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SYSTEMATIC REVIEW

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The high-density lipoprotein lipidome in metabolic syndrome: A systematic review

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Abstract

Background: Metabolic syndrome (MetS) is a cluster of cardiovascular risk factors, including low high-density lipoprotein cholesterol (HDL-C) levels. Although HDL-C is an established cardiovascular biomarker, in MetS this marker captures only a fraction of the profound alterations occurring within HDL particles. The cardiometabolic role of HDLs in MetS remains insufficiently understood because the functional properties and molecular components of HDLs, rather than HDL-C alone, are likely key determinants of cardiovascular risk. Since the early 2000s, research has revealed that HDL particles comprise over 280 proteins and more than 300 lipid species, underscoring their biological complexity. Moreover, HDL composition and function are extensively remodelled in MetS, highlighting the importance of characterising the differences in HDL composition between health and disease. In this systematic review, we aimed to examine differences in the HDL lipidome between MetS patients and healthy controls.

Methods: A comprehensive literature search was conducted in MEDLINE, Cochrane Library, and Web of Science. The PRISMA guidelines for systematic reviews were followed, and four records met the eligibility criteria.

Results: Overall, the HDL lipidome was markedly different in MetS compared with healthy individuals. MetS was consistently associated with higher levels of

triacylglycerides (TAGs) and phosphatidylinositol, alongside lower levels of several key lipid families, indicating a broad remodelling of HDL composition.

Conclusions: These findings indicate that the HDL lipidome is substantially altered in MetS, with potential consequences for HDL functionality. Although the mechanistic implications remain to be fully elucidated, TAG enrichment may contribute to lower HDL levels and changes in HDL surface lipids may impair essential functions such as cholesterol efflux. Further studies are needed to validate these patterns and determine their impact on HDL function and cardiometabolic risk.

KEYWORDS

cardiometabolic, composition, high-density lipoprotein, lipid, metabolic syndrome, obesity

1 | INTRODUCTION

Metabolic syndrome (MetS) is a condition that clusters different metabolic abnormalities, including central obesity, hypertension, impaired glucose metabolism and atherogenic dyslipidemia, which together raise the risk of developing cardiovascular disease (CVD). Impaired glucose metabolism in MetS frequently progresses to type 2 diabetes mellitus, one of its most common and clinically relevant comorbidities. A hallmark of MetS-associated dyslipidemia is the combination of low high-density lipoprotein cholesterol (HDL-C) and high triacylglyceride (TAG) levels.[1] Despite advancements in pharmacotherapy and an improved understanding of disease pathophysiology, the global prevalence of MetS and its associated comorbidities continues to rise, representing a major public health burden.[2] Furthermore, CVD, which is the primary complication of MetS, remains the leading cause of mortality worldwide.[3]

The inverse relationship between HDL-C and cardiovascular risk is well-established, with low HDL-C recognised as an independent risk factor for CVD.[4–6] However, this association is not causal. Clinical interventions aimed at raising HDL-C have not reduced cardiovascular events, and HDL-C exhibits a U-shaped relationship with mortality.[5,7–9] These observations highlight the need to move beyond HDL-C and consider the broader functional and compositional features of HDL that contribute to cardiovascular protection. HDL particles facilitate the removal of excess cholesterol from peripheral tissues and transport it to the liver for excretion, a process known as reverse cholesterol transport.[10,11] Beyond this central role, HDLs exhibit several other functionalities, including antioxidant, anti-inflammatory and antithrombotic activities. These functions are largely determined by the particle's cargo and structure.[12–16] HDLs are complex biomolecules composed of a wide variety of lipids and proteins. Recent advances in mass spectrometry (MS) have substantially improved our ability to characterise these particles. To date, over 280 proteins have been identified in the HDL proteome,[17] along with more than 300 lipid species,[18–20] highlighting the molecular heterogeneity and functional versatility of HDLs.

The lipid constituents of HDLs primarily are surface amphipathic lipids, including glycerophospholipids (glycerolPLs), sphingolipids and free cholesterol (FC), into which proteins are embedded and that surround a hydrophobic core rich in TAGs and cholesteryl esters (CEs).[18–23] Numerous species have been identified within these lipid families, and their abundance can vary depending on physiological and pathological conditions.[15,19–24]

While the HDL proteome has been extensively studied and even reviewed in dedicated databases,[18] the HDL lipidome remains comparatively underexplored.[6,24,25] Lipid molecules not only serve as structural elements but also play active roles in functionality, influencing membrane fluidity, receptor interactions, enzyme activity and signalling pathways.[12] However, the diversity, dynamic nature and analytical complexity of lipid species present significant challenges for their characterisation.[26] Consequently, there is limited consensus in the literature regarding HDL lipid composition, particularly under pathological conditions such as MetS.[18–22,24,25,27] This knowledge gap is critical, as changes in the HDL lipidome may significantly impair HDL function, potentially contributing to the residual cardiovascular risk observed in MetS.

Although quantitative changes in HDL levels are well documented in MetS[1,28] much less is known about the qualitative changes in HDL particles, specifically their lipidomic profiles. Therefore, this systematic review aims to synthesise current evidence on alterations in the HDL lipidome in individuals with MetS as compared with healthy controls.

2 | METHODOLOGY

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[29] This review was registered and accepted in PROSPERO (Registration No. CRD42024554174). Available from: https://www.crd.york.ac.uk/PROSPERO/view/CRD42024554174.

2.1 | Search strategy

A comprehensive literature search was conducted in three different databases: MEDLINE (Pubmed), Web of Science (WOS) and Cochrane Library. The following search strategy was applied: ('Metabolic Syndrome' OR 'obes*' OR 'insulin resistance' OR 'hypertension') AND ('HDL' OR 'High-density lipoprotein') AND ('lipid composition' OR 'lipidom*' OR 'lipid level'). The initial search was conducted in May 2024. An updated search was carried out in June 2025 after completion of the review to identify any newly published evidence. The search strategy was developed based on the Population, Intervention, Comparator and Outcome (PICO) criteria (Table 1).

2.2 | Selection criteria

Eligibility was assessed according to the following criteria: published records were included if the population consisted of individuals with MetS, the study subjects were human adults, HDL lipid composition was analysed, and type 2 diabetes mellitus was the only comorbidity allowed. Although CVD is the principal clinical outcome of MetS, it was not used as an inclusion criterion to avoid disease-related heterogeneity and to capture HDL alterations specifically attributable to MetS itself. Studies were excluded if the population presented other comorbidities and/or if they were interventional trials not including baseline comparisons between MetS and control groups. Included records comprised observational studies and clinical trials, while reviews, opinion papers, case reports, conference abstracts and studies with overlapping results were excluded.

2.3 | Data extraction and reliability

This review followed the PRISMA recommendations.[29] Duplicate records were removed using Excel. Screening and data extraction were performed independently by two authors, with discrepancies resolved by a third author. Screening was conducted sequentially: first by title, then abstract and finally full-text evaluation of eligible records. The variables collected included anthropometric characteristics of the study populations, HDL isolation techniques, bioinformatic approaches and HDL lipid composition. Specific single-lipid species were not prespecified, as these depended on what was reported in each study; all available lipid data were extracted and analysed as presented by the original authors.

TABLE 1 PICO criteria.

Criteria	Definition
Population	MetS patients
Intervention	None (baseline)
Comparator	Healthy control group (no MetS)
Outcomes	HDL lipid composition

Abbreviations: HDL, high-density lipoprotein; MetS, metabolic syndrome; PICO, Population, Intervention, Comparator and Outcome.

3 | RESULTS

3.1 | Search and record selection

After duplicate removal, a total of 900 records were retained for title screening. Of these, 140 were selected for abstract screening and 24 full-text articles were assessed for eligibility. Finally, 4 studies met the inclusion criteria and were included in this review (Figure 1).

3.2 | Clinical characteristics of the study populations

Table 2 summarises the clinical characteristics of the populations included in each study. All records diagnosed MetS based on the National Cholesterol Education Program Adult Treatment Panel III (NCEP:ATPIII) criteria.[19–22] In their 2017 publication, Denimal et al. applied a modified version of these criteria, diagnosing MetS in the presence of fasting hyperglycemia along with at least two additional NCEP:ATPIII criteria.[22]

Overall, the number of cases and controls included in each study was around 15–20 participants per group,[19,20,22] except for Khan et al., which included a larger study population.[21] The distribution of men and women was balanced across all studies.[19–22] The age was also comparable, ranging from 40 to 55 years, with no significant differences between MetS and control groups. The only exception was the study by Mocciaro et al.,[19] in which the control group was significantly younger; this difference was statistically corrected in the analysis. In terms of specific clinical variables, as expected, all the MetS populations exhibited higher body mass index (BMI), lower HDL-C concentrations and higher TAG

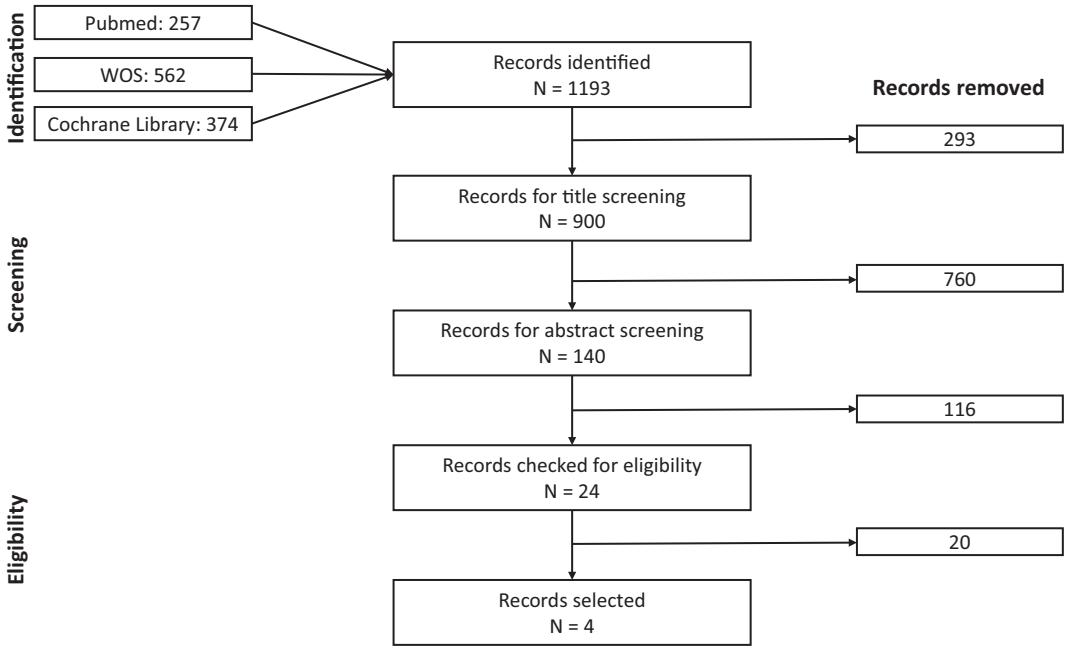

FIGURE 1 PRISMA flow diagram of the study selection process. Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; WOS, Web of Science.

levels relative to controls.[19–22] Interestingly, elevated fasting glucose was significantly higher in MetS only in the studies by Khan et al. and Mocciaro et al.[19,21]

3.3 | HDL lipid composition

All studies reported differences in HDL lipid composition between the MetS and control populations. However, there were key methodological differences among the studies, including the HDL isolation techniques, lipid extraction methods, HDL fractions analysed and the procedures to normalise HDL lipid levels (Table 3).

Ultracentrifugation is considered the gold standard for HDL isolation and was the method of choice in most of the included studies,[20–22] whereas Mocciaro et al. isolated HDL particles using size exclusion chromatography (SEC).[19] Additionally, ultracentrifugation allows the separation of HDL2 and HDL3 subfractions, which were specifically analysed by Denimal et al. [21]

HDL lipids were primarily extracted using adaptations of the Folch method with chloroform: methanol. However, for specific sphingolipid species, Denimal et al.[21,22] used an alternative protocol based on isopropanol:water:ethyl acetate. In their 2016 study, this method was applied to quantify ceramides and sphingosine 1 phosphate (S1P), whereas in the 2017 study it was used specifically for S1P.[21,22] Notably, in their 2017 study, Denimal et al. did not perform lipid extraction; instead, total HDL lipid composition was assessed using a Vista analyzer, rather than MS.[22]

A major limitation when comparing HDL lipid composition across studies is in the heterogeneity of normalisation strategies. These choices often depend on both the HDL isolation technique and lipid detection technology employed. This presents a challenge, as each study participant has a different concentration of HDLs in blood, a variation that becomes even more pronounced when comparing MetS and control populations, given that MetS is typically characterised by lower HDL levels. Most studies normalised lipid levels to HDL protein quantity or apolipoprotein A1 (apoA1) concentration, both of which serve as proxies for HDL quantity. Among the four records included in this review, different normalisation approaches were used. For example, Denimal et al.[22] used both HDL apoA1 and total protein concentration, though the latter was applied only for S1P species. In their previous study, Denimal et al. normalised by total HDL weight.[21] Mocciaro et al., in contrast, normalised using HDL total protein content.[19] Finally, Khan et al.[20] normalised lipid content by total phosphatidylcholine (PC) concentration in HDL, and individual lipid species were expressed relative to the total amount within their respective lipid family.[20]

3.3.1 | HDL surface lipids

Several glyceroPL and sphingolipid families were significantly modulated in MetS, with differences

TABLE 2 Clinical characteristics of the different populations included in the review.

	Denimal et al. [21]	Denimal et al. [22]	Khan et al. [20]	Mocciaro et al. [19]
N (N of men)	MetS: 26 (14) Ctrl: 50 (24)	MetS: 23 (11) Ctrl: 23 (13)	MetS: 95 (56) Ctrl: 40 (19)	MetS: 14 (9) Ctrl: 11 (6)
Age	MetS: 47 ± 11 Ctrl: 45 ± 16	MetS: 42 ± 15 Ctrl: 50 ± 19	MetS: 55 ± 6 Ctrl: 54 ± 4	MetS: 42± 10 Ctrl: 29 ± 2*
BMI	MetS: 45 ± 9 Ctrl: 24 ± 3*	MetS: 42 ± 6 Ctrl: 22 ± 3*	MetS: 32 (30–35) Ctrl: 24 (22–24)*	MetS: 33 ± 3 Ctrl: 23 ± 2*
WC	Ctrl: NR MetS: Women: 122 ± 18 Men: 125 ± 16	Ctrl: NR MetS: Women 129 ± 8 Men 120 ± 5	NR	MetS: 111 ± 7 Ctrl: 86 ± 8*
HDL-C	MetS: 0.9 ± 0.2 Ctrl: 1.6 ± 0.3*	MetS: 1.0 ± 0.2 Ctrl: 1.6 ± 0.3*	MetS: 1.2 (1.0–1.4) Ctrl: 1.7 (1.5–1.9)*	MetS: 0.9 ± 0.2 Ctrl: 1.6 ± 0.4*
ApoA1	NR	NR	MetS: 1.43 ± 0.24 Ctrl: 1.69 ± 0.22*	Significantly lower in MetS
Glucose	MetS: 5.2 ± 0.6 Ctrl: 5.2 ± 0.4	MetS: 5.3 ± 0.4 Ctrl: 5.1 ± 0.5	MetS: 5.8 (5.6–6.2) Ctrl: 4.8 (4.6–5.3)*	MetS: 5.7 ± 0.7 Ctrl: 5.0 ± 0.4*
T-C	MetS: 4.8 ± 1.1 Ctrl: 5.2 ± 0.9	MetS: 5.1 ± 1.0 Ctrl: 5.0 ± 1.0	MetS: 5.5 (4.9–6.2) Ctrl: 4.9 (4.6–5.0)*	MetS: 5 ± 1.1 Ctrl: 5.7 ± 1
LDL-C	MetS:3.2 ± 0.9 Ctrl: 3.4 ± 0.8	MetS: 3.2 ± 0.9 Ctrl: 3.0 ± 0.8	NR	MetS: 3.4 ± 1.1 Ctrl: 3.5 ± 0.9
TAG	MetS: 1.9 ± 0.7 Ctrl: 0.9 ± 0.3*	MetS: 1.9 ± 0.8 Ctrl: 1.0 ± 0.3 *	MetS: 1.5 (1.2–2.2) Ctrl: 0.6 (0.5–1.0)*	MetS: 1.5 ± 0.3 Ctrl: 0.8 ± 0.3*
BP	MetS $n = 9$	MetS $n = 14$	SBP: MetS: 136 (126–148) Ctrl: 121 (112–129)*	SBP: MetS: 122 ± 12 Ctrl: 116 ± 8 DBP: MetS: 80 ± 7 Ctrl: 78 ± 6
MetS criteria	NCEP:ATPIII	Modified NCEP:ATPIII	NCEP:ATPIII	NCEP:ATPIII
Comorbidities	No dysthyroid or renal disease	Non-diabetic, no renal or thyroid diseases	No diabetes, renal, hepatic or thyroid dysfunction	No autoimmune disease, cancer, endocrine disorders, or acute or chronic kidney failure

Note: Data are expressed as mean ± SD or median (interquartile range). (*) indicates statistical significance.

Abbreviations: ApoA1, apolipoprotein A1; BMI, body mass index; BP, blood pressure; Ctrl, control; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; NCEP:ATPIII, National Cholesterol Education Program Adult Treatment Panel III; NR, not reported; SBP, systolic blood pressure; TAG, triacylglyceride; T-C, total cholesterol; WC, waist circumference.

observed between HDL2 and HDL3 subfractions (Table 4). In general, ether-linked PLs were lower in HDL particles from MetS individuals,[20,21] as was S1P,[21,22] whereas phosphatidylinositol (PI) was consistently higher in MetS. Some discrepancies were found for other PLs. For example, phosphatidylethanolamine (PE) was only found to be higher in HDLs from MetS in HDL2, while it remained with no significant change in HDL3[21] and was unchanged in the study by Khan et al.[20] Similarly, lysoPC was reported as higher by Denimal et al. [21] but unchanged in the studies by Mocciaro et al. and Khan et al.[19,20] Most sphingomyelins (SMs) were found to be lower in HDLs from MetS patients compared to controls.[19,21,22] Additionally, FC levels were consistently lower in HDL from MetS individuals across multiple studies,[20–22] including when analysing HDL subfractions.[21]

3.3.2 | HDL core lipids

It is well established that HDL becomes enriched in TAGs in various metabolic conditions, including type 2 diabetes[30] and atherosclerosis.[31] This enrichment is primarily due to increased activity of cholesteryl ester transfer protein (CETP), which facilitates the exchange of TAGs for CEs between TAG-rich lipoproteins (TRLs) and HDLs.[32–35] In those records that measured TAG levels in

TABLE 3 Summary of methodological differences among included studies.

	Denimal et al. 2016[21]	Denimal et al. 2017[22]	Khan et al. 2018[20]	Mocciaro et al. 2022[19]
HDL isolation	Ultracentrifugation (HDL2 and HDL3 were separated)	Ultracentrifugation	Ultracentrifugation	SEC
Normalisation	% of total HDL weight	**S1P**: HDL ApoA1 and protein in HDLs **General lipids**: ApoA1 in the fraction	Total HDL-PC	HDL protein content
Lipid extraction	**S1P and Cer**: isopropanol:water: ethyl acetate **General lipids**: Folch method	**S1P**: isopropanol:water: ethyl acetate **General lipids**: no lipid extraction	Folch method	Folch method
MS technology	LC-MS/MS	**S1P**: LC-MS/MS **T-C, TAG, FC, and PL:** Vista analyzer:	LC-MS/MS	LC-MS **CE**: LC-MS/MS

Abbreviations: ApoA1, apolipoprotein A1; CE, cholesteryl ester; Cer, ceramide; FC, free cholesterol; HDL, high-density lipoprotein; LC–MS, liquid chromatography-mass spectrometry; LC–MS/MS, liquid chromatography–tandem mass spectrometry; MS, mass spectrometry; PC, phosphatidylcholine; PL, phospholipid; SEC, size exclusion chromatography; S1P, sphingosine-1-phosphate; TAG, triacylglyceride; T-C, total cholesterol.

TABLE 4 Summary of HDL surface lipid family changes in MetS versus controls.

	Denimal et al. [21] HDL2 HDL3	Denimal et al. 2017 [22] HDL	Khan et al. [20] HDL	Mocciaro et al. [19] HDL	Summary
PC	↔ ↔	↔	Measured but not reported	↔	↔
PE	↑ ↔	ND	↔	ND	NC
PI	↑ ↑	ND	↑ (uncorrected)	ND	↑
LysoPC	↑ ↑	ND	↔	↔	↔
EtheracylPC	↓ ↓	ND	↓	ND	↓
EtheracylPE	↓ ↓	ND	↓	ND	↓
SM	↓ ↓	ND	↓	↓	↓
Cer	↓ ↔	ND	↔	ND	NC
FC	↓ ↓	↓	↓	ND	↓
S1P	↓ ↓	↓	ND	ND	↓

Note: ↓ (red): significantly lower in MetS versus control; ↑ (green): significantly higher in MetS versus controls; ↔ (yellow): no significant difference; ND (grey): not detected; and NC (white): no concensus.

Abbreviations: Cer, ceramide; FC, free cholesterol; HDL, high-density lipoprotein; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphatidylinositol; NC, no consensus; ND, not detected; SM, sphingomyelin; S1P, sphingosine-1-phosphate.

HDLs, all reported higher HDL-TAG content in MetS patients, as expected.[19–22] In contrast, HDL-CE levels were lower or remained unchanged; therefore, no consensus was observed across studies (Table 5).

3.3.3 | HDL single lipids

Additionally, we further examined which specific HDL lipid species contributed to the observed modulations

TABLE 5 Summary of HDL core lipid changes in MetS versus controls.

	Denimal et al. [21] HDL2 HDL3	Denimal et al. [22] HDL	Khan et al. [20] HDL	Mocciaro et al. [19] HDL	Summary
CE	↓ ↓	↓	↔	↔	NC
TAG	↑ ↑	↑	↑	↑	↑
DAG	ND ND	ND	↑	↔	NC

Note: ↓ (red): significantly lower in MetS versus control; ↑ (green): significantly higher in MetS versus controls; ↔ (yellow): no significant difference; ND (grey): not detected; and NC (white): no concensus.

Abbreviations: CE, cholesteryl ester; DAG, diacylglyceride; HDL, high-density lipoprotein; NC, no consensus; ND, not detected; TAG, triacylglyceride.

in lipid families between MetS and control groups (Table 6). Consensus was determined based on the number of studies reporting the presence and direction of change for each lipid species. When a lipid was detected in three studies, consensus was accepted if no more than one study reported a discordant result. In cases where only two studies reported the same lipid, both had to show the same direction of change to be considered consistent.

Notably, there was a consensus on a lower quantity of different PC species, including odd-chain PCs such as PC(31:0) and PC(33:0), as well as saturated-fatty acid-containing PCs such as PC(30:0), PC(32:0) and PC(34:0).[19,20] Additionally, PC species containing linoleic acid (18:2),[21] including its lysoPL counterpart LysoPC(18:2),[19,20] were also found to be lower in MetS. Conversely, the only glyceroPL species that were consistently higher in MetS over the records included two PI species containing unsaturated fatty acids: PI(34:1), which likely contains oleic acid (18:1) and PI(36:4), likely containing arachidonic acid (20:4).[20,21] Moreover, several sphingolipids were commonly lower in MetS, including various SM species[19,20] and one ceramide with a saturated fatty acid in its acyl chain.[20,21]

4 | DISCUSSION

This systematic review synthesises current evidence on alterations in the HDL lipidome associated with MetS. Beyond lower HDL-C levels, which are a hallmark of MetS, we found that HDL lipid composition is broadly modulated in MetS. HDLs from individuals with MetS exhibit higher levels of TAG and PI, accompanied by lower levels of several PL families, including ether-linked lipids and reduced content of the bioactive lipid S1P. Collectively, these shifts suggest a broad remodelling of HDL particles in MetS, which may contribute to impaired HDL functionality and help explain the persistent cardiometabolic risk observed in this condition, despite standard lipid-lowering therapy.

Higher HDL-TAG levels in MetS are expected, as they reflect the enhanced interaction between TRLs and HDLs, driven by the hypertriglyceridemia that typically characterises MetS. It is well established that circulating TAG levels are inversely correlated with HDL-C concentrations.[32–35] Elevated TAG content within HDLs is associated with enhanced HDL catabolism,[28] which may contribute to the lower HDL levels in MetS. This may initiate a vicious cycle of declining HDL functionality, which has also been reported in MetS.[20] The enrichment in HDL-TAG is likely due, at least in part, to increased CETP activity, which mediates the exchange of CEs from HDLs for TAGs from TRLs.[28,35] However, evidence on CETP activity in MetS and related diseases remains controversial.[19,35–37] Interestingly, CE levels were not consistently lower in HDLs from MetS patients, whereas FC levels were lower. This may reflect an impaired capacity of HDLs in MetS to acquire FC from peripheral tissues. This interpretation is supported by the consistent observation of lower HDL-SM content in MetS, given that SM is positively associated with cholesterol efflux capacity,[20,38,39] as also shown by Khan et al.[20] The role of lecithin-cholesterol acyltransferase (LCAT) should also be considered. LCAT is essential for FC esterification, and although its activity is known to be altered in MetS, results remain controversial, with studies reporting both lower and higher activity.[19,40]

In the early 2000s, several pharmacological strategies were developed to increase HDL-C by inhibiting CETP. Despite successfully raising HDL-C levels, these interventions failed to reduce cardiovascular risk associated

TABLE 6 Modulation of individual HDL lipid species in MetS versus control subjects.

Lipid specie	Denimal et al.[21] HDL2 / HDL3	Khan et al.[20] HDL	Mocciaro et al.[19] HDL	Summary
PC(30:0)	ND / ND	↓	↓	↓
PC(31:0)	ND / ND	↓	↓	↓
PC(32:0)	ND / ↔	↓	↓	↓
PC(32:2)	ND / ND	↔	↔	↔
PC(33:0)	ND / ND	↓	↓	↓
PC(33:1)	ND / ND	↔	↔	↔
PC(34:0)	ND / ND	↓	↓	↓
PC(34:1)	ND / ↔	↔	↔	↔
PC(34:3)	ND / ND	↔	↔	↔
PC(35:3)	ND / ND	↔	↔	↔
PC(35:4)	ND / ND	↔	↔	↔
PC(36:1)	ND / ↔	↔	↔	↔
PC(36:2)	ND / ↓	↓	↓	↓
PC(36:3)	ND / ↔	↔	↔	↔
PC(37:5)	ND / ND	↔	↔	↔
PC(37:6)	ND / ND	↔	↔	↔
PC(38:5)	ND / ↔	↔	↔	↔
PC(38:6)	ND / ↔	↔	↔	↔
PC(40:6)	↔ / ND	↔	↔	↔
LysoPC(16:0)	↔ / ↑	↔	↔	↔
LysoPC(18:0)	↔ / ↔	↔	↔	↔
LysoPC(18:2)	↔ / ↔	↓	↓	↓
LysoPC(20:4)	↔ / ↔	↔	↔	↔
LysoPC(20:5)	ND / ND	↔	↔	↔
PE(34:2)	↔ / ↔	↔	ND	↔
PE(36:2)	↔ / ↔	↔	ND	↔
PE(36:4)	↔ / ↔	↔	ND	↔
PE(38:6)	↔ / ↔	↔	ND	↔
PE(40:6)	↔ / ↔	↔	ND	↔
PC(P-36:4)	↔ / ↔	↔	ND	↔
PC(P-36:5)	↔ / ↔	↔	ND	↔
PC(P-38:6)	↔ / ↔	↔	ND	↔
PI(34:1)	↑ / ↑	↑	ND	↑
PI(36:4)	↑ / ↑	↑	ND	↑
PI(38:4)	↔ / ↔	↔	ND	↔
SM(32:1)	ND / ND	↓	↓	↓
SM(33:1)	ND / ND	↓	↓	↓
SM(34:0)	ND / ND	↓	↓	↓
SM(34:1)	ND / ND	↓	↓	↓
SM(35:1)	ND / ND	↓	↓	↓
SM(36:1)	ND / ND	↔	↔	↔
SM(36:2)	ND / ND	↔	↔	↔

TABLE 6 (Continued)

Lipid specie	Denimal et al. [21] HDL2 / HDL3	Khan et al. [20] HDL	Mocciaro et al. [19] HDL	Summary
SM(36:3)	ND ND	↔	↔	↔
SM(39:1)	ND ND	↓	↓	↓
SM(41:1)	ND ND	↓	↔	NC
SM(42:1)	ND ND	↓	↓	↓
Cer(d18:0/22:0)	↔ ↔	↔	ND	↔
Cer(d18:0/24:1)	↔ ↔	↔	ND	↔
Cer(d18:1/24:0)	↓ ↓	↓	ND	↓
CE(15:0)	ND ND	↔	↔	↔
CE(18:0)	ND ND	↔	↔	↔
CE(20:3)	ND ND	↔	↔	↔

Note: ↓ (red): significantly lower in MetS versus control; ↑ (green): significantly higher in MetS versus controls; ↔ (yellow): no significant difference; ND (grey): not detected; and NC (white): no concensus.

Abbreviations: CE, cholesteryl ester; Cer, ceramide; HDL, high-density lipoprotein; NC, no consensus; ND, not detected; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphatidylinositol; SM, sphingomyelin.

with HDL-C raises.[7] This discrepancy stimulated further research into other components and functions of HDLs, shifting attention toward its qualitative features.

Alterations in HDL lipid composition may significantly impair HDL functionality. S1P, for example, is a well-characterised functional lipid with vasoprotective properties. It acts as a signalling molecule in endothelial cells and other tissues.[22] Lower S1P content in HDLs from MetS patients has been associated with lower nitric oxide production by endothelial cells.[22,41] Moreover, S1P interacts with a family of receptors highly expressed on immune cells; thus, alterations in HDL-S1P content could influence inflammatory responses,[16,42] further exacerbating the chronic low-grade inflammation characteristic of MetS.

Interestingly, PI was the only PL family consistently found to be higher in HDL from MetS patients.[20,21] PI is involved in membrane signalling, and its enrichment has been associated with improved HDL functionality.[43–45] This finding underscores the need for further research into the specific roles of individual HDL lipids in mediating HDL function. It is also essential to consider how the global lipidomic profile may influence the functionality of specific components. For instance, although PI levels may be higher in MetS, concomitant changes in other lipid classes could potentially attenuate its beneficial effects. In particular, two PI species, PI(34:1) and PI(36:4), were consistently higher in HDLs from MetS patients. The former likely contains oleic acid, while the latter may incorporate arachidonic acid, suggesting that the fatty acid composition of these molecules could modulate their functional impact.

Although several patterns were consistent across the included studies, such as higher HDL-TAG and lower concentrations of ether-linked PLs, S1P, SM and FC in MetS, other lipid alterations showed greater variability. These discrepancies likely reflect differences in study populations, HDL isolation techniques and analytical approaches as well as the limited number of available studies. Moreover, plasma lipidomic studies indicate that patients with MetS exhibit distinct systemic lipid profiles depending on their HDL-C levels, underscoring the metabolic heterogeneity of the condition.[46] Notably, the populations included in this review were consistently characterised by reduced HDL-C. Additionally, different components of MetS may induce distinct patterns of HDL remodelling and may differentially contribute to global lipidomic changes observed in the syndrome, as suggested by mechanistic studies in hypercholesterolemia models.[47] Nevertheless, this systematic review highlights the global changes occurring in MetS and, by synthesising the available evidence, provides an integrated overview of the HDL lipidome in this complex disease.

Additionally, the magnitude and relative contribution of individual lipid species to the overall lipidomic signature also differed between studies, underscoring the need for methodological standardisation in HDL lipidomics. Future work should aim to characterise HDL lipid changes in MetS using larger and more diverse populations, while systemically evaluating the influence of different HDL isolation methods. In addition, reporting subfraction-specific lipid changes will be essential to determine how closely HDL2 and HDL3 alterations mirror those observed in the total HDL pool and to better understand their functional implications.

5 | CONCLUSIONS

Taken together, HDLs in MetS exhibit substantial alterations in their lipid composition, characterised by an increase in TAG and PI content and a lower content of several surface lipid families. Despite some consistent findings, methodological heterogeneity across studies poses a significant challenge for comparative interpretation. Moreover, the limited

number of studies investigating the HDL lipidome underscores the need to further expand research in this area.

AUTHOR CONTRIBUTIONS

EGC designed the study, performed the research, collected data, analysed data and wrote the paper. GGJ performed the research, collected data, analysed data and wrote the paper; MEM designed the study, collected data and wrote the paper. GM designed the study. EO, wrote the paper. SMdP wrote the paper. LMV designed the study, collected data, analysed data.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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