BMJ Nutrition, Prevention & Health

Prevalence of polypharmacy and associated side effects in individuals with metabolic dysfunction-associated steatotic liver disease (MASLD): a systematic review and meta-analysis

Sarah Armes ,[1] Jenneffer Tibaes,[1] Ramya Rajaram,[1] Mark W Ruddock ,[2] Mary Jo Kurth,[2] Peter Fitzgerald,[2] Rajna Golubic,[1,3] Sumantra Ray[1,4]

To cite: Armes S, Tibaes J, Rajaram R, *et al*. Prevalence of polypharmacy and associated side effects in individuals with metabolic dysfunction-associated steatotic liver disease (MASLD): a systematic review and meta-analysis. *BMJ Nutrition, Prevention & Health* 2025;**0**. doi:10.1136/bmjnph-2025-001236

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjnph-2025-001236).

For numbered affiliations see end of article.

Correspondence to
Sarah Armes;
s.armes@nnedpro.org.uk and

Jenneffer Tibaes;
j.tibaes@nnedpro.org.uk

SA and JT are joint first authors. RG and SR are joint senior authors.

Received 19 March 2025
Accepted 9 July 2025

ABSTRACT

Objectives Metabolic dysfunction-associated steatotic liver disease (MASLD) is a prevalent chronic condition often accompanied by multiple comorbidities requiring complex pharmacological management. This review aims to examine the prevalence of polypharmacy in patients with MASLD, alongside an exploration of reported associations with side effects and observed relationships with patient-reported outcomes.

Methods We conducted a systematic review using MEDLINE, CINAHL, Embase, Cochrane CENTRAL and Scopus databases, supplemented by a grey literature search, from inception to August 2024. Inclusion criteria were randomised controlled trials, cohort studies or case-control studies that evaluated the prevalence of polypharmacy and its consequences in adults with MASLD. Three reviewers independently performed study selection and data extraction. The quality of included studies was assessed using the Newcastle-Ottawa Scale. The primary outcome was the prevalence of polypharmacy, with secondary outcomes including side effects and quality of life (QoL). A meta-analysis with a random-effect model was performed.

Results Six studies were included, of which three (totalling 2194 participants) were used in a meta-analysis. Polypharmacy prevalence ranged from 25% to 89%, with a pooled prevalence of 81% (95% CI 59 to 93), I^2=99.5%. Adverse outcomes associated with polypharmacy included increased risk of hepatic encephalopathy-related hospitalisations, reduced QoL across physical and mental health domains, and augmented liver disease progression, particularly in individuals with advanced MASLD. Commonly used medications, such as anticholinergics and insulin, were linked to significant symptom burdens and metabolic dysregulation. Risk of bias assessments revealed that 50% of included studies had high risk due to limitations in study design, such as cross-sectional design and inconsistent definitions of polypharmacy, which reduced the certainty of evidence.

Conclusions Polypharmacy is highly prevalent in MASLD and associated with poorer clinical outcomes and reduced QoL. Interventions such as deprescribing programmes and enhanced medication management strategies are needed to mitigate risks and optimise patient care.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Metabolic dysfunction-associated steatotic liver disease (MASLD) is a common chronic condition often requiring multiple medications due to associated comorbidities. Polypharmacy has been associated with adverse clinical outcomes, including increased risk of drug-related complications and reduced quality of life (QoL).

WHAT THIS STUDY ADDS

⇒ This systematic review and meta-analysis provides a comprehensive assessment of polypharmacy prevalence in MASLD, estimating a pooled prevalence of 65%. The study highlights associations between polypharmacy and adverse outcomes, including increased hepatic encephalopathy-related hospitalisations, worsened QoL and accelerated liver disease progression.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Findings highlight the need for deprescribing strategies and personalised medication management to reduce risks. Future research should refine polypharmacy definitions and assess targeted interventions to improve patient outcomes and healthcare policies.

BACKGROUND

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease, is a chronic liver condition characterised by the abnormal accumulation of fat in the liver in individuals who consume little or no alcohol.[1] It encompasses a spectrum of liver abnormalities, ranging from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH), a more severe form involving liver inflammation and cell injury.[2] Around 10–30% of individuals with simple steatosis

progress to MASH, which can lead to fibrosis, cirrhosis and hepatocellular carcinoma,[3] which is associated with particularly poor survival outcomes.

MASLD is one of the most prevalent liver diseases worldwide, with an estimated global prevalence of 30% in the general population, increasing from 22% to 37% from 1991 to 2019.[4] Traditionally considered a condition associated with middle-aged or older adults, MASLD is increasingly diagnosed in younger adults and children.[5] This shift in demographics reflects the rising prevalence of obesity, sedentary lifestyles and unhealthy dietary patterns in these populations. MASLD is strongly associated with metabolic comorbidities including obesity, type 2 diabetes (T2D), insulin resistance, hyperlipidaemia and hypertension, collectively referred to as metabolic syndrome,[6] which significantly increases the risk of cardiovascular disease, stroke and other complications. Given that MASLD is closely linked to metabolic syndrome, its management often requires a comprehensive, multifaceted approach to manage the underlying metabolic abnormalities, reduce liver fat accumulation and prevent disease progression.[7] This typically includes lifestyle modifications, pharmacological interventions and, in some cases, investigational therapies.[8]

Pharmacological interventions for MASLD aim to address underlying metabolic issues such as insulin resistance, dyslipidaemia and inflammation. Common medications include insulin sensitisers like metformin and pioglitazone,[9] lipid-lowering agents like statins,[10] and emerging treatments such as glucagon-like peptide-1 receptor agonists (eg, liraglutide, semaglutide, tirzepatide)[11] and sodium-glucose co-transporter 2 inhibitors,[12] which help improve insulin resistance, reduce liver fat and manage comorbid conditions like diabetes and dyslipidaemia. However, a significant concern in MASLD management is polypharmacy, defined as the use of five or more concurrent medications.[13] Polypharmacy has been associated with various negative outcomes, including drug interactions, greater symptom burden, medication non-adherence, inappropriate prescribing, adverse drug events, hospitalisation, falls, functional decline, lower quality of life (QoL) and increased mortality.[14] This risk is further compounded by altered liver enzyme activity in MASLD patients, including reduced expression and activity of several cytochrome P450 enzymes, including decreased activity of CYP3A4.[15] The inhibition and induction of the CYP enzymes significantly affect drug pharmacokinetics by altering absorption, distribution, metabolism and clearance,[16] potentially leading to reduced drug efficacy or heightened toxicity. The complexity of medication regimens in polypharmacy also contributes to poor medication adherence, as patients may struggle with multiple medications, managing complex dosing schedules and dealing with the side effects of various drugs.[17] Non-adherence to medication regimens, in turn, can negatively affect the overall management of both MASLD and associated conditions, potentially leading to disease progression and poor long-term outcomes.

This review aims to determine the prevalence of polypharmacy in patients with MASLD. We also aim to synthesise the current evidence regarding reported associations between polypharmacy and side effects, and to explore observed relationships with patient-reported outcomes and other clinical outcomes in this population.

METHODS

We registered our review protocol on PROSPERO (CRD42024574460). This systematic review was conducted in adherence to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement.[18]

Eligibility criteria

We included studies that met predefined eligibility criteria structured according to the Population, Intervention, Comparison, Outcome (PICO) or Population, Exposure, Comparator, Outcome (PECO) framework (table 1).

Information Sources

The systematic search was conducted using the following bibliographic databases: MEDLINE, CINAHL, Embase, Cochrane Central Register of Controlled Trials (CENTRAL) and Scopus, covering studies from database inception to August 2024. Additionally, grey literature searches were performed in ClinicalTrials.gov and Google Scholar to identify potentially relevant unpublished studies. The search was restricted to English language publications, and references of included studies were also screened for eligible articles.

Search strategy

A detailed search strategy combining controlled vocabulary and keywords such as “polypharmacy”, “metabolic dysfunction–associated steatotic liver disease (MASLD)”, “non-alcoholic fatty liver disease (NAFLD)”, “side effects” and “quality of life” was employed for each database. The search strategy for MEDLINE can be found in the supplementary material (online supplemental appendix A). Searches were limited to human studies, and no restrictions were placed on publication year.

Selection process

Three independent reviewers (JT, SA, RR) screened the titles and abstracts of all retrieved studies using Covidence software (Veritas Health Innovation Ltd). Full-text articles were retrieved for potentially eligible studies, and the inclusion criteria were applied. Any disagreements between reviewers were resolved by consensus among the three reviewers.

Data collection process

Data were independently extracted by three reviewers (JT, SA and RR) using a data extraction form adapted from the ‘Data collection form’ of The Cochrane Collaboration. Discrepancies in data extraction were resolved through discussion or consultation with a

Table 1 Summary of Population, Intervention, Comparison, Outcome (PICO) / Population, Exposure, Comparator, Outcome (PECO) framework for study inclusion and exclusion criteria

Component	Inclusion/exclusion criteria
Population	► Studies involving adult participants (aged ≥18 years) with a diagnosis of MASLD. MASLD diagnosis could be established using imaging modalities, liver biopsy or biochemical markers. ► Studies restricted to paediatric populations or those not reporting data specific to MASLD were excluded.
Intervention/exposure	► For interventional studies: multiagent pharmacological therapies targeting MASLD or its associated comorbidities (eg, diabetes, hypertension, dyslipidaemia). Single-agent intervention studies were excluded. ► For observational studies: polypharmacy was the primary exposure of interest, with studies required to provide a clear definition and threshold (eg, ≥5 medications).
Comparator	► Participants with MASLD who did not meet the polypharmacy threshold (eg, <5 medications) or those receiving alternative lifestyle-based interventions.
Outcomes	► Primary: prevalence of polypharmacy, typically defined as the use of ≥5 medications, reported as a proportion of the study population. ► Secondary: types of medications used, adverse effects and associations with quality of life, hospitalisation, emergency visits, liver function, disease progression and mortality were extracted if reported but were not the primary focus of the review. Effect estimates included risk ratios and standardised mean differences.
Study design	► Eligible study designs included RCTs, quasi-RCTs, single-arm trials and observational studies (cohort, cross-sectional and case-control), with no restrictions on sample size. ► Excluded were non-original articles (eg, reviews, protocols, abstracts, case reports, theses) and studies terminated early due to recruitment issues.

MASLD, metabolic dysfunction-associated steatotic liver disease; RCTS, randomised controlled trials.

third reviewer (RG). Extracted data included study characteristics (authors, year, design, location), participant demographics (sample size, age, sex), MASLD diagnostic criteria, polypharmacy interventions and study outcomes (eg, prevalence of polypharmacy, QoL, types and frequencies of side effects). When data were not available, the study authors were contacted via email to obtain the missing information.

Quality assessment

Quality assessment of the included full text articles, all of which were observational in design, was independently assessed by three reviewers (JT, SA and RR). Any disagreements were resolved through consensus. We assessed the risk of bias and quality of the included studies using the Newcastle-Ottawa Scales (NOS) for case-control and cohort studies, and modified NOS for cross-sectional studies.[19] These tools consist of seven to eight domains depending on the type of study design. Studies were categorised based on total scores as being of either high quality (total score ≥7) or low quality (total score <7).

Analysis and data synthesis

Continuous variables were presented as means (±SD) or medians (IQR), as appropriate, while categorical variables were presented as numbers (percentages). We conducted a meta-analysis to estimate the pooled proportion of events across studies using the meta and metafor packages in R V.4.3.3. Effect sizes were pooled using an inverse variance random-effect model with 95% CI. A logit transformation (PLOGIT) was applied to stabilise variances, and an inverse variance weighting approach was used to assign greater weight to studies with smaller variance. Between-study variance (τ^2) was estimated using the restricted maximum likelihood (REML) method, with CI computed using the Q-profile method. The Hartung-Knapp-Sidik-Jonkman method was used to calculate CI for the random-effect model. Heterogeneity was assessed using Cochran's Q statistic, and the I^2 statistic quantified the proportion of total variation due to heterogeneity. Egger's test was not performed, as it is recommended to have a minimum of 10 studies for reliable results. Only three studies were included in the meta-analysis, as they consistently defined polypharmacy as the use of five or more medications and were conducted in comparable clinical settings. Studies that used different definitions or thresholds for polypharmacy, or that focused only on specific medication classes were excluded from the meta-analysis and instead summarised narratively. To assess the robustness of our pooled estimate, we performed a sensitivity analysis by including one additional study conducted in a community-based primary care setting.

RESULTS

Study selection

A flow diagram depicting the selection process is presented in figure 1. Of the 12 614 records identified,

9430 remained after duplicates were removed. Title and abstract screening led to 183 articles being selected for full-text review. Despite attempts to contact authors, two full-text articles were unavailable. Of the 181 articles assessed, six met the eligibility criteria and were included in the final review.

Study characteristics

A total of six articles were collected and included in the review, from Alrasheed *et al*,[20] Alrasheed *et al*,[21] Patel *et al*,[22] Patel *et al*,[23] Miele *et al*[24] and Montrose *et al*.[25] The characteristics of the included studies are presented in table 2 and online supplemental

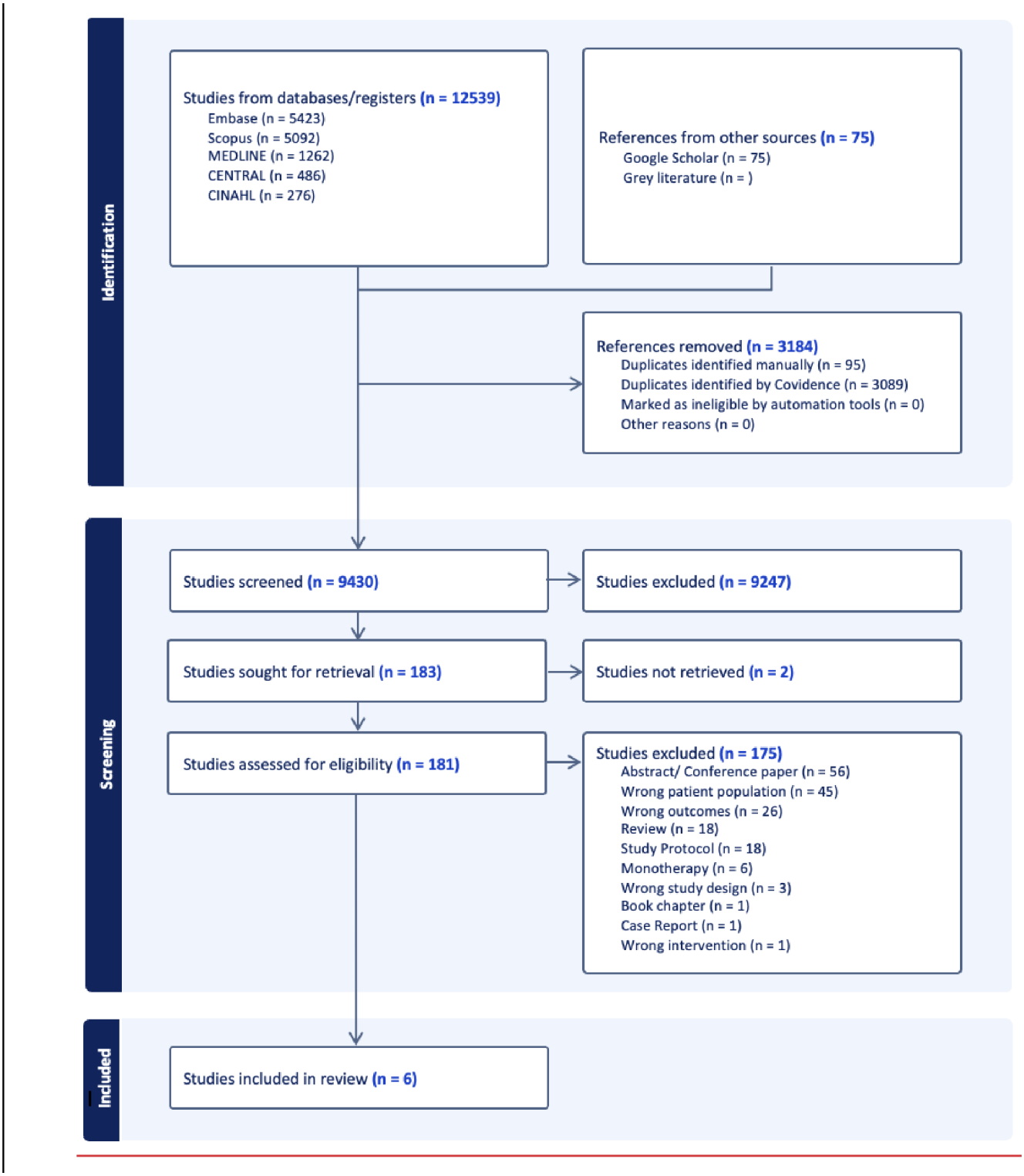

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-analyses flowchart of the study selection of six studies eligible for the systematic review.

Table 2 Characteristics of the included studies

First author, year	Country	Study design	Population	Number of subjects	Mean age (years) M (±SD)	Aim	Outcomes	Prevalence of polypharmacy
Alrasheed 2022a[20]	USA	Retrospective, cross-sectional study	MASLD patients of age 18 or older who had a histologic diagnosis of MASLD	N=1067	48.64±11.8	To examine the association between polypharmacy and health-related QoL in MASLD adult patients.	QoL was measured using the SF-36 instrument.	834/1067
Alrasheed 2022b[21]	USA	Retrospective, cross-sectional study	MASLD patients of age 18 or older who had a histologic diagnosis of MASLD	N=1032	48.6±11.8	To examine the effect of polypharmacy on patient-reported liver symptoms in MASLD adult patients and to examine the patient-reported symptoms that affect QoL.	QoL was measured using the SF-36, patient-reported liver symptoms.	803/1032
Patel 2017[22]	Australia	Cohort study	Patients with MASLD and diabetes	N=95	59.6±9.4	To describe the number and type of chronic conditions present in, and medications taken by, a cohort of patients with diabetes and MASLD at risk of clinically significant liver disease, attending a hospital or primary care diabetes service.	Number of medications, co-morbidities, patients (%) taking 1–4 medications, patients (%) taking 5–9 medications and patients (%) taking >10 medications.	85/95
Patel 2018[23]	Australia	Cross-sectional study	Patients with MASLD from diabetes clinics and primary care	N=230	57±12	To examine the relationship between steatosis quantified by CAP values and glycaemic/ metabolic control.	Metabolic control (HbA1c ≥7%, hypertriglyceridaemia), requirement for insulin, presence of metabolic syndrome and CAP scores for liver steatosis.	≥3 diabetes medications 51/230
Miele 2022[24]	Italy	Retrospective cohort study	Adults aged 18 years or older attending Italian primary care services with data from 2008 to 2017.	N=151 431	57±16	To determine the prevalence of MASLD and the probability of liver fibrosis in Italian primary care services, assess associated comorbidities, and identify determinants of MASLD using non-invasive tests (NITs).	MASLD has been associated with worsening kidney function and polypharmacy use	66181/151431
Montrose 2024[25]	USA	Retrospective cohort study	Patients aged 18–80 with cirrhosis, seen at hepatology clinics during 2019, without prior liver transplant, including those with MASLD.	N=1039 (378 with MASLD)	58.8±11.8 (no data for those with MASLD)	To examine the association between medication burden, anticholinergic use and HE-related hospitalisations in patients with cirrhosis.	HE-related hospitalisations, medication burden in MASLD patients, prevalence of anticholinergic use in MASLD patients, complications of liver disease, and all-cause mortality.	The average number of chronic medications for MASLD patients was 9.6 (4.6).

CAP, controlled attenuation parameter; HE, hepatic encephalopathy; LSM, liver stiffness measurement; M, mean; N, number of patients; PP, polypharmacy; QoL, quality of life; SF-36, 36-Item Short Form Survey.

appendix B. Six studies investigated the prevalence of polypharmacy in adults with MASLD or related conditions. Study designs included cross-sectional (n=3) and cohort (n=3) studies, conducted across the USA, Australia, Italy and India. Due to the design of these studies, no statements can be made about causality. The sample sizes varied widely, ranging from 95 to 151 431 participants. Female representation ranged from 36% to 63%, with mean ages between 48.6±11.8 and 59.6±9.4 years.

Methodological quality

The remaining six articles were independently assessed for methodological quality by three reviewers (JT, SA and RR). The assessment of study quality according to the NOS risk of bias assessments for cohort, case-control and cross-sectional studies is provided in the additional file (online supplemental appendix C). Overall, 3/3 cohort (100%) and 0/3 cross-sectional studies (0%) were reported to be of good quality.

Definition of polypharmacy

A medication threshold of ≥5 medications was the most commonly used threshold (four studies, 67%) to define the use of polypharmacy. Notably, one study differentiated between standard polypharmacy (5–9 medications) and hyper-polypharmacy (more than 10 medications).[22] In contrast, two studies did not provide a clear definition: Patel *et al* used a threshold of ≥3 diabetes medications,[23] while Montrose *et al* reported the average number of chronic medications used.[25]

Prevalence of polypharmacy

Polypharmacy prevalence in MASLD adults varied across studies depending on the population and polypharmacy definitions. The results are graphically represented in figure 2. Pooled analysis of three studies showed a prevalence of 81% (95% CI 59 to 93). The analysis revealed significant heterogeneity (I^2=99.5%), suggesting substantial variability among the studies. The studies by Alrasheed *et al* assessed two cohorts of MASLD patients in the USA, reporting polypharmacy (≥5 medications) in 78.2% (834/1067)[20] and 77.8% (803/1032)[21] of participants. Miele *et al* evaluated a large cohort of adults in Italian primary care and found polypharmacy in 43.7% (66 181/151 431) of the total population.[24] The studies by Patel *et al* investigated polypharmacy among patients with diabetes and MASLD in Australia, with a polypharmacy prevalence of 89.5% (85/95)[22] and 22.2% (51/230).[23] Montrose *et al* focused on MASLD patients within a US-based cirrhosis cohort, reporting that the average number of chronic medications for MASLD patients was 9.6.[25]

To evaluate the robustness of the pooled estimate, we conducted a sensitivity analysis restricted to three studies with similar settings and consistent definitions of polypharmacy. When the broader-scope community-based study by Miele *et al*[24] was included, the estimated prevalence decreased by 6%. Heterogeneity remained high: τ^2 (REML, 95% CI) = 0.97 (0.28 to 13.71); χ^2 = 873.20, df=3, p<0.001; I^2 = 99.6% (99.5% to 99.7%). This decrease in prevalence may reflect differences in prescribing practices, as primary care-only patients often have simpler medication regimens and may not have access to or require input from secondary or specialist care for the management of more complex pharmacotherapies.

Associations between polypharmacy and patient outcomes

Due to the heterogeneity in study methodologies and outcome measures, a narrative synthesis was conducted to summarise the key findings of polypharmacy on patient outcomes.

Quality of life (QoL)

Alrasheed *et al* demonstrated that the number of medications was significantly associated with the physical component summary (PCS) and mental component summary (MCS) scores.[20] For each additional medication, the PCS score decreased by 1.224 units (p<0.01), and MCS

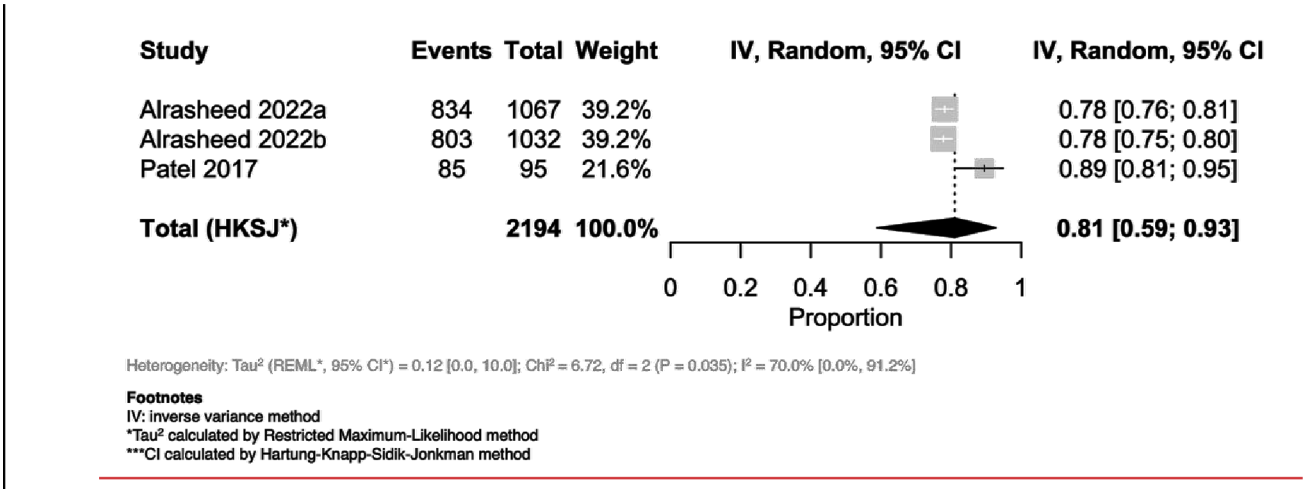

Figure 2 Forest plot showing polypharmacy prevalence among adults with MASLD. HKSJ, Hartung-Knapp-Sidik-Jonkman; MASLD, metabolic dysfunction-associated steatotic liver disease.

score decreased by 0.725 units (p<0.01). Additionally, the number of medications was significantly associated with lower QoL in physical functioning (β=−1.158, Standard Error (SE)=0.164, p<0.01), energy (β=−0.694, SE=0.164, p<0.01), social functioning (β=−0.794, SE=0.176, p<0.01), bodily pain (β=−1.240, SE=0.171, p<0.01) and general health (β=−0.902, SE=0.154, p<0.01).

In a related study, Alrasheed *et al* reported that patients with polypharmacy also had a higher frequency and severity of patient-reported liver symptoms compared with non-polypharmacy patients (p<0.01).[21] Fatigue (38.7%), trouble sleeping (23.9%) and muscle aches/cramps (20.8%) were the most commonly reported symptoms in the polypharmacy group. These patients also reported higher symptom severity across most domains except for jaundice (p=0.656). Notably, symptom burden was more severe in polypharmacy patients with steatohepatitis, irrespective of its severity level.

Medication use and comorbidities

Patel *et al* identified that older age, ischaemic heart disease and osteoarthritis were more common in patients taking ≥5 medications (p≤0.05).[22] The study also observed that statin use was higher among patients with lower liver stiffness measurements (LSM <8.2 kPa) compared with those with higher stiffness (92% vs 73%, p=0.03); however, this association was no longer significant after adjusting for confounders like age, gender, body mass index and the number of comorbidities. A more recent study by Patel *et al* found that increasing controlled attenuation parameter was associated with poorer diabetes control, defined by HbA1c ≥7%, increasing number of diabetes medications prescribed, and requiring insulin, and hypertriglyceridaemia.[23]

Hospitalisations and mortality

Montrose *et al* reported that cirrhotic patients, including those with MASLD, experienced a substantial medication burden, with 59% of the cohort taking ≥5 medications.[25] Moreover, the average number of chronic medications for MASLD patients was 9.6 (4.6). Anticholinergic medication use was observed in 21% of participants and was significantly associated with hepatic encephalopathy (HE)-related hospitalisations (Hazard Ratio: 1.71, 95% CI 1.11 to 2.63). Furthermore, both medication burden and anticholinergic use were independent predictors of HE-related hospitalisations, emphasising the adverse effects of polypharmacy in this high-risk population.

DISCUSSION

This review highlights the high prevalence of polypharmacy among adults with MASLD, with a pooled rate of 81% across three studies totalling 2194 participants. Similar trends are seen in other chronic conditions, with a systematic review reporting a 50% prevalence in individuals with diabetes,[26] and research on chronic liver disease (CLD) showing a 31% prevalence.[27] These findings highlight the widespread occurrence of polypharmacy across chronic conditions.

Our review identified that polypharmacy was associated with poor clinical outcomes, including reduced QoL, increased symptom burden and a higher prevalence of comorbidities. Alrasheed *et al* reported significantly lower QoL scores across multiple domains of the 36-Item Short Form Survey, particularly in physical functioning, vitality and general health, among patients with polypharmacy.[20] Similarly, a cross-sectional study in CLD patients found that moderate polypharmacy was associated with a decreased QoL (p<0.05), with a significant relationship between the physical health category and disease severity (p<0.05).[28] Patel *et al* identified a significant association between polypharmacy and certain health conditions, including ischaemic heart disease and osteoarthritis.[22] Furthermore, a retrospective study found that individuals with polypharmacy and hyper-polypharmacy (≥10 medications per day), compared with those using fewer than five medications, were at a significantly higher risk of kidney failure, cardiovascular events and all-cause mortality, indicating an elevated risk of adverse outcomes associated with polypharmacy.[29]

The high medication burden observed by Montrose *et al* underscores the potential risks of adverse drug interactions and increased healthcare utilisation in MASLD patients with polypharmacy.[25] Farooq *et al* highlighted a significant number of drug interactions in patients with CLD, with major drug interactions linked to polypharmacy and more frequent in prescriptions with more medications.[28] Therefore, healthcare providers must take additional precautions to avoid inappropriate prescribing, minimise side effects and ensure drug safety.

Montrose *et al* emphasise the need for deprescribing strategies to reduce medication burden and minimise risks of HE and infection-related hospitalisations.[25] Deprescribing offers a promising intervention for mitigating the adverse effects of polypharmacy in MASLD,[30] helping reduce pill burden, adverse drug events and financial strain.[31] However, barriers to deprescribing practices among clinicians include a prescribing culture that prioritises adding medications, limited clinician time and training on deprescribing frameworks, and therapeutic inertia where long-term medications are rarely re-evaluated.[32] Addressing these issues requires a shift towards prudent prescribing, wider adoption of non-pharmacological options, better clinician education and patient-centred care with shared decision-making.[32] This also underscores the need for improved medical education, particularly in nutrition, to prevent drug-nutrient interactions and support deprescribing through dietary interventions where appropriate.[33]

Polypharmacy carries substantial health and economic costs, including adverse drug reactions, increased healthcare use and frequent hospitalisations. These challenges are compounded by the global

rise in MASLD, with Europe seeing a 1.1% annual increase since 1991.[4] This trend highlights the need for non-pharmacological strategies,[34] as reliance on pharmacological treatments may lead to unsustainable healthcare costs. Lifestyle changes—particularly weight loss through diet and physical activity—are key to reducing liver fat and improving liver function. In a 52-week study of MASH patients, 58% of those who lost at least 5% of body weight achieved disease resolution, increasing to 90% among those who lost 10% or more.[35] A meta-analysis further confirmed that weight loss improves biomarkers, liver steatosis, MASLD activity score and MASH presence.[36]

While calorie reduction is central to MASLD care, diets enhancing glycaemic control may offer additional benefits. A 2-week trial comparing calorie restriction and a very low-carb diet found both reduced weight, liver triglycerides and AST, with the low-carb diet achieving greater triglyceride reduction, linked to macronutrient composition.[37] A recent systematic review and meta-analysis found that anti-inflammatory diets, such as low-carbohydrate or Mediterranean diets, may offer modest improvements in the physical component of health-related QoL among older adults with one or more chronic conditions.[38] The Mediterranean diet, characterised by low refined carbohydrates and high levels of monounsaturated fatty acids, omega-3 fatty acids and fibre, has demonstrated positive effects on MASLD, with a recent meta-analysis finding that the Mediterranean diet significantly lowered alanine aminotransferase (p=0.02), Fatty Liver Index (p<0.001) and liver stiffness (p=0.05) in adults with metabolic dysfunction and liver-related conditions.[39] Additionally, Unwin *et al* demonstrated that adopting a lower-carbohydrate diet resulted in 46% of T2D patients achieving drug-free remission, with a relative reduction in diabetes medication prescriptions, resulting in a £50 885 annual decrease in the T2D prescribing budget compared with the area average.[40] These findings highlight the potential of dietary strategies to reduce medication use and healthcare costs.

There are several limitations to this review. The substantial heterogeneity (I^2 = 70%) prevented a meta-analysis on patient outcomes, limiting the ability to draw definitive conclusions. Additionally, the lack of standardised definitions of polypharmacy and varying thresholds, ranging from ≥3 to ≥10 medications, complicates direct comparisons with existing literature.[13] All included studies were observational, which prevents the establishment of causal relationships. Furthermore, the majority of studies were conducted in high-income countries, with the largest study population from Italy,[24] limiting the generalisability of the findings.

Another important limitation is that none of the included studies reported detailed information on the types or classes of medications counted toward polypharmacy. This precludes analysis of potentially relevant medication patterns, such as those related to MASLD pathophysiology (eg, glucose-lowering, lipid-modifying or hepatotoxic agents), as well as the inclusion or exclusion of over-the-counter drugs, supplements or short-term prescriptions. Additionally, 50% of the included studies were of low quality, which necessitates caution in interpreting the results. Despite these limitations, this review lays the groundwork for future research into polypharmacy in MASLD and the development of targeted interventions.

Future research on polypharmacy in adults with MASLD should focus on prospective, longitudinal cohort studies to establish causal relationships between polypharmacy and clinical outcomes. Another important area for future research is the examination of deprescribing frameworks, including the barriers and facilitators to deprescribing in MASLD populations, which could provide valuable insights into how to reduce polypharmacy-related risks. Given the rising prevalence of MASLD, future research should prioritise non-pharmacological interventions, such as diet, exercise and behavioural changes, to reduce polypharmacy and improve patient outcomes. Moreover, research that seeks to quantify the benefits of improved deprescribing practices alongside nutrition and lifestyle interventions could inform the development of future MASLD practice pathways. Finally, there is a lack of comprehensive cost-utility analyses addressing the benefits of deprescription and preventive care in MASLD.

CONCLUSION

In conclusion, polypharmacy is highly prevalent among adults with MASLD, with associations with reduced QoL and increased risk of comorbidities. While deprescribing offers a promising solution to mitigate the risks associated with polypharmacy, challenges such as prescribing culture and therapeutic inertia must be addressed. Furthermore, as the prevalence of MASLD continues to rise, the financial sustainability of pharmacological interventions becomes increasingly questionable. In this context, lifestyle interventions, particularly dietary modifications, present an effective approach to reducing the need for medications, improving patient outcomes and minimising polypharmacy-related risks. Future research should focus on longitudinal cohort studies to establish causal relationships, standardise definitions of polypharmacy, explore deprescribing frameworks and prioritise non-pharmacological interventions, such as lifestyle modifications, to enhance the management of MASLD and reduce the associated healthcare burden.

Author affiliations
[1]NNEdPro Global Institute for Food Nutrition and Health, Cambridge, UK

[2]Randox Laboratories Ltd, Crumlin, UK
[3]Diabetes Trials Unit, Oxford Centre for Diabetes Endocrinology and Metabolism, Oxford, UK
[4]School of Biomedical Sciences, Ulster University, Coleraine, UK

Acknowledgements This work was supported by Randox Health, whose contribution played a meaningful role in the development of this study. The authors gratefully acknowledge Dr Federica Amati for her insightful feedback on the manuscript and for facilitating the introduction between NNEdPro and Randox, which contributed meaningfully to the development of this work.

Contributors All authors contributed to the design of the review. MR, MK and PF were involved in conceptualisation, review and editing. SA, JT and RR developed and implemented the protocol, search strategy and data extraction process. RG assisted in resolving discrepancies in data extraction. Meta-analyses were performed by JT. The manuscript was written by SA and JT, with RG and SR providing critical supervision and guidance throughout the project. SR acted as the guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests No, there are no competing interests.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data extracted and analysed during this systematic review and meta-analysis are available from the corresponding author upon reasonable request.

ORCID iDs
Sarah Armes http://orcid.org/0000-0002-7318-4512
Mark W Ruddock http://orcid.org/0000-0003-0988-2436

REFERENCES

1 European association for the study of the liver (easl). In: *European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). Obesity Facts*. 17. August 7, 2024: 374–443.
2 Bedossa P. Pathology of non-alcoholic fatty liver disease. *Liver Int* 2017;37 Suppl 1:85–9.
3 Glen J, Floros L, Day C, *et al*. Non-alcoholic fatty liver disease (NAFLD): summary of NICE guidance. *BMJ* 2016;354:i4428.
4 Le MH, Yeo YH, Li X, *et al*. 2019 Global NAFLD Prevalence: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2022;20:2809–17.
5 Perumpail BJ, Manikat R, Wijarnpreecha K, *et al*. The prevalence and predictors of metabolic dysfunction-associated steatotic liver disease and fibrosis/cirrhosis among adolescents/young adults. *J Pediatr Gastroenterol Nutr* 2024;79:110–8.
6 Younossi ZM, Koenig AB, Abdelatif D, *et al*. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016;64:73–84.
7 Corrao S, Calvo L, Granà W, *et al*. Metabolic dysfunction-associated steatotic liver disease: A pathophysiology and clinical framework to face the present and the future. *Nutr Metab Cardiovasc Dis* 2025;35:103702.
8 Zeng J, Fan JG, Francque SM. Therapeutic management of metabolic dysfunction associated steatotic liver disease. *United European Gastroenterol J* 2024;12:177–86.
9 Iogna Prat L, Tsochatzis EA. The effect of antidiabetic medications on non-alcoholic fatty liver disease (NAFLD). *Hormones (Athens)* 2018;17:219–29.
10 Boutari C, Pappas PD, Anastasilakis D, *et al*. Statins' efficacy in non-alcoholic fatty liver disease: A systematic review and meta-analysis. *Clin Nutr* 2022;41:2195–206.
11 Rezaei S, Tabrizi R, Nowrouzi-Sohrabi P, *et al*. GLP-1 Receptor Agonist Effects on Lipid and Liver Profiles in Patients with Nonalcoholic Fatty Liver Disease: Systematic Review and Meta-Analysis. *Can J Gastroenterol Hepatol* 2021;2021:8936865.
12 Wei Q, Xu X, Guo L, *et al*. Effect of SGLT2 Inhibitors on Type 2 Diabetes Mellitus With Non-Alcoholic Fatty Liver Disease: A Meta-Analysis of Randomized Controlled Trials. *Front Endocrinol (Lausanne)* 2021;12:635556.
13 Masnoon N, Shakib S, Kalisch-Ellett L, *et al*. What is polypharmacy? A systematic review of definitions. *BMC Geriatr* 2017;17:230.
14 Fried TR, O'Leary J, Towle V, *et al*. Health outcomes associated with polypharmacy in community-dwelling older adults: a systematic review. *J Am Geriatr Soc* 2014;62:2261–72.
15 Jamwal R, de la Monte SM, Ogasawara K, *et al*. Nonalcoholic Fatty Liver Disease and Diabetes Are Associated with Decreased CYP3A4 Protein Expression and Activity in Human Liver. *Mol Pharm* 2018;15:2621–32.
16 Armani S, Geier A, Forst T, *et al*. Effect of changes in metabolic enzymes and transporters on drug metabolism in the context of liver disease: Impact on pharmacokinetics and drug-drug interactions. *Br J Clin Pharmacol* 2024;90:942–58.
17 Kassaw AT, Sendekie AK, Minyihun A, *et al*. Medication regimen complexity and its impact on medication adherence in patients with multimorbidity at a comprehensive specialized hospital in Ethiopia. *Front Med (Lausanne)* 2024;11:1369569.
18 PRISMA PC. . Transparent reporting of systematic reviews and meta-analyses. Fluxograma Prisma Statement; 2015.10. 41–58.
19 Peterson J, Welch V, Losos M, *et al*. *The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses*. 2. . Ottawa: Ottawa Hospital Research Institute, 2011:1–2.
20 Alrasheed M, Guo JJ, Lin AC, *et al*. The effect of polypharmacy on quality of life in adult patients with nonalcoholic fatty liver disease in the United States. *Qual Life Res* 2022;31:2481–91.
21 Alrasheed M, Guo JJ, Lin AC, *et al*. Association between polypharmacy, patient-reported symptoms, and quality of life among nonalcoholic fatty liver disease patients in the United States. *Drugs Ther Perspect* 2022;38:490–8.
22 Patel PJ, Hayward KL, Rudra R, *et al*. Multimorbidity and polypharmacy in diabetic patients with NAFLD: Implications for disease severity and management. *Medicine (Baltimore)* 2017;96:e6761.
23 Patel PJ, Hossain F, Horsfall LU, *et al*. Controlled attenuation parameter in NAFLD identifies risk of suboptimal glycaemic and metabolic control. *J Diabetes Complicat* 2018;32:799–804.
24 Miele L, Grattagliano I, Lapi F, *et al*. Non-alcoholic fatty liver disease and the risk of fibrosis in Italian primary care services: GPS-NAFLD Study: GPS-NAFLD Study. *Liver Int* 2022;42:2632–45.
25 Montrose JA, Desai A, Nephew L, *et al*. Medication burden and anticholinergic use are associated with overt HE in individuals with cirrhosis. *Hepatol Commun* 2024;8:e0460.
26 Remelli F, Ceresini MG, Trevisan C, *et al*. Prevalence and impact of polypharmacy in older patients with type 2 diabetes. *Aging Clin Exp Res* 2022;34:1969–83.
27 Danjuma MI-M, Naseralallah L, Ansari S, *et al*. Prevalence and global trends of polypharmacy in patients with chronic liver disease: A systematic review and meta-analysis. *Medicine (Baltimore)* 2023;102:e32608.
28 Farooq J, Sana MM, Chetana PM, *et al*. Polypharmacy in chronic liver disease patients: Implications for disease severity, drug-drug interaction, and quality of life. *Saudi Pharm J* 2023;31:101668.
29 Kimura H, Tanaka K, Saito H, *et al*. Association of Polypharmacy with Kidney Disease Progression in Adults with CKD. *Clin J Am Soc Nephrol* 2021;16:1797–804.
30 Farrell B, Raman-Wilms L, Sadowski CA, *et al*. A Proposed Curricular Framework for an Interprofessional Approach to Deprescribing. *Med Sci Educ* 2023;33:551–67.
31 Halli-Tierney AD, Scarbrough C, Carroll D. Polypharmacy: Evaluating Risks and Deprescribing. *Am Fam Physician* 2019;100:32–8.

32 Doherty AJ, Boland P, Reed J, *et al*. Barriers and facilitators to deprescribing in primary care: a systematic review. *BJGP Open* 2020;4:bjgpopen20X101096.
33 Jones G, Macaninch E, Mellor DD, *et al*. Putting nutrition education on the table: development of a curriculum to meet future doctors' needs. *BMJNPH* 2022;5:208–16.
34 Chan WK, Chuah KH, Rajaram RB, *et al*. Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): A State-of-the-Art Review. *Journal of Obesity & Metabolic Syndrome* 2023;32:197–213.
35 Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, *et al*. Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis. *Gastroenterology* 2015;149:367–78.
36 Koutoukidis DA, Astbury NM, Tudor KE, *et al*. Association of Weight Loss Interventions With Changes in Biomarkers of Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-analysis. *JAMA Intern Med* 2019;179:1262–71.
37 Browning JD, Baker JA, Rogers T, *et al*. Short-term weight loss and hepatic triglyceride reduction: evidence of a metabolic advantage with dietary carbohydrate restriction. *Am J Clin Nutr* 2011;93:1048–52.
38 Law L, Heerey JJ, Devlin BL, *et al*. Effect of anti-inflammatory diets on health-related quality of life in adults with chronic disease: a systematic review and meta-analysis. *BMJNPH* 2025;8:314–26.
39 Haigh L, Kirk C, El Gendy K, *et al*. The effectiveness and acceptability of Mediterranean diet and calorie restriction in non-alcoholic fatty liver disease (NAFLD): A systematic review and meta-analysis. *Clin Nutr* 2022;41:1913–31.
40 Unwin D, Khalid AA, Unwin J, *et al*. Insights from a general practice service evaluation supporting a lower carbohydrate diet in patients with type 2 diabetes mellitus and prediabetes: a secondary analysis of routine clinic data including HbA1c, weight and prescribing over 6 years. *BMJNPH* 2020;3:285–94.