frontiers | Frontiers in Nutrition

TYPE Mini Review
PUBLISHED 24 September 2025
DOI 10.3389/fnut.2025.1673517

OPEN ACCESS

EDITED BY
Philippe Gérard,
Institut National de recherche pour l'agriculture, l'alimentation et l'environnement (INRAE), France

REVIEWED BY
Tiziana Maria Mahayri,
Academy of Sciences of the Czech Republic (ASCR), Czechia

*CORRESPONDENCE
Priyankar Dey
priyankar.dey@thapar.edu;
priyankardey28@gmail.com

RECEIVED 26 July 2025
ACCEPTED 12 September 2025
PUBLISHED 24 September 2025

CITATION
Dey P (2025) Gut microbial signatures associated with the Indian lean MASLD phenotype.
Front. Nutr. 12:1673517.
doi: 10.3389/fnut.2025.1673517

Gut microbial signatures associated with the Indian lean MASLD phenotype

Priyankar Dey*

Department of Biotechnology, Thapar Institute of Engineering and Technology, Patiala, Punjab, India

Lean Metabolic Dysfunction-associated Steatotic Liver Disease (MASLD) is a substantial challenge in India, manifesting in individuals with normal BMI and indicative of a *'metabolically obese normal weight'* phenotype. This review delineates the unique gut microbial signatures that characterize Indian lean MASLD, distinguishing it from obese MASLD. Principal modifications encompass substantial decreases in *Faecalibacterium* (particularly *F. prausnitzii*), *Ruminococcus*, *Lactobacillus*, *Lachnospira*, and *Subdoligranulum*, alongside an increase in pro-inflammatory *Escherichia-Shigella*. Dysbiotic patterns in India are influenced by factors such as fiber-deficient diets rich in refined carbohydrates, visceral obesity, insulin resistance, and genetic predispositions, including the PNPLA3 rs738409 polymorphism. Microbial alterations can contribute to disease by compromising gut barrier integrity, facilitating endotoxemia, and affecting the generation of beneficial metabolites. The combination signature of increased *Escherichia-Shigella* and decreased *Lachnospira/Subdoligranulum* exhibits significant diagnostic accuracy for detecting lean MASLD in the Indian population. These findings highlight lean MASLD as a mechanistically unique condition necessitating customized diagnostic and treatment approaches beyond standard weight management.

KEYWORDS

NAFLD, NASH, MASLD, microbiota, lean, obese, BMI

1 Introduction

Non-alcoholic Fatty Liver Disease (NAFLD) encompasses a wide range of hepatic disorders, beginning with simple hepatic steatosis (non-alcoholic fatty liver; NAFL), characterized by the buildup of lipids in the liver. This may evolve to Non-alcoholic Steatohepatitis (NASH), a more severe variant marked by inflammation and hepatocellular damage, frequently resulting in advanced liver conditions such as fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) (1). The terminology related to fatty liver disease has recently evolved, introducing the unifying terms Metabolic Dysfunction-associated Steatotic Liver Disease (MASLD) (2) and Metabolic Dysfunction-associated Steatohepatitis (MASH) (3). This reclassification transcends the prior focus on alcohol use, clearly recognizing the robust metabolic processes of the condition (4). The diagnosis of MASLD necessitates evidence of hepatic steatosis, characterized by above 5% fat accumulation in hepatocytes, together with the presence of at least one of five cardiometabolic risk factors. The criteria encompass overweight or obesity, prediabetes or diabetes mellitus, raised triglycerides, and low high-density lipoprotein levels (4). This change in terminology and diagnostic standards expands the clinical viewpoint, promoting a multidisciplinary approach for patient management. The extensive clinical scope, especially pertinent in India given the significant prevalence of diabetes and prediabetes, emphasizes the growing necessity for a comprehensive, multidisciplinary approach to diagnosis and management.

The role of gut microbiota in the pathogenesis of MASLD is well established (5, 6). Nevertheless, studying the gut microbiota composition in lean MASLD patients is crucial, as their condition exemplifies a notable metabolic contradiction that contests the traditional obesity-focused concept of hepatic disease causation (7). Given that these patients do not possess the primary contributor to insulin resistance and hepatic steatosis (excess adiposity), the progression of their disease clearly suggests the involvement of alternate, significant pathogenic pathways. Investigating their microbiome could allow understanding the microbial contributions from the overwhelming effects of obesity, potentially identifying unique microbial signatures, pathways (e.g., specific bile acid alterations, endotoxin production, or metabolite generation), or dysbiosis patterns specifically driving liver injury in this phenotype. This knowledge could be essential for comprehending fundamental disease mechanisms beyond adiposity, developing targeted diagnostic biomarkers for lean individuals who are frequently underdiagnosed, and formulating innovative microbiome-modulating therapeutics effective across all NAFLD subtypes, particularly for this high-risk group where conventional weight-loss recommendations are less relevant.

2 The emerging phenotype of lean MASLD

Lean MASLD denotes the occurrence of fatty liver disease in persons who do not satisfy the criteria for overweight or obesity, generally characterized by a Body Mass Index (BMI) below 25 kg/m^2 among Asian populations (8). Notwithstanding their normal BMI, these patients often display modest yet considerable changes in body composition, including increased total body and regional adiposity, especially in visceral and deep subcutaneous adipose tissues. Standard anthropometric measurements frequently fail to appropriately identify concerns related to fat compartmentalization. This phenotype is commonly referred to as '*metabolically obese normal weight*' (MONW) (8). Lean MASLD is an escalating global health issue, with an estimated prevalence of 4.1%, and is particularly prevalent among Asian populations (9). In India, the incidence of MASLD in lean individuals is significant, as evidenced by a biopsy-based study indicating that 33.7% of lean liver donors were affected by MASLD (10). The prevalence of MASLD in South Asia varies significantly, ranging from 9 to 45% (11). Research in India indicates that lean MASLD patients may exhibit markedly abnormal metabolic profiles, such as dyslipidemia and impaired glucose metabolism, similar to those found in obese individuals, despite having lower fasting plasma glucose and insulin resistance levels (12). In fact, it was suggested that central obesity is an independent factor influencing advanced fibrosis in lean individuals with MASLD (13). The significant occurrence of lean MASLD in India, despite ostensibly normal BMI, underscores the '*metabolically obese normal weight*' phenotype and it was suggested that MASLD definition is more suitable to lean NAFLD patients than MAFLD (14). This suggests that BMI alone is an inadequate measure of metabolic health, particularly in Asian populations, and that underlying fat distribution, especially visceral adiposity, and hereditary factors are significant contributors to the disease (4). This discovery contests traditional obesity-focused perspectives of MASLD, highlighting the necessity for more refined diagnostic and risk stratification methodologies. In these settings, the gut microbiome may function as a significant diagnostic or therapeutic target, irrespective of manifest obesity.

Despite a rise in the prevalence among the general population, lean MASLD is frequently underdiagnosed in India owing to various factors. The therapeutic focus on obesity as a principal risk factor results in the neglect of cases in individuals with a normal BMI, even though data indicate that lean MASLD accounts for 9.7% of all MASLD cases (15). Secondly, restricted availability of non-invasive diagnostic techniques (e.g., transient elastography) in primary care environments impedes early identification of such conditions in the non-obese individuals (16). Third, asymptomatic progression and clinician unawareness lead to missed diagnosis, especially in lean individuals with metabolic disorders such as diabetes (4). Ultimately, regional variations in healthcare infrastructure and inadequate incorporation of lean-specific screening in guidelines increase underdiagnosis (17, 18). Overcoming these obstacles necessitates comprehensive diagnostic criteria and improved clinician education regarding metabolic disorders beyond obesity.

3 Gut microbial signatures in Indian lean MASLD

3.1 Distinct microbial profiles

Recent studies repeatedly demonstrate that lean MASLD patients possess distinct gut microbial signatures and display considerably different gut microbial diversity, a metric of microbial community dissimilarity, in comparison to both obese MASLD patients and healthy controls (12). This indicates that the pathogenic mechanisms behind lean MASLD may be fundamentally different from those in obese MASLD (19). In general, MASLD patients may exhibit an elevation in Proteobacteria at the phylum level (20) and changed Firmicutes/Bacteroidetes ratios (21); however, specific microbial alterations are more severe and distinctive in lean individuals. The persistent identification of unique gut microbial signatures in lean MASLD patients, in contrast to obese MASLD patients, strongly substantiates the argument that lean MASLD is not simply a less severe variant of the obese condition, but rather a distinct mechanistic phenotype (9). This indicates that diagnostic indicators and therapy techniques designed for obese MASLD may not be immediately applicable or ideally successful for lean persons, requiring customized approaches that address their distinct microbial profiles.

3.2 Key microbial taxa

Numerous significant microbial genera and species have been associated with lean MASLD, with particular findings relevant to the Indian population (Table 1).

3.2.1 *Faecalibacterium*

A reduction of *Faecalibacterium* is associated with the pathophysiology of MASLD as demonstrated in a BMI- and sex-matched study of MASLD patients within a large study cohort (22). This association was irrespective of BMI and adiposity. However, a prospective pilot investigation revealed that lean NASH patients had

TABLE 1 Gut microbial signatures in Indian lean MASLD and their clinical significance.

Microbial taxa	Change in lean MASLD	Key associations/mechanisms	Diagnostic/therapeutic relevance
Faecalibacterium	↓ Decreased	• Specifically reduced *F. prausnitzii* (key butyrate producer)	• Protective role
		• Loss linked to impaired gut barrier, inflammation	• Potential probiotic target (requires supportive prebiotics/diet)
Ruminococcus	↓ Decreased	• Contrasts with *increases* often seen in obese MASLD/fibrosis	• Highlights lean vs. obese distinction
		• Includes beneficial (amylolytic) and harmful (*R. gnavus*) species	• Species-level analysis critical
Lactobacillus	↓ Decreased	• More depleted vs. obese MASLD	• Probiotic potential complex (strain-dependent)
		• Paradoxically *increased* in advanced fibrosis	• Depletion may reflect severe gut milieu
		• Strain-specific effects	
Bifidobacterium	↓ Decreased	• Reduced in overweight/obese MASLD	• Universal therapeutic target (probiotics) across MASLD phenotypes
		• Linked to endotoxemia	
		• Enhances barrier function and metabolism	
Lachnospira	↓ Decreased	• Part of a diagnostic signature combination	• Combined with ↓*Subdoligranulum* and ↑*Escherichia-Shigella* for lean MASLD diagnosis (AUC=0.82)
Subdoligranulum	↓ Decreased	• Part of a diagnostic signature combination	• Combined with ↓*Lachnospira* and ↑*Escherichia-Shigella* for lean MASLD diagnosis (AUC=0.82)
Escherichia-Shigella	↑ Increased	• Pro-inflammatory	• Combined with ↓*Lachnospira* and ↓*Subdoligranulum* for lean MASLD diagnosis (AUC=0.82)
		• Part of a diagnostic signature combination	
Blautia	Context-dependent	• Increased linked to PNPLA3 rs738409 CC genotype	• Role ambiguous (potential driver)
		• Associated with inflammation/fibrosis in some studies	• Highlights host gene-microbe interactions

a 3-fold reduction in the abundance of *Faecalibacterium* compared to control groups (19). Reduced *Faecalibacterium*, particularly its predominant strain *F. prausnitzii*, is noted in overall MASLD participants compared to healthy controls, with further reductions in individuals with more severe fibrosis (stage 3–4) (23). *F. prausnitzii* is a prominent butyrate-producing bacterium (24). Butyrate is recognized for its anti-inflammatory characteristics and its function in preserving gut barrier integrity (25). Preclinical studies suggest that *F. prausnitzii* supplementation enhances glucose homeostasis, inhibits hepatic lipid accumulation, mitigates liver damage and fibrosis, and restores compromised gut barrier function in mouse models of MASLD (26). Nonetheless, one study observed that oral gavage of *F. prausnitzii* did not ameliorate diet-induced steatohepatitis in mice, despite its correlation with MASLD severity in humans (23). The persistent finding of diminished *Faecalibacterium* in lean NASH and more severe MASLD, along with its established function as a beneficial butyrate producer, clearly indicates its protective significance. Although why reduced *Faecalibacterium* levels is observed in Indian lean MASLD patients remains unexplored, it is likely attributable to a fiber-deficient diet (27), coupled with a metabolic milieu marked by pronounced insulin resistance, visceral fat accumulation, and chronic inflammation, despite the absence of overt obesity (28). This establishes a gut milieu unsuitable to *F. prausnitzii*, while its reduction further intensifies gut barrier impairment and inflammation, accelerating the advancement of MASLD. Genetic predisposition and environmental variables, such as antibiotic usage, could also contribute to this dysbiotic profile (29). Moreover, the divergence between human associations and mouse intervention studies underscores the intricacy of microbiome interventions, merely introducing a beneficial bacterium may be insufficient if the gut environment is not favorable for its colonization or if other factors, such as diet and host genetics, diminish its efficacy. This indicates that future therapies may require the integration of probiotics with prebiotics or alternative dietary adjustments to establish a conducive environment for these advantageous bacteria.

3.2.2 *Ruminococcus*

Indian lean MASLD patients exhibited a 3-fold reduction in the amount of *Ruminococcus* (19). In contrast, certain investigations including general MASLD patients indicated elevated amounts of *Ruminococcus* relative to controls (30). Significantly, the abundance of *Ruminococcus* has been independently correlated with liver fibrosis ($F \geq 2$) (19). *Ruminococcus gnavus* has been associated with pro-inflammatory markers, inflammation, and fibrosis in patients with MASLD (31). The genus *Ruminococcus* exhibits significant heterogeneity, encompassing both advantageous and potentially harmful species, hence complicating the understanding of its function (6). *R. gnavus* is recognized for its impact on host metabolism and its ability to provoke either pro-inflammatory or anti-inflammatory responses (32). The populations are susceptible to nutritional alterations (6). The conflicting results regarding *Ruminococcus* (reduced in lean NASH, while elevated in general MASLD and correlated with fibrosis) highlight the necessity for species-level differentiation and patient stratification (lean vs. obese, fibrosis stage). This implies that certain

Ruminococcus species may have contradictory effects on liver health, or their influence is contingent upon context (e.g., affected by food or other concurrent dysbiosis). General analyses at the genus level may obscure significant specific effects, necessitating additional research to investigate species-specific roles and their interactions within the intricate gut ecosystem. Nevertheless, the reduced abundance of *Ruminococcus* in Indian lean MASLD patients is likely attributable to a confluence of dietary and metabolic variables. The common diet characterized by high-processed carbohydrates and low-resistant starch (e.g., refined rice and wheat) deprives amylolytic *Ruminococcus* spp. of their principal fermentable substrates (33). Simultaneously, metabolic dysfunction, marked by visceral fat accumulation, insulin resistance, and systemic inflammation even at reduced BMI, facilitates gut dysbiosis and barrier impairment (34). This milieu promotes pro-inflammatory mucin-degrading *Ruminococcus* strains (e.g., *R. gnavus*), which may temporarily proliferate but ultimately lead to pathogenic alterations, while diminishing beneficial fiber-utilizing species essential for butyrate synthesis and gut health.

3.2.3 *Lactobacillus*

Supplementation of probiotic *Lactobacillus* has proved to ameliorate diet-induced NASH in animal models (35). Lean MASLD patients demonstrated a higher depletion in *Lactobacillus* relative to overweight and obese NASH patients (19). Liver fibrosis (≥ F2) correlated with a heightened prevalence of *Lactobacilli*, while obese MASLD patients exhibited an enrichment of *Lactobacilli* (19). Patients with general MASLD exhibit elevated levels of *Lactobacillus* in comparison to healthy controls (5). Nevertheless, these diverse associations, numerous *Lactobacillus* strains are acknowledged as probiotics that confer advantageous outcomes in rodent models of MASLD, such as enhancing insulin sensitivity, mitigating inflammation, and decreasing lipogenesis (21). Particular strains such as *L. acidophilus* have shown preventive potential against MASLD-related HCC by generating valeric acid and enhancing gut barrier integrity (36). *L. plantarum* can mitigate redox-induced hepatocellular injury (37), and inflammation associated with MASLD (38). Probiotic treatment with several *Lactobacillus* spp. has demonstrated efficacy in ameliorating hepatic steatosis and diminishing liver inflammation (21). The apparently contradicting results regarding *Lactobacillus* (deficiency in lean MASLD but relatively elevated levels in fibrotic and obese MASLD) further indicate species- or strain-specific effects. Although remains unexplored, this is likely attributable to differing metabolic and nutritional interactions. Lean NASH in Indians is significantly linked to the 'thin-fat' phenotype, characterized by elevated visceral adiposity and insulin resistance despite a lower BMI, which induces severe gut inflammation and barrier impairment, resulting in a more adverse microenvironment for commensal lactobacilli compared to certain obese conditions (8, 39). Moreover, dietary elements specific to this population, such as elevated consumption of antimicrobial spices (e.g., turmeric, chili) and widespread intake of refined carbohydrates, may more effectively inhibit *Lactobacillus* than diets linked to obesity-related MASLD. Ironically, some *Lactobacillus* spp. may exacerbate inflammation in metabolic disorders, perhaps resulting in increased suppression within the markedly inflammatory lean MASLD environment (40). Although numerous *Lactobacillus* strains are recognized as probiotics that positively influence liver function, an over-proliferation of specific species or a dysbiosis within the genus may exacerbate disease, particularly in cases of severe fibrosis (41). This suggests that merely enhancing *Lactobacillus* proliferation may not consistently yield advantages, a detailed comprehension of particular strains and their metabolic roles is essential for successful probiotic applications.

3.2.4 *Bifidobacterium*

Patients with overweight MASLD demonstrated reduced abundance of *Bifidobacterium* (19). Within the wider South Asian population, diminished cecal *Bifidobacterium* levels have been linked to increased endotoxemia, which contributes to diabetes, obesity, and MASLD. *Bifidobacterium* spp. are acknowledged as advantageous probiotics (42). They are recognized for their ability to repair intestinal barrier integrity, diminish endotoxemia, and enhance lipid metabolism and insulin sensitivity. *B. animalis* subsp. Lactis V9 has demonstrated the capacity to lower liver transaminases, diminish TLR4 and TLR9 levels, and mitigate liver inflammation (43). The persistent observation of diminished *Bifidobacterium* in overweight NASH and its correlation with endotoxemia in South Asians underscores its essential function in preserving gut barrier integrity and mitigating systemic inflammation. This underscores that *Bifidobacterium* depletion is a prevalent dysbiotic characteristic among various MASLD phenotypes (lean, overweight, obese) and indicates that *Bifidobacterium*-containing probiotics may serve as a universally advantageous therapeutic approach, especially in the Indian context where its levels are observed to be diminished.

3.2.5 *Blautia*

In a recent study, *Blautia* exhibited a substantial rise in persons possessing the PNPLA3 rs738409 CC genotype throughout a 4-year duration (44). Several investigations involving general MASLD patients have indicated elevated levels of *Blautia* in comparison to controls (30). Nonetheless, alternative therapies, such as inulin administration, have demonstrated the capacity to down-regulate *Blautia* abundance, indicating a potentially adverse impact in some situations (45). The significance of *Blautia* in obesity and liver disease is seen as controversial, with certain research indicating advantageous effects while others recognize it as a contributing component (46). *Blautia* has been demonstrated to induce liver inflammation and hepatic fibrosis in murine models (47). The conflicting results regarding *Blautia* underscore the intricacy of analyzing microbial alterations. The distinct correlation between *Blautia* elevation and the PNPLA3 CC genotype indicates a gene-microbe interaction that may affect disease progression. This underscores that the influence of a certain genus can be significantly context-dependent, shaped by host genetics, co-existing microbial species, and unique eating habits. It warns against oversimplified categorization of 'good' and 'bad' (48) and advocates for a more refined comprehension of strain-specific functions and their interactions with host variables.

3.2.6 Other signatures

A study conducted in India comparing lean and non-lean MASLD patients revealed a notable increase of *Escherichia-Shigella* and a reduction of *Lachnospira* and *Subdoligranulum* especially in the lean MASLD subgroup (12). The amalgamation of these bacterial genera showed significant diagnostic precision (AUC of 0.82) in differentiating lean from non-lean MASLD patients (12). The identification of *Escherichia-Shigella* enrichment and *Lachnospira*/*Subdoligranulum* depletion as distinct signatures for Indian lean MASLD is a significant finding, offering concrete, regionally pertinent

microbial targets that may function as diagnostic biomarkers or therapeutic intervention points. The elevated diagnostic precision indicates significant potential for clinical utilization. Finally, gut microbial diversity has emerged as a critical indicator of overall metabolic health, where a depleted diversity is generally indicative of metabolic disease. In fact, patients with MASLD show a marked reduction in the gut microbiota diversity compared to healthy cohorts (49–51). However, whether the gut microbial diversity of lean MASLD patients, especially in the case of the Indian cohort, follows a similar trend of reduction, requires further study.

4 Conclusion

Lean MASLD is a unique and escalating difficulty, especially among the Indian population, as traditional BMI-based diagnoses of obesity may obscure underlying metabolic abnormalities (Figure 1). The pathogenesis of lean MASLD could be closely associated with gut dysbiosis, marked by distinct microbial changes, including diminished *Faecalibacterium*, *Ruminococcus*, and *Lactobacillus* in lean MASLD, as well as a reduction of *Lachnospira* and *Subdoligranulum* and an increase of *Escherichia-Shigella* in Indian lean MASLD. These microbial alterations lead to liver damage by compromising gut barrier integrity, elevating endotoxemia, and modifying the synthesis of microbial metabolites. The advancement of lean MASLD is significantly affected by a complex interaction of genetic factors, particularly the PNPLA3 rs738409 (G/G) genotype, which can directly change the composition of the gut microbiome. Concurrent lifestyle modifications, such as the embrace of Western food patterns abundant in refined carbs and unbalanced fats, together with sedentary behaviors, aggravate gut dysbiosis and influence the distinct metabolic characteristics of lean MASLD in

Aspect	Key Findings in Indian Lean MASLD
Clinical Definition & Prevalence	Defined as MASLD in individuals with a BMI < 25 kg/m². Prevalent in India, with a biopsy-based study finding 33.7% of lean liver donors had MASLD. Represents a significant 'metabolically obese normal weight' (MONW) phenotype.
Primary Clinical Features	Normal BMI but altered body composition with increased visceral and deep subcutaneous adiposity. Often underdiagnosed due to a focus on obesity, lack of non-invasive diagnostics in primary care, and asymptomatic progression.
Key Metabolic Differences	Exhibit dyslipidemia and impaired glucose metabolism similar to obese MASLD, though with lower fasting plasma glucose and HOMA-IR. Central obesity is an independent driver of advanced fibrosis. Strong association with the PNPLA3 rs738409 genetic polymorphism.
Gut Microbial Diversity	Displays a distinct gut microbial community structure (beta diversity) compared to both healthy controls and obese MASLD patients, suggesting a unique pathophysiology. Overall microbial diversity is often reduced.
Key Microbial Alterations	• Decreased: *Faecalibacterium* (esp. *F. prausnitzii*), *Ruminococcus*, *Lactobacillus*, *Bifidobacterium*, *Lachnospira*, *Subdoligranulum* • Increased: *Escherichia-Shigella* (pro-inflammatory), *Blautia* (context-dependent)
Diagnostic Microbial Signature	The combination of ↑*Escherichia-Shigella* + ↓*Lachnospira* + ↓*Subdoligranulum* shows significant diagnostic accuracy for distinguishing lean MASLD (AUC = 0.82)
Proposed Mechanisms of Pathogenesis	Dysbiosis leads to reduced beneficial short-chain fatty acids (e.g., butyrate), compromised gut barrier integrity, increased endotoxemia, and systemic inflammation, driving liver injury independently of overt obesity.
Influencing Factors	Diet (high in refined carbs, low in fiber), visceral adiposity, insulin resistance, genetic predisposition (e.g., PNPLA3), and likely environmental factors like antibiotic use.
Therapeutic Implications	Highlights the need for phenotype-specific management. Microbiome-targeted therapies (e.g., specific probiotics, prebiotics, FMT) are promising avenues for lean MASLD where weight-loss strategies are less relevant.

FIGURE 1
Summary of the major clinical, metabolic, and gut microbial characteristics of the Indian lean MASLD phenotype.

India. The unique pathophysiological pathways present in lean MASLD require customized diagnostic and treatment strategies. Microbiome-targeted therapies, including probiotics, prebiotics, and Fecal Microbiota Transplantation, exhibit significant potential, especially due to their proven effectiveness in non-obese individuals. These solutions provide a tailored approach for addressing MASLD in a demographic where conventional weight-loss therapies may be less effective. Future research should emphasize larger, methodologically designed studies targeting the Indian population to clarify specific microbial signatures, their functional aspects, and the long-term effectiveness of microbiome-modulating strategies in the prevention and treatment of lean MASLD.

Author contributions

PD: Funding acquisition, Writing – original draft, Formal analysis, Resources, Visualization, Validation, Conceptualization, Project administration, Writing – review & editing, Investigation, Data curation.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. Funding received from the Indian Council of Medical Research (IIRPIG-2024-01-00034) is thankfully acknowledged.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

References

1. Pandey H, Goel P, Srinivasan VM, Tang DWT, Wong SH, Lal D. Gut microbiota in non-alcoholic fatty liver disease: pathophysiology, diagnosis, and therapeutics. *World J Hepatol*. (2025) 17:106849. doi: 10.4254/wjh.v17.i6.106849

2. Chan WK, Chuah KH, Rajaram RB, Lim LL, Ratnasingam J, Vethakkan SR. Metabolic dysfunction-associated Steatotic liver disease (MASLD): a state-of-the-art review. *J Obes Metab Syndr*. (2023) 32:197–213. doi: 10.7570/jomes23052

3. Patel RH, Parikh C, Upadhyay H, Sonaiya S, Ramnath P, Singh S, et al. Resmetirom in the management of metabolic dysfunction-associated steatohepatitis (MASH): a comprehensive review of current evidence and therapeutic potential. *Cureus*. (2024) 16:e74772. doi: 10.7759/cureus.74772

4. Zargar AH, Bhansali A, Majumdar A, Maheshwari A, Bhattacharyya A, Dasgupta A, et al. Management of metabolic dysfunction-associated steatotic liver disease (MASLD)-an expert consensus statement from Indian diabetologists' perspective. *Diabetes Obes Metab*. (2025) 27:3–20. doi: 10.1111/dom.16496

5. Schwenger KJ, Clermont-Dejean N, Allard JP. The role of the gut microbiome in chronic liver disease: the clinical evidence revised. *JHEP Rep*. (2019) 1:214–26. doi: 10.1016/j.jhepr.2019.04.004

6. Brandl K, Schnabl B. Intestinal microbiota and nonalcoholic steatohepatitis. *Curr Opin Gastroenterol*. (2017) 33:128–33. doi: 10.1097/MOG.0000000000000349

7. Xu R, Pan J, Zhou W, Ji G, Dang Y. Recent advances in lean NAFLD. *Biomed Pharmacother*. (2022) 153:113331. doi: 10.1016/j.biopha.2022.113331

8. Das K, Chowdhury A. Lean NASH: distinctiveness and clinical implication. *Hepatol Int*. (2013) 7:806–13. doi: 10.1007/s12072-013-9477-5

9. Haag M, Winter S, Kemas AM, Tevini J, Feldman A, Eder SK, et al. Circulating metabolite signatures indicate differential gut-liver crosstalk in lean and obese MASLD. *JCI Insight*. (2025) 10:943. doi: 10.1172/jci.insight.180943

10. Kuchay MS, Martínez-Montoro JI, Choudhary NS, Fernández-García JC, Ramos-Molina B. Non-alcoholic fatty liver disease in lean and non-obese individuals: current and future challenges. *Biomedicine*. (2021) 9:346. doi: 10.3390/biomedicines9101346

11. Pati GK, Singh SP. Nonalcoholic fatty liver disease in South Asia. *Euroasian J Hepatogastroenterol*. (2016) 6:154–62. doi: 10.5005/jp-journals-10018-1189

12. Anirvan P, Khan ZH, Bhuyan P, Dixit S, Dash R, Mishra P, et al. Gut microbiota and genetic polymorphisms appear to drive disease expression of nonalcoholic fatty liver disease in lean individuals. *J Clin Exp Hepatol*. (2025) 15:102503. doi: 10.1016/j.jceh.2025.102503

13. De A, Bhagat N, Mehta M, Singh P, Rathi S, Verma N, et al. Central obesity is an independent determinant of advanced fibrosis in lean patients with nonalcoholic fatty liver disease. *J Clin Exp Hepatol*. (2025) 15:102400. doi: 10.1016/j.jceh.2024.102400

14. De A, Bhagat N, Mehta M, Taneja S, Duseja A. Metabolic dysfunction-associated steatotic liver disease (MASLD) definition is better than MAFLD criteria for lean patients with NAFLD. *J Hepatol*. (2024) 80:e61–2. doi: 10.1016/j.jhep.2023.07.031

15. Prasad M, Bhardwaj N, Gupta E, Thomas SS. Prevalence and predictors for lean fatty liver disease in general population attending a COVID-19 vaccination center in a tertiary care hospital in India. *Euroasian J Hepato Gastroenterol*. (2024) 14:145–50. doi: 10.5005/jp-journals-10018-1438

16. Rajan V, Das A, Venkatachalam J, Lohani K, Lahariya C. Managing metabolic dysfunction-associated steatotic liver disease (MASLD) in primary care settings: a review. *Prevent Med*. (2025) 2:183–91. doi: 10.4103/PMRR.PMRR_159_24

17. Mohan V, Joshi S, Kant S, Shaikh A, Sreenivasa Murthy L, Saboo B, et al. Prevalence of metabolic dysfunction-associated steatotic liver disease: mapping across different Indian populations (MAP study). *Diab Ther*. (2025) 16:1435–50. doi: 10.1007/s13300-025-01748-1

18. Ramesh PR, Krishnan P, Prabu S, Srinivasan V, Niranjan V. Diagnosis and management of metabolic dysfunction-associated steatotic liver disease in south Asians-a clinical review. *Obesity Pillars*. (2024) 12:100142. doi: 10.1016/j.obpill.2024.100142

19. Duarte SMB, Stefano JT, Miele L, Ponziani FR, Souza-Basqueira M, Okada L, et al. Gut microbiome composition in lean patients with NASH is associated with liver damage independent of caloric intake: a prospective pilot study. *Nutr Metab Cardiovasc Dis*. (2018) 28:369–84. doi: 10.1016/j.numecd.2017.10.014

20. Zhou J, Tripathi M, Sinha RA, Singh BK, Yen PM. Gut microbiota and their metabolites in the progression of non-alcoholic fatty liver disease. *Hepatoma Res*. (2021) 7:11. doi: 10.20517/2394-5079.2020.134

21. Ren TY, Li XY, Fan JG. Probiotics for treatment of nonalcoholic fatty liver disease: it is worth a try. *Clin Mol Hepatol*. (2021) 27:83–6. doi: 10.3350/cmh.2020.0298

22. Iino C, Endo T, Mikami K, Hasegawa T, Kimura M, Sawada N, et al. Significant decrease in Faecalibacterium among gut microbiota in nonalcoholic fatty liver disease:

a large BMI- and sex-matched population study. *Hepatol Int*. (2019) 13:748–56. doi: 10.1007/s12072-019-09987-8

23. Münte E, Viebahn G, Khurana A, Fujiki J, Nakamura T, Lang S, et al. *Faecalibacterium prausnitzii* is associated with disease severity in MASLD but its supplementation does not improve diet-induced Steatohepatitis in mice. *Microorganisms*. (2025) 13:675. doi: 10.3390/microorganisms13030675

24. Parsaei M, Sarafraz N, Moaddab SY, Ebrahimzadeh Leylabadlo H. The importance of *Faecalibacterium prausnitzii* in human health and diseases. *New Microbes New Infect*. (2021) 43:100928. doi: 10.1016/j.nmni.2021.100928

25. Dey P. Targeting gut barrier dysfunction with phytotherapies: effective strategy against chronic diseases. *Pharmacol Res*. (2020) 161:105135. doi: 10.1016/j.phrs.2020.105135

26. Shin JH, Lee Y, Song EJ, Lee D, Jang SY, Byeon HR, et al. *Faecalibacterium prausnitzii* prevents hepatic damage in a mouse model of NASH induced by a high-fructose high-fat diet. *Front Microbiol*. (2023) 14:1123547. doi: 10.3389/fmicb.2023.1123547

27. Narayan S, Lakshmipriya N, Vaidya R, Bai MR, Sudha V, Krishnaswamy K, et al. Association of dietary fiber intake with serum total cholesterol and low density lipoprotein cholesterol levels in urban Asian-Indian adults with type 2 diabetes. *Indian J Endocrinol Metab*. (2014) 18:624–30. doi: 10.4103/2230-8210.139215

28. Bilic-Curcic I, Berkovic MC, Virovic-Jukic L, Mrzljak A. Shifting perspectives–interplay between non-alcoholic fatty liver disease and insulin resistance in lean individuals. *World J Hepatol*. (2021) 13:80–93. doi: 10.4254/wjh.v13.i1.80

29. Tarantino G, Citro V. Could adverse effects of antibiotics due to their use/misuse be linked to some mechanisms related to nonalcoholic fatty liver disease? *Int J Mol Sci*. (2024) 25:93. doi: 10.3390/ijms25041993

30. Del Chierico F, Nobili V, Vernocchi P, Russo A, De Stefanis C, Gnani D, et al. Gut microbiota profiling of pediatric nonalcoholic fatty liver disease and obese patients unveiled by an integrated meta-omics-based approach. *Hepatology*. (2017) 65:451–64. doi: 10.1002/hep.28572

31. Gupta H, Min BH, Ganesan R, Gebru YA, Sharma SP, Park E, et al. Gut microbiome in non-alcoholic fatty liver disease: from mechanisms to therapeutic role. *Biomedicine*. (2022) 10:550. doi: 10.3390/biomedicines10030550

32. Juge N. Microbe profile: *Ruminococcus gnavus*: the yin and yang of human gut symbionts. *Microbiology*. (2023) 169:383. doi: 10.1099/mic.0.001383

33. Leung C, Rivera L, Furness JB, Angus PW. The role of the gut microbiota in NAFLD. *Nat Rev Gastroenterol Hepatol*. (2016) 13:412–25. doi: 10.1038/nrgastro.2016.85

34. Portincasa P, Khalil M, Graziani A, Frühbeck G, Baffy G, Garruti G, et al. Gut microbes in metabolic disturbances. Promising role for therapeutic manipulations? *Eur J Intern Med*. (2024) 119:13–30. doi: 10.1016/j.ejim.2023.10.002

35. Sabirin F, Lim SM, Neoh CF, Ramasamy K. Hepatoprotection of probiotics against non-alcoholic fatty liver disease in vivo: a systematic review. *Front Nutr*. (2022) 9:844374. doi: 10.3389/fnut.2022.844374

36. Lau HC, Zhang X, Ji F, Lin Y, Liang W, Li Q, et al. *Lactobacillus acidophilus* suppresses non-alcoholic fatty liver disease-associated hepatocellular carcinoma through producing valeric acid. *EBioMedicine*. (2024) 100:104952. doi: 10.1016/j.ebiom.2023.104952

37. Rezgui R, Walia R, Sharma J, Sidhu D, Alshagadali K, Ray Chaudhuri S, et al. Chemically defined *Lactobacillus plantarum* cell-free metabolites demonstrate cytoprotection in HepG2 cells through Nrf2-dependent mechanism. *Antioxidants*. (2023) 12:930. doi: 10.3390/antiox12040930

38. Kim DY, Park JY, Gee HY. *Lactobacillus plantarum* ameliorates NASH-related inflammation by upregulating L-arginine production. *Exp Mol Med*. (2023) 55:2332–45. doi: 10.1038/s12276-023-01102-0

39. De A, Mehta M, Singh P, Bhagat N, Mitra S, Das A, et al. Lean Indian patients with non-alcoholic fatty liver disease (NAFLD) have less metabolic risk factors but similar liver disease severity as non-lean patients with NAFLD. *Int J Obes*. (2023) 47:986–92. doi: 10.1038/s41366-023-01346-w

40. Dey P, Ray Chaudhuri S. Cancer-associated microbiota: from mechanisms of disease causation to microbiota-centric anti-Cancer approaches. *Biology*. (2022) 11:757. doi: 10.3390/biology11050757

41. Rao SSC, Rehman A, Yu S, Andino NM. Brain fogginess, gas and bloating: a link between SIBO, probiotics and metabolic acidosis. *Clin Transl Gastroenterol*. (2018) 9:162. doi: 10.1038/s41424-018-0030-7

42. Dey P. Gut microbiota in phytopharmacology: a comprehensive overview of concepts, reciprocal interactions, biotransformations and mode of actions. *Pharmacol Res*. (2019) 147:104367. doi: 10.1016/j.phrs.2019.104367

43. Campagnoli LIM, Marchesi N, Vairetti M, Pascale A, Ferrigno A, Barbieri A. Age-related NAFLD: the use of probiotics as a supportive therapeutic intervention. *Cells*. (2022) 11:827. doi: 10.3390/cells11182827

44. Sato S, Iino C, Sasada T, Furusawa K, Yoshida K, Sawada K, et al. A 4-year cohort study of the effects of PNPLA3 rs738409 genotypes on liver fat and fibrosis and gut microbiota in a non-fatty liver population. *Environ Health Prev Med*. (2025) 30:17–7. doi: 10.1265/ehpm.24-00365

45. Bao T, He F, Zhang X, Zhu L, Wang Z, Lu H, et al. Inulin exerts beneficial effects on non-alcoholic fatty liver disease via modulating gut microbiome and suppressing the lipopolysaccharide-toll-like receptor 4-Mψ-nuclear factor-κB-nod-like receptor protein 3 pathway via gut-liver Axis in mice. *Front Pharmacol*. (2020) 11:558525. doi: 10.3389/fphar.2020.558525

46. Chanda W, Jiang H, Liu SJ. The ambiguous correlation of Blautia with obesity: a systematic review. *Microorganisms*. (2024) 12:768. doi: 10.3390/microorganisms12091768

47. Yang M, Qi X, Li N, Kaifi JT, Chen S, Wheeler AA, et al. Western diet contributes to the pathogenesis of non-alcoholic steatohepatitis in male mice via remodeling gut microbiota and increasing production of 2-oleoylglycerol. *Nat Commun*. (2023) 14:228. doi: 10.1038/s41467-023-35861-1

48. Dey P. Good girl goes bad: understanding how gut commensals cause disease. *Microb Pathog*. (2024) 190:106617. doi: 10.1016/j.micpath.2024.106617

49. Schnabl B, Damman CJ, Carr RM. Metabolic dysfunction–associated steatotic liver disease and the gut microbiome: pathogenic insights and therapeutic innovations. *J Clin Invest*. (2025) 135:423. doi: 10.1172/JCI186423

50. Jiménez-González C, Alonso-Peña M, Argos Vélez P, Crespo J, Iruzubieta P. Unraveling MASLD: the role of gut microbiota, dietary modulation, and AI-driven lifestyle interventions. *Nutrients*. (2025) 17:1580. doi: 10.3390/nu17091580

51. Cai W, Qiu T, Hu W, Fang T. Changes in the intestinal microbiota of individuals with non-alcoholic fatty liver disease based on sequencing: an updated systematic review and meta-analysis. *PLoS One*. (2024) 19:e0299946. doi: 10.1371/journal.pone.0299946