathy.

Table 1. Study Characteristics

Author	Year	Count-ry	Study Design	Sam-ple (N)	Age Mean±SD/ Median (IQR)	Neuropat-hy Type	Apolipop-rotein Indicator	Study Mean±SD/ Median (IQR)	Control Mean±SD/ Median (IQR)
Gonzalez et al.[23]	2010	Spain	Case-control study	198	68±10.4	Diabetic foot	Apo B	1.07±0.30	0.96±0.25
Aryan et al.[24]	2017	Iran	Case-control study	939	57.9±9.7	Neuropath y	Apo B,	88.1±27.5	85.8±26.2
							Apo A1,	141.8±28.5	135.6±27.9
							Apo B/Apo A1 ratio	0.63±0.22	0.64±0.24
Moosaie et al.[25]	2020	Iran	Case-cohort study	1057	59.3±9.14	Neuropath y	Apo B	92.21± 27.90	91.07±26.82
							Apo A1	131.58± 29.35	134.07± 28.89
							Apo B/Apo A1 ratio	0.71±0.36	0.68±0.32
Rinkel et al.[26]	2021	Nethe rlands	Cohort-study	410	65.7(54.5-75.4)	Diabetic Foot	Apo B	0.9 (0.6–1.2)	0.9 (0.8–1.1)
Nanda et al.[27]	2022	India	Cross-sectional study	152	51.37 ± 10	Neuropath y and diabetic foot	Apo A1	76.0±31.5	97.0±24.5

Risk of bias

All five studies in this review demonstrated a low risk of bias, as indicated by their scores of ≥7 on the NOS. The consistently high scores across these studies suggest that they employed rigorous research designs, minimised potential confounding factors, and utilised reliable methods for data collection and outcome assessment. A comprehensive overview of the risk of bias for each study is presented in the supplementary materials

Sensitivity analysis

To assess the robustness of the pooled results, sensitivity analyses were planned by excluding studies with a high risk of bias. However, since all five included studies were rated as having low risk of bias based on the NOS, no studies were excluded. As a result, the original pooled estimates remained unchanged, and further sensitivity analyses were not necessary.

Association between ApoB levels and neuropathy/DFU

Four studies explored the relationship between ApoB levels and the presence of neuropathy or DFU. The combined analysis revealed that there was no statistically significant association between elevated ApoB levels and the occurrence of neuropathy or DFU (OR = 1.1; 95% CI: 0.93–1.27; $p > 0.05$). The heterogeneity among these studies was moderate ($I^2 = 37\%$, $\tau^2=0.024$), suggesting that the results were relatively consistent across different study populations and designs. These findings indicate that, although ApoB is known for its role in lipid metabolism and cardiovascular risk, its direct contribution to the development of neuropathic complications in diabetic patients remains unclear based on the current evidence (Figure 2).

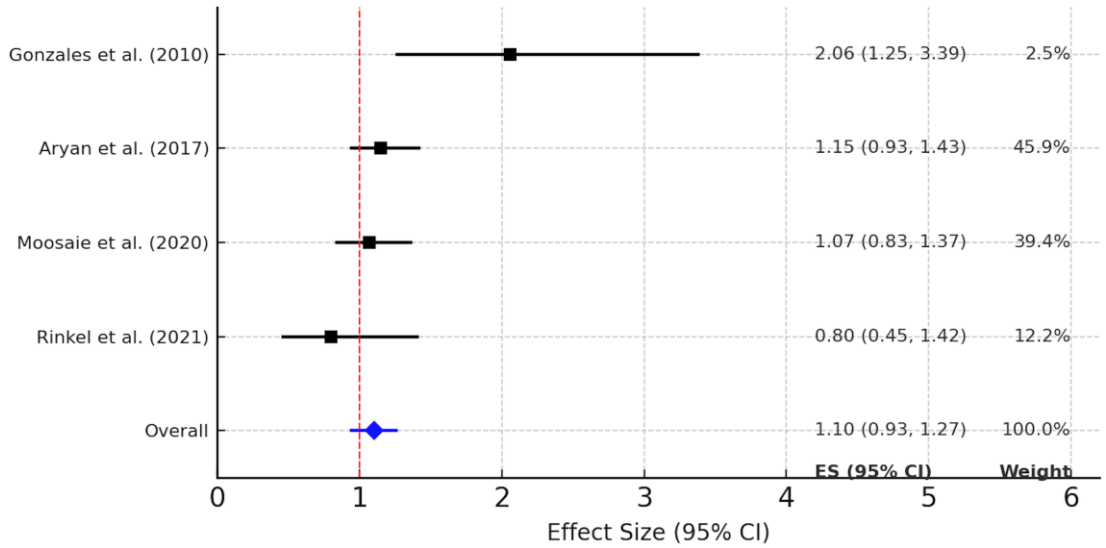

Figure 2. Association between ApoB levels and neuropathy/DFU

Association between ApoA1 levels and neuropathy/DFU

Three studies investigated the ApoA1 levels and the presence of neuropathy or DFU association. The pooled analysis did not demonstrate a significant relationship, with an odds ratio of 0.86 (95% CI: 0.20–1.52; $p > 0.05$). However, a high degree of heterogeneity was observed among these studies (I^2 = 96.2%, τ^2=0.810), indicating considerable variability in the study populations, methodologies, or outcomes. Despite the known protective role of ApoA1 in metabolic and inflammatory processes, the current evidence does not consistently support its association with neuropathic complications in diabetic patients (Figure 3).

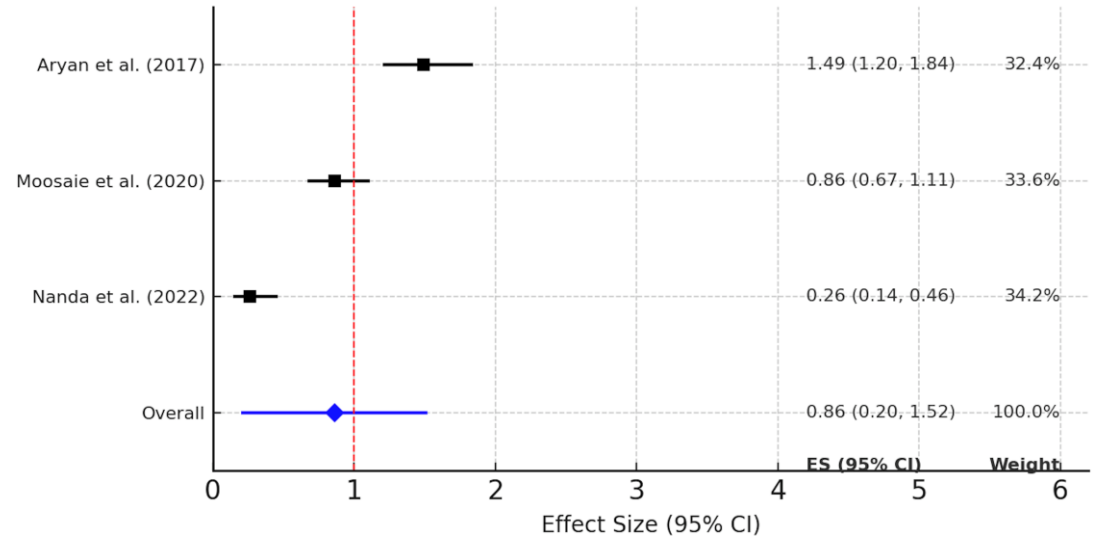

Figure 3. Association between ApoA1 levels and neuropathy/DFU

Association between the ratio of ApoB/ApoA1 levels and neuropathy/DFU

Two studies explored the association between the ApoB/ApoA1 ratio and the occurrence of neuropathy or DFU. The combined results revealed no significant correlation, with an odds ratio of 1.01 (95% CI: 0.84–1.17; $p > 0.05$). The heterogeneity between these studies was moderate (I^2 = 42.6%, τ^2=0.031), suggesting some variability in study designs or populations, but not to an extent that undermines the overall analysis. Although the ApoB/ApoA1 ratio is widely recognised as a marker for cardiovascular risk and metabolic imbalance, current evidence does not indicate a direct association with neuropathic complications in diabetes (Figure 4).

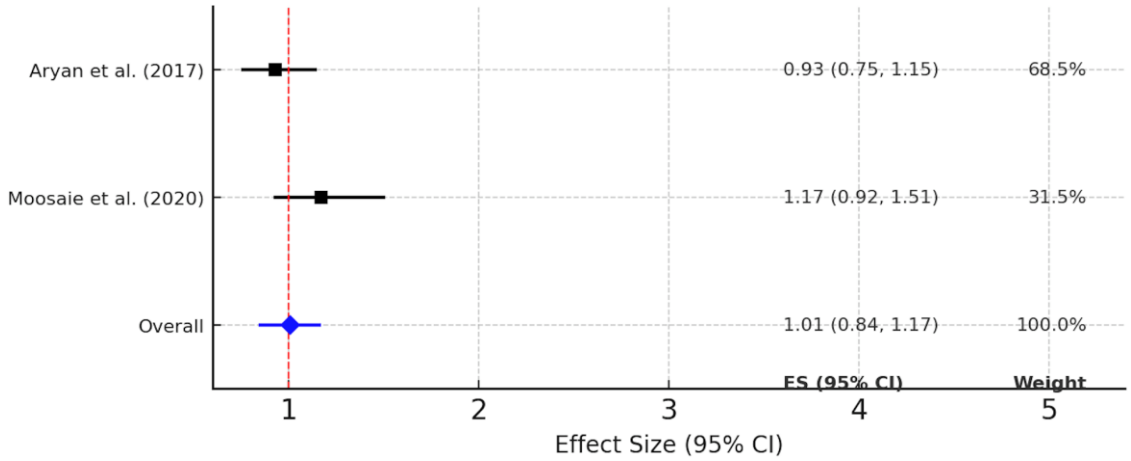

Figure 4. Association between the ratio of ApoB/ApoA1 levels and neuropathy/DFU

Publication bias

Publication bias was examined in the studies exploring the association between ApoB and ApoA1 levels and the risk of diabetic neuropathy, as shown in the supplementary materials. This suggests that smaller or negative studies in these areas may be underrepresented in the published literature. In contrast, no signs of publication bias were found in analyses evaluating the ApoB/ApoA1 ratio and neuropathy association, indicating more consistent and balanced reporting of results in that particular area.

DISCUSSION

This systematic review evaluated the association between apolipoprotein markers—ApoB, ApoA1, and the ApoB/ApoA1 ratio—and the risk of diabetic neuropathy and diabetic foot ulcers (DFU). Our analysis found no statistically significant associations between these biomarkers and the occurrence of neuropathy or DFU. However, this absence of association should not be construed as definitive evidence of no relationship. Rather, it likely reflects current limitations in the available evidence, including methodological heterogeneity, small sample sizes, and unmeasured confounding variables. Given these constraints, the clinical utility of these biomarkers in this context remains uncertain, and we do not support their use as standalone screening tools for neuropathy or DFU at this time.

Our findings are consistent with those of Ulloque-Badaracco et al., who also reported no significant association between ApoA1, ApoB, or their ratio and DFU risk.[28] However, they differ from the findings of Nanda et al., who observed that lower ApoA1 levels were associated with increased DFU risk.[27] ApoA1, the principal protein component of HDL, is well-known for its anti-inflammatory and anti-atherogenic properties, particularly its role in modulating macrophage activity.[27] It promotes M2 macrophage polarization and upregulates IL-10, thereby reducing pro-inflammatory cytokine expression. Animal studies further support these mechanisms, showing that ApoA1 administration can suppress inflammation through multiple pathways.[29] In clinical settings, particularly among patients with DFU, markedly lower ApoA1 levels have been observed, underscoring its role as a potential independent biomarker for DFU complications.[25,27] Although our meta-analysis did not find a significant association between ApoA1 and diabetic neuropathy, the inverse correlation between ApoA1 and TNF-α observed in some studies suggests a biologically plausible anti-inflammatory role that may influence neuropathy development. This relationship, however, may be obscured in pooled analyses by residual confounding and varying diagnostic criteria.[27,30]

Similarly, while ApoB levels were not statistically elevated in patients with diabetic neuropathy, a consistent trend toward higher ApoB concentrations was observed. ApoB has a central role in lipid metabolism by facilitating the assembly, secretion, and transport of lipoproteins.[31] Its two major forms, ApoB-48 and ApoB-100, serve distinct physiological functions

— the former mediates dietary lipid transport from the intestine, while the latter is involved in hepatic VLDL formation and regulation through LDL receptor interactions.[32,33] In diabetic patients, chronic hyperglycemia and insulin resistance often derange lipid metabolism, thereby increasing VLDL and LDL levels and contributing to hyperlipidemia and atherosclerosis. This vascular dysfunction may impair nerve perfusion, contributing to the development of diabetic neuropathy.[32] Thus, while the current statistical analysis did not show a significant effect, the biological plausibility of ApoB's involvement in neuropathy remains strong and warrants further investigation.[31,34]

The ApoB/ApoA1 ratio serves as a crucial indicator of lipid metabolism, reflecting the balance between HDL and LDL.[35] This ratio is vital for cardiovascular health and may have implications for conditions such as diabetic neuropathy. HDL transports cholesterol to the liver for excretion, therefore reducing cardiovascular disease risk, while LDL can contribute to atherosclerotic plaque formation, elevating the risk of stroke and cardiovascular disease. A balanced ApoB/ApoA1 ratio indicates a healthier lipid profile.[35,36] However, current evidence on its direct association with diabetic neuropathy and DFU remains inconclusive. The limited number of studies, along with conflicting findings, highlights the need for more robust research to determine whether this ratio could serve as a predictive marker for diabetic microvascular complications. Given the limited prognostic performance of apolipoproteins in this context, future studies should also consider alternative biomarkers involved in key pathophysiological pathways, such as oxidative stress, endothelial dysfunction, and neuroinflammation. Promising candidates include malondialdehyde (MDA), advanced glycation end-products (AGEs), and proinflammatory cytokines such as IL-6 and TNF-α.[37]

This systematic review also has several limitations that should be acknowledged. First, the analysis did not adjust for potential confounding factors such as lifestyle behaviours, sociodemographic characteristics, glycemic control, or other comorbid conditions, all of which may influence apolipoprotein levels and neuropathy risk. Future studies should aim to incorporate these variables into their analyses to provide more accurate and unbiased estimates. Second, publication bias was detected for studies examining ApoB and ApoA1, suggesting that smaller or non-significant findings may be underrepresented in the literature. This emphasises the need for greater transparency in research reporting and the inclusion of negative or null findings in future publications. Third, we acknowledge that variations in apolipoprotein assay methods across the included studies—such as differences in laboratory protocols, calibration standards, and reference ranges—may have introduced measurement heterogeneity, potentially affecting the comparability of results. Finally, the relatively small number of eligible studies and the heterogeneity among their methodologies limit the generalisability of these findings.

CONCLUSION

Analysis of the available studies revealed no statistically significant association between ApoB, ApoA1, or the ApoB/ApoA1 ratio and the risk of diabetic neuropathy or diabetic foot complications. Although these biomarkers currently lack consistent prognostic value, their mechanistic roles in nerve ischemia and inflammation warrant further investigation in phenotypically stratified cohorts. These findings highlight the need for future research using longitudinal and multi-omics approaches to better understand apolipoprotein involvement in neuropathy. While current evidence does not support the routine clinical use of these markers, continued exploration may inform more personalised screening strategies.

CONFLICT OF INTEREST

The authors state that they have no conflicts of interest related to the publication of this article.

REGISTRATION AND PROTOCOL

This review was not registered.

ACKNOWLEDGMENTS

None.

DATA AVAILABILITY STATEMENT

All data generated or analysed in this study are presented within the published article and its supplementary materials. Additional datasets used and/or analysed during the study can be obtained from the corresponding author upon reasonable request.

SUPPLEMENTARY MATERIAL(S)

The following supporting information can be found in the supplementary materials:

- Appendix 1: Risk of bias assessment (the Newcastle–Ottawa Scale (NOS) and adapted NOS for cross-sectional studies).
- Appendix 2: Funnel plot for publication bias.
- Appendix 3: Syntax and PRESS Checklist
- Appendix 4: PRISMA Checklist

AUTHOR CONTRIBUTIONS

All authors (EG, TD, AS and IB) contributed significantly to the research. EG, TD, AS and IB conceptualised the study, as well as data collection. EG and TD conducted the risk of bias assessment and performed the data analysis, while AS and IB interpreted the results. The manuscript was drafted by EG and TD, with all authors actively participating in the critical revision and finalisation of the manuscript.

DECLARATION OF USING AI

Artificial intelligence (AI) tools were used in the preparation of this manuscript to assist with tasks such as grammar refinement, sentence restructuring, formatting suggestions, and improving overall clarity. The content, interpretation of results, and scientific arguments presented in the manuscript were developed and validated by the authors, who take full responsibility for their accuracy and integrity. No AI tool was used to generate or interpret original scientific findings, statistical analyses, or study conclusions.

LIST OF ABBREVIATIONS

ApoA1 (Apolipoprotein A1), ApoB (Apolipoprotein B), DM (Diabetes Mellitus), DFU (Diabetic Foot Ulcer), IDF (International Diabetes Federation), VLDL (Very Low-Density Lipoproteins), LDL (Low-Density Lipoproteins), HDL (High-Density Lipoproteins), TNF-α (Tumor Necrosis Factor-alpha), IL-10 (Interleukin-10), PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses), NOS (Newcastle–Ottawa Scale), NOS-CS (Newcastle–Ottawa Scale for Cross-Sectional Studies), OR (Odds Ratio), CI (Confidence Interval), IQR (Interquartile Range), SD (Standard Deviation), and lnOR (Natural Logarithm of Odds Ratio).

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