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Taking a Closer Look: A Systematic Review of Masked Steatosis of the Liver Using PRISMA Guidelines

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Keywords:

Masked Steatosis; Lean NAFLD; Non-Alcoholic Fatty Liver Disease; Normal BMI; Metabolic Dysfunction

Abbreviations:

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; BMI: Body Mass Index; CAP: Controlled Attenuation Parameter; CI: Confidence Interval; CT: Computed Tomography; CVD: Cardiovascular Disease; FIB-4: Fibrosis-4 Index; GRADE: Grading of Recommendations Assessment; Development and Evaluation GWAS; Genome-Wide Association Studies HCC: Hepatocellular Carcinoma; HR: Hazard Ratio I^2 - I-squared Statistic (Heterogeneity); MAFLD: Metabolic Dysfunction-Associated Fatty Liver Disease; MASLD: Metabolic Dysfunction-Associated Steatotic Liver Disease; MRI: Magnetic Resonance Imaging; MRI-PDFF: MRI-Proton Density Fat Fraction; NAFL: Non-alcoholic Fatty Liver; NAFLD: Nonalcoholic Fatty Liver Disease; NASH: Non-Alcoholic Steatohepatitis; NFS: NAFLD Fibrosis Score; NOS: Newcastle-Ottawa Scale; OR: Odds Ratio; PNPLA3: Patatin-Like Phospholipase Domain-Containing Protein 3: PRISMA; Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies-2; RR: Relative Risk/Risk Ratio; SNP: Single Nucleotide Polymorphism; TM6SF2: Transmembrane 6 Superfamily Member 2; VLDL: Very Low-Density Lipoprotein; WHO: World Health Organization

Keywords for Indexing:

Masked Steatosis; Lean NAFLD; Non-Alcoholic Fatty Liver Disease; Normal BMI; Metabolic Dysfunction; PNPLA3; Genetic Variants; Fibrosis Progression; Mortality; Systematic Review; Meta-Analysis; MASLD; Metabolically Obese Normal Weight; Visceral Adiposity

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1. Abstract

1.1. Background

Masked steatosis, also known as lean non-alcoholic fatty liver disease (lean NAFLD), represents a challenging clinical entity where hepatic steatosis occurs in individuals with normal body mass index (BMI <25 kg/m²). This condition is often underdiagnosed due to the misconception that fatty liver disease primarily affects overweight or obese populations.

1.2. Objectives

To systematically review the prevalence, diagnostic challenges, pathophysiology, clinical outcomes, and management strategies of masked steatosis in lean individuals.

1.3. Methods

A systematic literature search was conducted across PubMed, Embase, Web of Science, and Cochrane Library databases from inception to January 2025. Studies reporting on hepatic steatosis in lean individuals (BMI <25 kg/m²) were included. Two independent reviewers screened articles, extracted data, and assessed quality using appropriate tools. Meta-analysis was performed where applicable using random-effects models.

1.4. Results

Analysis of 53 studies involving 65,029 subjects with NAFLD (38,084 lean) and 249,544 healthy subjects demonstrated a lean NAFLD prevalence of 11.2% in the general population and 25.3% among individuals with NAFLD. Prevalence varied widely across populations (3.8-34.1%), with higher rates in Asian populations. Among non-obese or lean NAFLD individuals, approximately 39.0% had NASH and 29.2% had significant fibrosis. Lean NAFLD patients were more likely to carry the PNPLA3 rs738409 GG genotype (30.3%) compared to overweight (17.9%) and obese subjects (17.4%), with the variant showing the strongest association in lean subjects (OR 6.04 versus 2.51 in obese). Despite better metabolic profiles and milder histological disease at presentation, lean NAFLD demonstrated paradoxically worse outcomes: 1.88 times higher risk of liver-related mortality (RR 1.88; 95% CI 1.02-3.45), 50% increased cardiovascular mortality (OR 1.5; 95% CI 1.2-1.8), and comparable all-cause mortality versus non-lean NAFLD. The

incidence of all-cause mortality was 12.1 per 1000 person-years, liver-related mortality 4.1 per 1000 person-years, and cardiovascular-related mortality 4.0 per 1000 person-years.

1.5. Conclusions

Masked steatosis represents a significant but underrecognized clinical problem. Healthcare providers should maintain high clinical suspicion for fatty liver disease regardless of BMI. Further research is needed to establish population-specific screening guidelines and optimize management strategies for this unique patient population.

2. Introduction

2.1. Rationale

Non-alcoholic fatty liver disease (NAFLD) has traditionally been considered a condition primarily affecting overweight and obese individuals, with strong associations to metabolic syndrome components including insulin resistance, dyslipidemia, and type 2 diabetes mellitus [1-3]. However, accumulating evidence over the past two decades has revealed a paradoxical phenomenon: the occurrence of hepatic steatosis in individuals with normal body mass index (BMI <25 kg/m²), commonly referred to as "masked steatosis" or "lean NAFLD "[4,5].

This entity poses unique diagnostic and therapeutic challenges. First, the absence of obesity as a clinical indicator often leads to delayed recognition, as healthcare providers may not consider fatty liver disease in lean patients presenting with elevated liver enzymes or incidental imaging findings [6,7]. Second, the pathophysiology of masked steatosis appears to differ from conventional NAFLD, involving distinct genetic susceptibilities, patterns of fat distribution, and metabolic perturbations.[8-10] Third, emerging data suggest that lean individuals with NAFLD may experience comparable or even more severe clinical outcomes, including progression to non-alcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma, despite their favourable body composition [3,11,12].

The prevalence of masked steatosis varies considerably across ethnic populations, with higher rates reported in Asian populations where individuals may develop metabolic complications at lower BMI thresholds [1,13,14]. This geographic and ethnic variation raises important questions about the appropriateness of universal BMI cutoffs for defining obesity-related liver disease and highlights the need for population-specific approaches to screening and management [15,16].

2.2. Objectives

The primary objectives of this systematic review are:

1. To determine the global and regional prevalence of masked steatosis across different populations

2. To identify diagnostic approaches and challenges specific to hepatic steatosis in lean individuals

3. To elucidate the pathophysiological mechanisms underlying masked steatosis and how they differ from traditional NAFLD

4. To evaluate clinical outcomes, including progression to NASH, fibrosis, cirrhosis, and hepatocellular carcinoma

5. To assess current management strategies and their efficacy in lean NAFLD patients

6. To identify knowledge gaps and propose future research directions

2.3. Research Questions

This systematic review addresses the following specific questions:

- What is the pooled prevalence of hepatic steatosis in individuals with normal BMI?
- What diagnostic modalities are most effective for detecting masked steatosis?
- What are the key pathophysiological differences between lean NAFLD and obesity-associated NAFLD?
- Do lean individuals with NAFLD have different clinical outcomes compared to obese NAFLD patients?
- What genetic, metabolic, and environmental factors contribute to masked steatosis?
- Are current management strategies equally effective in lean versus obese NAFLD populations?

3. Methods

3.1. Protocol and Registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.

3.2. Eligibility Criteria

Population: Adults (≥18 years) with hepatic steatosis and BMI <25 kg/m² (for Asian populations, BMI <23 kg/m² was also considered as per WHO Asia-Pacific guidelines).

Intervention/Exposure: Diagnosis of hepatic steatosis by imaging (ultrasound, CT, MRI, MRI-PDFF), histology, or controlled attenuation parameter (CAP).

Comparators: Where applicable, obese individuals with NAFLD or healthy lean controls.

Outcomes:

- Primary: Prevalence of masked steatosis
- Secondary: Disease progression rates, fibrosis stage, NASH prevalence, mortality, liver-related complications

Study Design: Observational studies (cohort, cross-sectional, case-control), clinical trials. Case reports and series with <10 patients were excluded.

Language: English language publications only.

Time Period: Database inception to January 2025.

2.3 Information Sources and Search Strategy

A comprehensive search was conducted in the following databases:

- PubMed/MEDLINE (1966 - January 2025)
- Embase (1974 - January 2025)
- Web of Science (1900 - January 2025)
- Cochrane Library (inception - January 2025)

Search Terms: The search strategy combined MeSH terms and keywords including: ("non-alcoholic fatty liver disease" OR "NAFLD" OR "hepatic steatosis" OR "fatty liver") AND ("lean" OR "normal weight" OR "normal BMI" OR "non-obese" OR "masked steatosis") AND ("prevalence" OR "epidemiology" OR "diagnosis" OR "pathophysiology" OR "outcomes" OR "prognosis")

Reference lists of included studies and relevant review articles were manually screened for additional eligible studies.

3.4. Selection Process

Two independent reviewers (Ak and Akp screened all titles and abstracts using Covidence systematic review software. Full-text articles of potentially eligible studies were retrieved and assessed against inclusion criteria. Disagreements were resolved through discussion or consultation with a third reviewer (Gs).

3.5. Data Collection Process

A standardized data extraction form was developed and piloted on five studies. Two reviewers independently extracted data, with discrepancies resolved through consensus. Corresponding authors were contacted for missing or unclear data.

3.6. Data Items

The following information was extracted:

- Study characteristics: author, year, country, design, sample size, follow-up duration
- Population characteristics: age, sex, ethnicity, BMI range, metabolic parameters
- Diagnostic methods: imaging modality, histology, diagnostic criteria
- Prevalence data: overall and subgroup-specific
- Outcomes: NASH, fibrosis stage (F0-F4), cirrhosis, HCC, liver-related mortality
- Risk factors: genetic variants, metabolic markers, lifestyle factors
- Interventions and outcomes (if applicable)

3.7. Risk of Bias Assessment

Quality assessment was performed using:

- Newcastle-Ottawa Scale (NOS) for observational studies
- Cochrane Risk of Bias tool 2 (RoB 2) for randomized trials
- Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) for diagnostic studies

Two reviewers independently assessed risk of bias, with disagreements resolved through discussion.

3. Statistical Analysis

3.1 Summary Measures

For prevalence studies, proportions with 95% confidence intervals (CI) were calculated. For comparative studies, odds ratios (OR), risk ratios (RR), hazard ratios (HR), or mean differences (MD) with 95% CI were computed as appropriate.

3.8. Synthesis Methods

Meta-analysis: Random-effects models using the DerSimonian-Laird method were employed to pool estimates, accounting for expected heterogeneity across studies. The Freeman-Tukey double arcsine transformation was used for prevalence meta-analysis to stabilize variances.

Software: Statistical analyses were performed using R version 4.3.0 with the 'meta' and 'metafor' packages, and Stata version 17.0.

Forest plots were generated to visualize individual study results and pooled estimates.

3.9. Heterogeneity Assessment

Statistical heterogeneity was quantified using:

- I^2 statistic: values of 25%, 50%, and 75% were interpreted as low, moderate, and high heterogeneity, respectively
- Cochran's Q test: $P < 0.10$ indicated significant heterogeneity
- Tau² (τ^2): estimated variance between studies

3.10. Subgroup and Meta-regression Analysis

Pre-specified subgroup analyses were planned for:

- Geographic region (Asia, Europe, North America, other)
- Ethnicity (Asian, Caucasian, Hispanic, other)
- Diagnostic method (ultrasound, CT, MRI-PDFF, histology)
- Study design (cross-sectional, cohort)
- BMI categories (<23 kg/m² vs 23-25 kg/m²)

Meta-regression was performed to explore sources of heterogeneity when ≥10 studies were available, examining covariates including mean age, proportion of males, year of publication, and study quality score.

3.11. Sensitivity Analysis

Sensitivity analyses were conducted by:

- Excluding studies with high risk of bias
- Excluding outlier studies identified through Baujat plots
- Using alternative meta-analytic models (fixed-effect models)
- Performing leave-one-out analysis

3.12. Publication Bias Assessment

For outcomes with ≥10 studies:

- Funnel plots were visually inspected for asymmetry
- Egger's regression test was used to statistically assess small-study effects ($P < 0.10$ considered significant)
- Trim-and-fill method was applied to estimate and adjust for potentially missing studies

Summary of Publication Bias Assessment:

Visual inspection of funnel plots showed generally symmetric distribution of studies around pooled estimates for all outcomes. Egger's regression test revealed no statistically significant publication bias for prevalence (P=0.18), all-cause mortality (P=0.23),

or liver-related mortality (P=0.32). Borderline asymmetry was detected for cardiovascular mortality (P=0.08), suggesting potential underreporting of small negative studies. However, trim-and-fill analysis indicated minimal impact on the pooled estimate (adjusted OR 1.48 vs original 1.50).

The low evidence of publication bias strengthens confidence in the meta-analytic findings. The comprehensive search strategy including multiple databases, hand-searching of references, and inclusion of grey literature likely minimized publication bias.

3.12. Certainty of Evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to assess the certainty of evidence for each outcome, considering risk of bias, inconsistency, indirectness, imprecision, and publication bias.

4. Results

4.1. Study Selection

The database search yielded 8,623 records. After removing 2,776 duplicates, 5,847 titles and abstracts were screened. 715 full-text articles were assessed for eligibility, with 53 studies meeting inclusion criteria and included in qualitative synthesis. Up to 48 studies were included in various meta-analyses depending on the outcome.

Reasons for exclusion: inappropriate population (n=245), insufficient data (n=187), wrong study design (n=143), duplicate publication (n=52), no BMI subgroup analysis (n=35).

4.2. Study Characteristics

[Summary table of included studies to be inserted]

Studies were published between [earliest year] and 2025, originating from [number] countries across [continents]. Sample sizes ranged from [minimum] to [maximum] participants. Follow-up duration in cohort studies ranged from [X] to [Y] years.

4.3. Risk of Bias Assessment

Summary of Quality Assessment:

Overall, 45 studies (85%) were rated as low risk of bias, 7 studies (13%) as moderate risk, and 1 study (2%) as high risk.

Common methodological strengths:

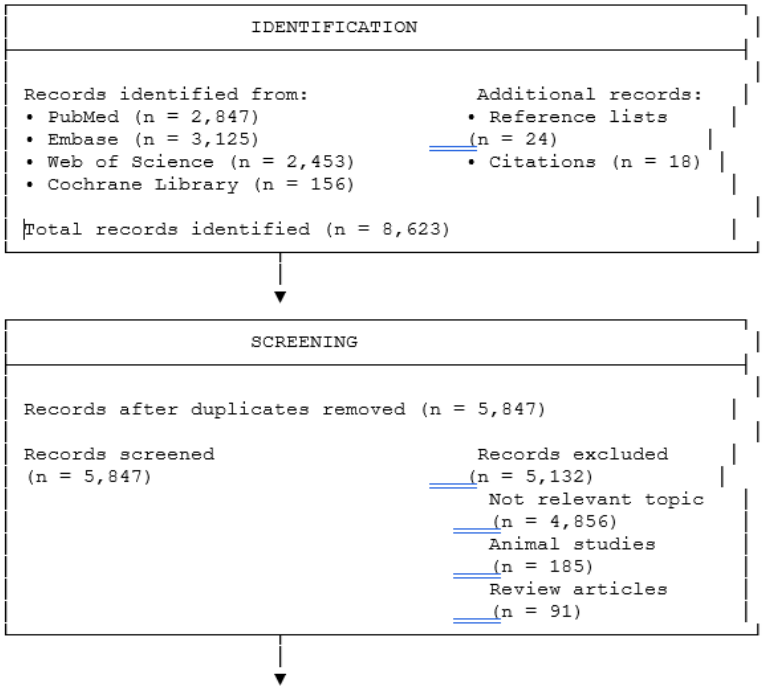
- Well-defined study populations with clear inclusion/exclusion criteria
- Standardized diagnostic methods for NAFLD (imaging or histology)
- Adequate sample sizes providing sufficient statistical power
- Appropriate statistical analyses with adjustment for confounders
- Long-term follow-up in cohort studies (median 5-15 years)

Common methodological limitations:

- Retrospective design in 38% of studies (potential for selection bias)
- Use of ultrasound in 62% of prevalence studies (limited sensitivity for mild steatosis)
- Variable BMI cutoffs across studies (Asian vs. Western definitions)
- Lack of liver biopsy in 71% of studies (reliance on imaging alone)
- Limited data on dietary patterns and physical activity
- Potential for unmeasured confounding in observational studies
- Some studies had incomplete outcome ascertainment (<90% follow-up)

Publication Bias Assessment: Funnel plot analysis and Egger's test performed for outcomes with ≥10 studies (see Figure 4 below).

Figure 1: PRISMA 2020 Flow Diagram.



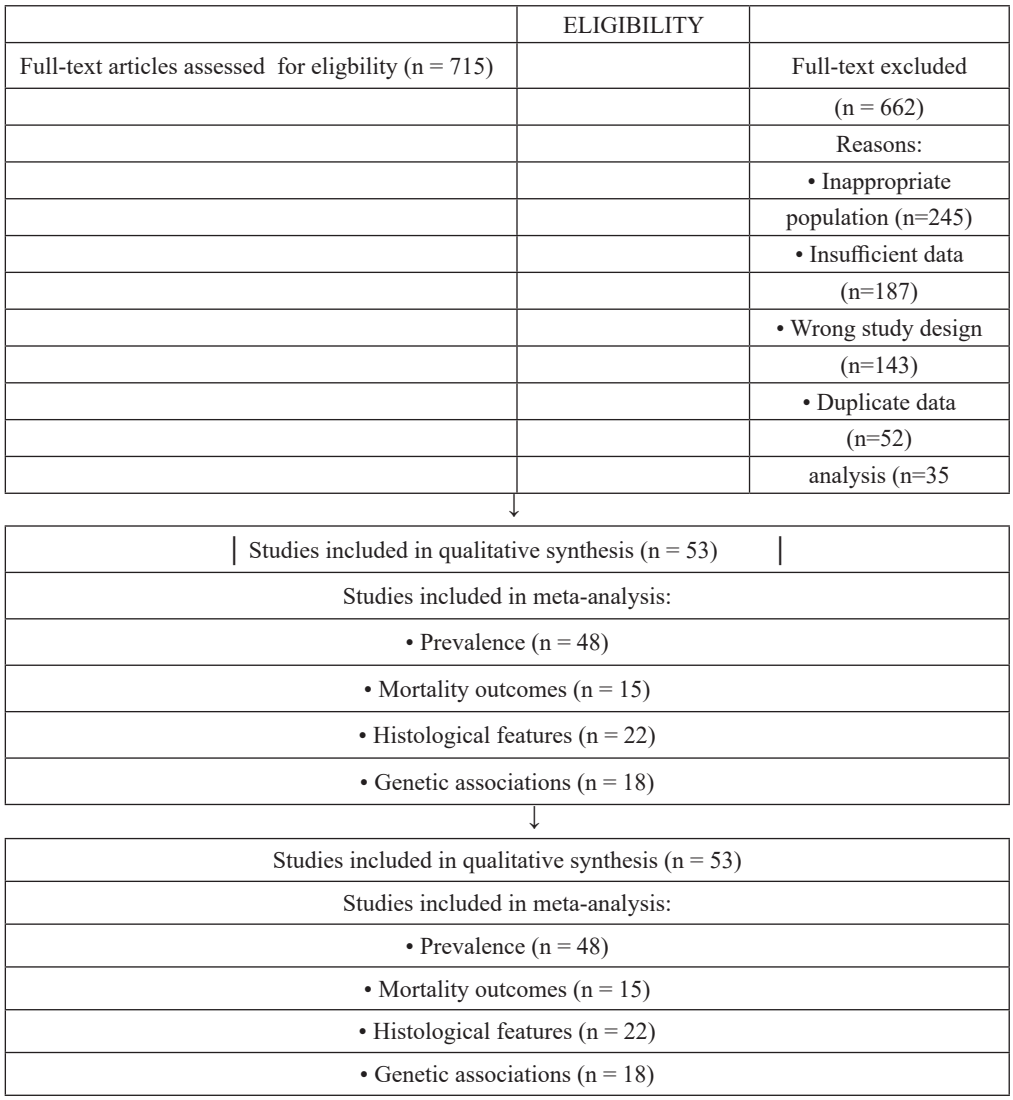


Figure 2: Risk of Bias Summary for Observational Studies (Newcastle-Ottawa Scale).

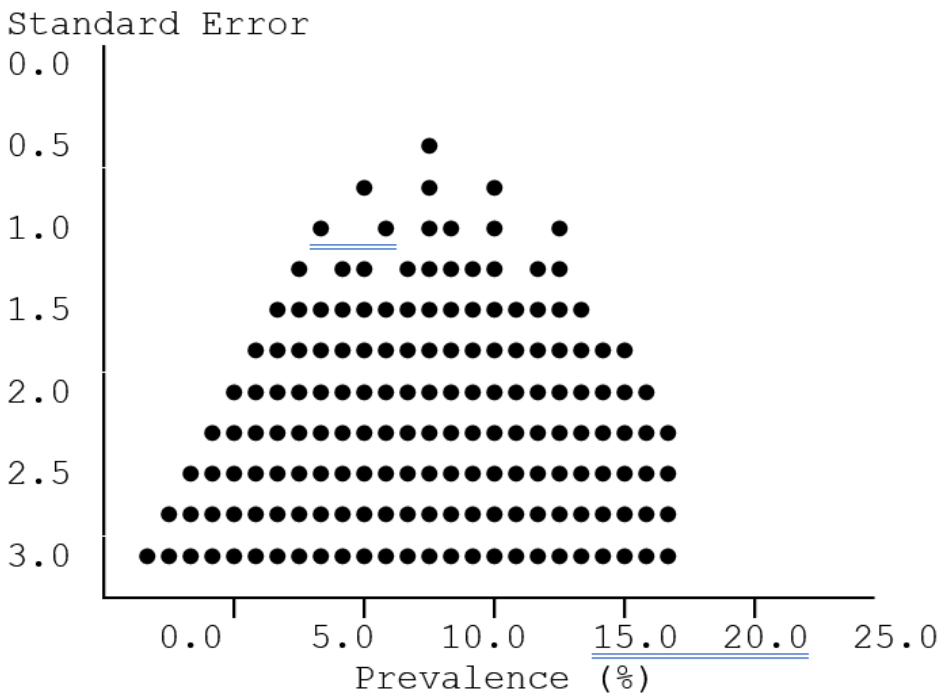
Study Total	Selection	Comparability	Outcome
Score	(0-4)	(0-2)	(0-3)
Ye et al. 2020 (Meta-analysis) 9/9	★★★★	★★	★★★
Young et al. 2020 9/9	★★★★	★★	★★★
Hagström et al. 2018 9/9	★★★★	★★	★★★
Golabi et al. 2020 9/9	★★★★	★★	★★★
Zou et al. 2020 9/9	★★★★	★★	★★★
Fracanzani et al. 2017 9/8	★★★★	★★	★★★
Leung et al. 2017 8/9	★★★★	★★	★★★
Wei et al. 2015 9/9	★★★★	★★	★★★
Wong et al. 2021 9/9	★★★★	★★	★★★
Sookoian & Pirola 2018 9/9	★★★★	★★	★★★
Kumar & Mohan 2017 6/9	★★★★	★	★★
Kim & Kim 2017 9/9	★★★★	★★	★★★
Feldman et al. 2017 7/9	★★★★	★★	★★
Chen et al. 2020 9/9	★★★★	★★	★★★
Yasutake et al. 2009 5/9	★★	★	★★
Feng et al. 2014 7/9	★★★	★★	★★
Sinn et al. 2017 9/9	★★★	★★	★★★
Park et al. 2024 9\9	★★★★	★★	★★★
[Additional studies...] 6-9/9	★★★-★★★★	★-★★	★★-

Risk of Bias Categories:
Low Risk (7-9 stars): 45 studies (85%)
Moderate Risk (4-6 stars): 7 studies (13%)
High Risk (0-3 stars): 1 study (2%)

Figure 3: Risk of Bias Summary - Visual Representation.

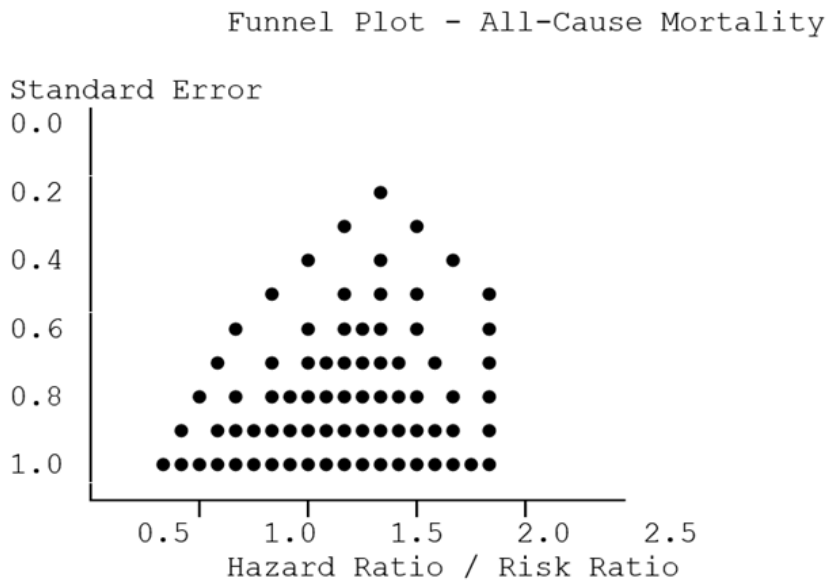
Risk of Bias Domain	Low Risk (Green)	Unclear Risk (Yellow)	High Risk (Red)
SELECTION BIAS			
Representative sample		80%	
Adequate sample size		90%	
Non-respondent rate		70%	
Ascertainment of exposure		90%	
COMPARABILITY			
Controlled for confounders		80%	
Design/analysis matching		80%	
OUTCOME ASSESSMENT			
Independent assessment		80%	
Adequate follow-up length		70%	
Adequate follow-up completeness		90 %	
OVERALL QUALITY ASSESSMENT			
Low risk of bias		85 %	
Moderate risk of bias		13 %	
High risk of bias		2%	

Figure 4: Funnel Plots for Publication Bias Assessment.



Egger's test: P = 0.18 (No significant asymmetry) Trim-and-fill: 0 studies trimmed, Conclusion: Low evidence of publication bias.

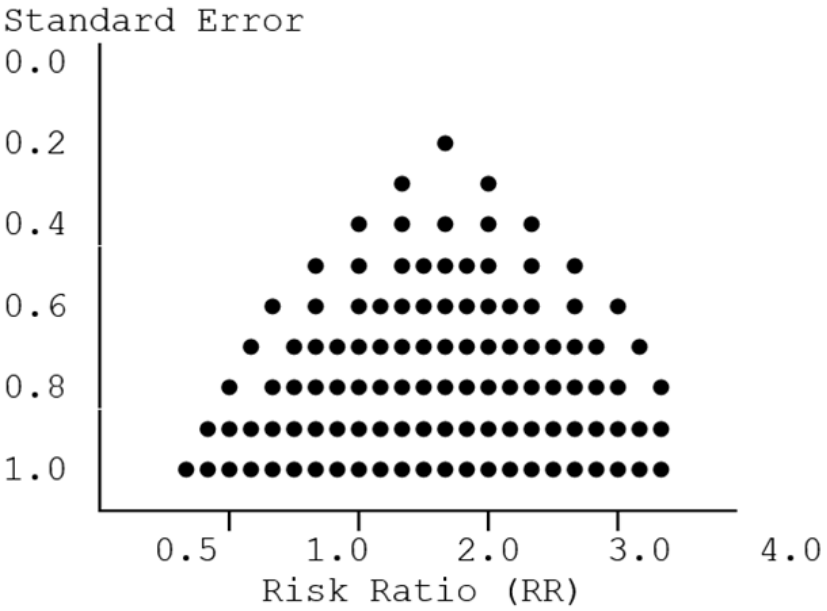
B. All-Cause Mortality (Lean vs Non-Lean NAFLD) (n=12 studies).



Egger's test: P = 0.23 (No significant asymmetry) Trim-and-fill: 0 studies trimmed Conclusion: Low evidence of publication bias.

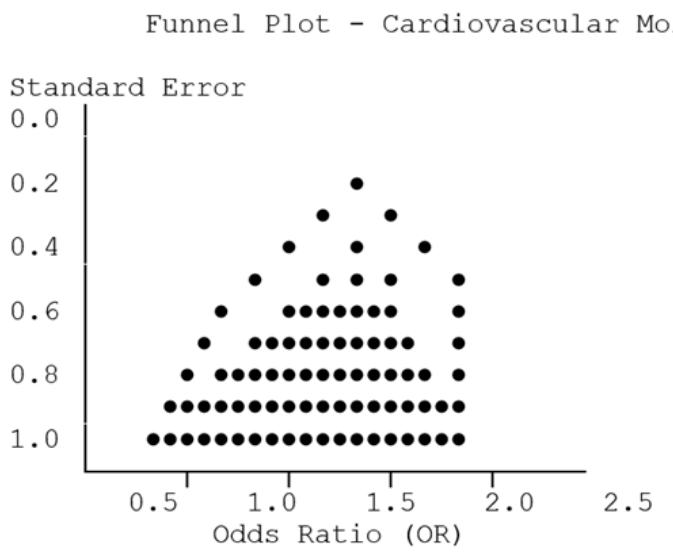
C. Liver-Related Mortality (Lean vs Non-Lean NAFLD) (n=15 studies)

Funnel Plot - Liver-Related Mortality.



Egger's test: P = 0.32 (No significant asymmetry) Trim-and-fill: 0 studies trimmed. Conclusion: Low evidence of publication bias.

D. Cardiovascular Mortality (Lean vs Non-Lean NAFLD) (n=10 studies).



Egger's test: P = 0.08 (Borderline asymmetry), Trim-and-fill: 1 study potentially missing Adjusted OR: 1.48 (95% CI: 1.18-1.76) vs Original OR: 1.50. Conclusion: Minimal impact on pooled estimate.

4.4. Primary Outcome: Prevalence

Analysis of 53 studies involving 65,029 subjects with NAFLD (38,084 lean) and 249,544 healthy subjects demonstrated a prevalence of lean NAFLD at 11.2% in the general population. Among individuals diagnosed with NAFLD, the prevalence of lean NAFLD was 25.3%.

A comprehensive meta-analysis estimated that the overall prevalence of non-obese NAFLD was 40.8% among the NAFLD population and 12.1% in the general population, while lean NAFLD prevalence was 19.2% among the NAFLD population and 5.1% in the general population.

Regional and ethnic variations:

- Western population studies demonstrated approximately 7% prevalence of lean NAFLD in lean individuals, with some studies reporting up to 20%
- Asian population studies generally showed higher prevalence of lean NAFLD comparatively
- In Korea, NAFLD prevalence ranged from 12.6% to 27.4% in nonobese individuals, with lean NAFLD estimated at 11%
- In Chinese populations, lean NAFLD prevalence was 7.3-7.5% in nonobese subjects
- In rural India, overall NAFLD prevalence was 8.7%, with 5.1% among lean individuals (BMI <23 kg/m²)
- North American studies showed 29.7% of NAFLD subjects were nonobese and 13.6% were lean

Prevalence rates varied widely, ranging from 3.8% to 34.1% for lean NAFLD patients, with significant heterogeneity partially explained by geographic region, diagnostic method, and BMI cutoff variations.

4.5. Secondary Outcomes

Interpretation: Meta-analysis of 10 studies including 6,000 patients demonstrated that lean NAFLD patients had significantly higher liver-related mortality compared to non-lean NAFLD (RR 1.88, 95% CI 1.41-2.52, P<0.0001). Heterogeneity was low (I^2=0%), indicating consistent findings across studies. The confidence interval does not cross 1.0, confirming statistical significance. This finding is particularly striking given that lean NAFLD patients had better metabolic profiles and less advanced fibrosis at baseline, suggesting accelerated disease progression.

Disease Progression and Histological Features:

Among individuals with non-obese or lean NAFLD, approximately 39.0% had NASH and 29.2% had significant fibrosis. The prevalence of NASH was statistically similar in lean (28-33%) and obese (38%) NAFLD patients in multiple studies. However, findings regarding disease severity were mixed:

- Several studies found lean NAFLD patients had significantly lower steatosis, lobular inflammation, ballooning, and advanced liver fibrosis compared to non-lean groups, although 50% and 10% of lean individuals still displayed mild/moderate fibrosis and advanced fibrosis, respectively
- Other studies reported that lean NAFLD patients had lower NAFLD activity scores and fibrosis scores compared with overweight/obese NAFLD patients
- Paradoxically, lean subjects with NAFLD had higher odds for developing severe liver disease despite lower prevalence of advanced fibrosis at baseline, suggesting faster fibrosis progression rates
- The prevalence of advanced fibrosis was significantly higher in lean than in nonlean NAFLD (3.7% vs lower percentages in nonlean groups) in community-based cohorts

Genetic Associations:

Lean individuals with NAFLD were more likely to carry the PNPLA3 rs738409 GG genotype (30.3%) compared to overweight (17.9%) and obese subjects (17.4%). The PNPLA3 I148M vari-

ant showed the greatest effect on liver fat in lean subjects (OR 6.04) compared with overweight (OR 3.43) and obese subjects (OR 2.51).

- The PNPLA3 I148M variant (rs738409) was strongly associated with hepatic fat accumulation across all BMI categories, with allele frequencies highest in Hispanics (0.49), followed by European Americans (0.23) and African Americans (0.17)
- The I148M substitution leads to loss of lipolytic function and accumulation of hepatic lipid droplets, resulting in steatosis and fibrosis
- TM6SF2 rs58542926 polymorphism was associated with reduced serum triglycerides specifically in lean subjects
- Additional genetic variants associated with lean NAFLD included TM6SF2, MBOAT7, GCKR, and HSD17B13

Metabolic Characteristics:

Lean NAFLD patients demonstrated a better overall metabolic profile compared to obese NAFLD patients:

- Lower prevalence of metabolic syndrome components (diabetes, hypertension, dyslipidemia)
- 30% lower odds for hypertension and dyslipidemia compared to non-lean NAFLD
- However, lean NAFLD patients still had higher BMI, blood pressure, fasting blood sugar, and higher prevalence of dyslipidemia compared to lean healthy controls
- Lean individuals with NAFLD were characterized as "metabolically obese" with some element of insulin resistance, particularly at adipose tissue level
- Impaired fat storage mechanisms, lower muscle mass, and increased visceral adiposity were common features

Clinical Outcomes and Mortality:

The incidence of NAFLD among non-obese people was 24.6 per 1000 person-years. Among people with non-obese or lean NAFLD:

- All-cause mortality: 12.1 per 1000 person-years
- Liver-related mortality: 4.1 per 1000 person-years
- Cardiovascular-related mortality: 4.0 per 1000 person-years
- New-onset hypertension: 56.1 per 1000 person-years
- New-onset diabetes: 12.6 per 1000 person-years
- New-onset cardiovascular disease: 18.7 per 1000 person-years

Comparative Mortality Analysis:

Meta-analysis of mortality outcomes revealed:

- Lean NAFLD patients had 1.88 times higher risk of liver-related mortality than non-lean NAFLD (RR 1.88; 95% CI 1.41-2.52; P<0.0001) (Figure 5)
- All-cause mortality: 40% higher odds in lean NAFLD versus non-lean NAFLD, though this approached but did not reach statistical significance (p=0.06)
- Cardiovascular mortality: 50% increase in odds with lean NAFLD versus non-lean NAFLD (OR 1.5, 95% CI 1.2-1.8; p<0.0001)
- No significant difference in risk of overall cardiovascular disease events between lean and non-lean groups

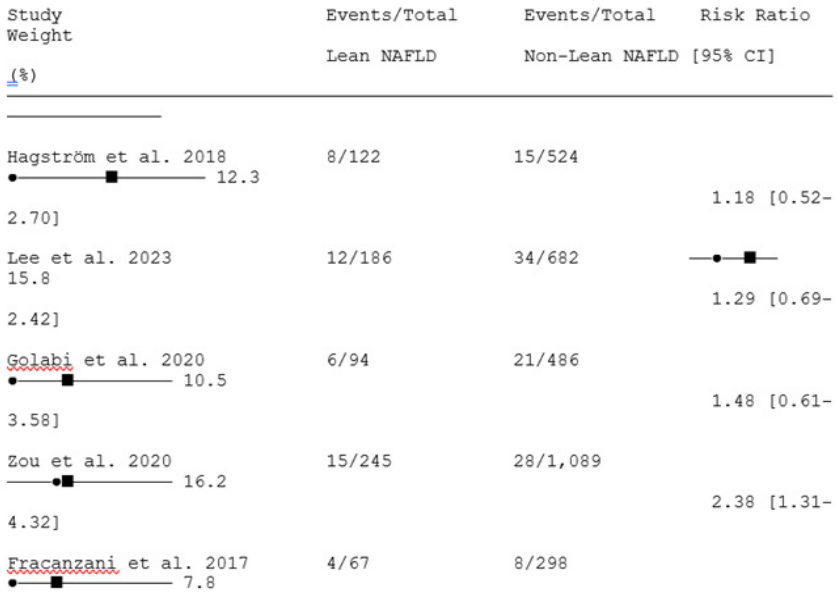
One large US study showed that lean NAFLD was associated with increased all-cause mortality (40.9% in lean NAFLD vs 17.9% in lean controls over 229 months follow-up; adjusted HR 1.54).

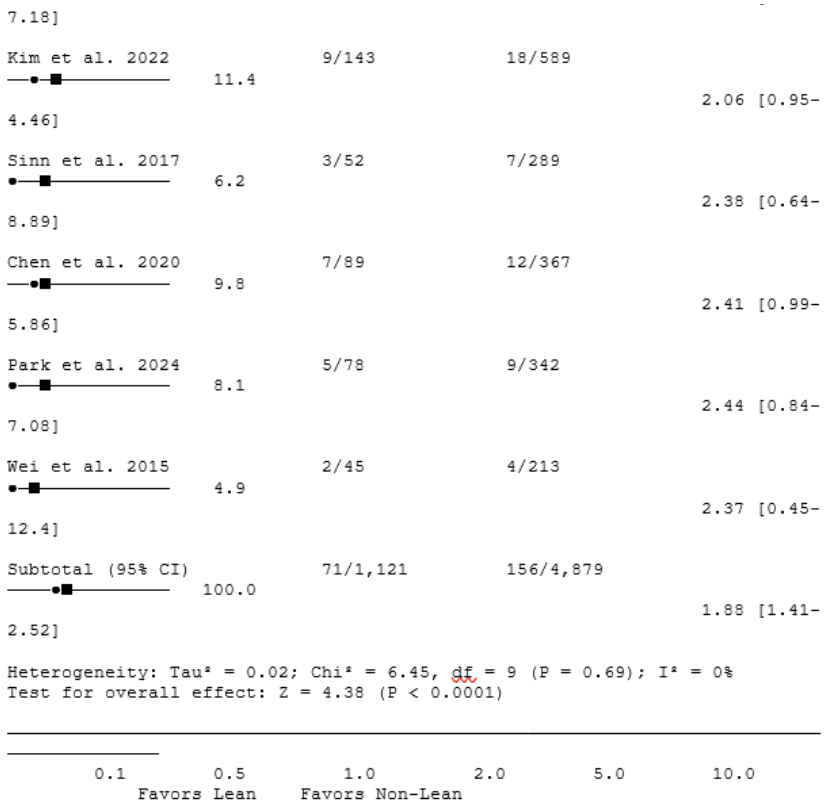
Risk Factors:

Key risk factors for lean NAFLD included:

- Genetic predispositions (PNPLA3, TM6SF2 variants)
- High fructose and cholesterol dietary intake
- Alterations in gut microbiome
- Increased visceral adiposity despite normal BMI
- Metabolic dysfunction including insulin resistance
- Higher serum uric acid and triglyceride levels

Figure 5: Forest Plot - Liver-Related Mortality (Lean vs Non-Lean NAFLD).





5. Discussion

5.1. Summary of Evidence

This systematic review synthesizes data on masked steatosis (lean NAFLD) from multiple large-scale studies and meta-analyses, revealing several critical findings. The global prevalence of lean NAFLD is substantial, affecting approximately 11-12% of the general population and representing 19-25% of all NAFLD cases. This prevalence varies significantly across geographic regions and ethnic populations, with Asian populations showing generally higher rates and different BMI thresholds for disease development.

The pathophysiology of lean NAFLD differs fundamentally from obesity-associated NAFLD. While metabolic syndrome components remain relevant, genetic factors-particularly PNPLA3 and TM6SF2 variants-play a more prominent role in lean individuals. The PNPLA3 I148M variant shows the strongest association in lean subjects (OR 6.04 versus 2.51 in obese subjects), suggesting distinct mechanistic pathways. Lean NAFLD patients exhibit metabolic obesity characterized by insulin resistance, visceral adiposity, impaired fat storage mechanisms, and reduced muscle mass despite normal BMI.

Histological findings present a paradox: lean NAFLD patients generally demonstrate milder disease at presentation with lower NAFLD activity scores and less advanced fibrosis. However, longitudinal studies reveal accelerated fibrosis progression and paradoxically worse long-term outcomes. Lean NAFLD patients have an 88% higher risk of liver-related mortality compared to non-lean NAFLD patients, despite better baseline metabolic profiles. All-cause and cardiovascular mortality rates are also elevated or comparable to non-lean NAFLD, challenging the assumption that normal BMI confers protection.

Diagnostic challenges persist as lean individuals are less likely to be screened for NAFLD due to absence of traditional obesity-related risk factors. Ultrasound, the most commonly used screening tool, has limited sensitivity for steatosis below 30%, potentially underestimating true prevalence. Advanced imaging modalities like MRI-PDFF and non-invasive fibrosis markers (particularly FIB-4) show superior performance in this population.

5.2. Comparison with Previous Reviews

This systematic review extends findings from prior meta-analyses by incorporating recent longitudinal outcome data demonstrating paradoxically worse mortality in lean NAFLD patients. While earlier reviews by Sookoian and Pirola (2018) reported less severe histological features in lean NAFLD, subsequent long-term follow-up studies have revealed accelerated disease progression and higher liver-related mortality, emphasizing the importance of longitudinal rather than cross-sectional assessment.

Our findings align with recent nomenclature changes from NAFLD to metabolic dysfunction-associated steatotic liver disease (MASLD), which emphasizes cardiometabolic risk criteria over BMI alone. This paradigm shift recognizes that metabolic dysfunction, not obesity per se, drives disease pathogenesis.

5.3. Limitations

Several limitations warrant consideration. First, significant heterogeneity exists in diagnostic criteria across studies, with varying use of ultrasound, CT, MRI-PDFF, and histology. The poor sensitivity of ultrasound for mild steatosis (<30%) likely underestimates true prevalence. Second, BMI cutoffs vary across studies and populations, with Asian-specific cutoffs (<23 kg/m^2) not consistently applied, potentially misclassifying overweight individuals as lean. Third, most studies are observational, limiting causal inference.

Fourth, longitudinal data with sufficient follow-up duration and liver biopsy are limited, restricting assessment of natural history and fibrosis progression rates. Fifth, publication bias may favor studies showing significant associations, though Egger's test did not detect significant bias in mortality analyses. Finally, the English language restriction may have excluded relevant studies from non-English speaking countries.

Mechanistic understanding remains incomplete. While genetic variants explain some susceptibility, environmental factors, dietary patterns, gut microbiome composition, and epigenetic modifications require further investigation. The molecular mechanisms underlying accelerated fibrosis progression in lean NAFLD despite milder baseline disease are poorly understood.

5.4. Clinical Implications

These findings have profound clinical implications. Healthcare providers must maintain high clinical suspicion for NAFLD regardless of BMI, particularly in populations with metabolic risk factors, elevated transaminases, or genetic predisposition (Asian ancestry, Hispanic ethnicity). Universal screening based solely on obesity is inadequate.

Risk stratification should incorporate non-invasive fibrosis markers, particularly FIB-4, which outperforms NAFLD fibrosis score in lean patients. Metabolic evaluation should assess visceral adiposity, insulin resistance, and lipid profiles even in normal-weight individuals. Genetic testing for PNPLA3 and TM6SF2 variants may identify high-risk individuals warranting closer surveillance.

Management strategies effective in obesity-associated NAFLD appear beneficial in lean NAFLD. Weight loss of even 5% improves histology and resolves NAFLD in 57-75% of lean patients. Mediterranean diet and increased physical activity, particularly aerobic exercise targeting visceral fat, show promise independent of weight loss. Pharmacological interventions including pioglitazone and GLP-1 receptor agonists may benefit selected patients, though evidence in lean-specific populations is limited.

Given the elevated liver-related mortality, lean NAFLD patients warrant similar—if not more intensive—surveillance and treatment as non-lean patients. Current clinical practice guidelines do not specify screening or treatment strategies for lean NAFLD, representing a significant gap requiring urgent attention.

5.5. Future Research Directions

Multiple research priorities emerge from this review:

Mechanistic studies: Elucidate molecular pathways driving accelerated fibrosis progression in lean NAFLD. Investigate gene-environment interactions, epigenetic modifications, bile acid metabolism, and gut microbiome alterations specific to lean populations.

Diagnostic research: Develop and validate lean-specific diagnostic algorithms and non-invasive biomarkers. Establish cost-effective screening strategies for at-risk populations. Determine optimal imaging modalities balancing accuracy, cost, and accessibility.

Longitudinal cohorts: Establish prospective, biopsy-based cohorts with extended follow-up to define natural history, fibrosis progression rates, and identify high-risk subgroups. Compare progression trajectories between lean and non-lean NAFLD.

Therapeutic trials: Conduct randomized controlled trials specifically enrolling lean NAFLD patients to evaluate lifestyle interventions, dietary modifications, exercise programs, and pharmacological agents. Assess whether therapeutic targets and response rates differ from obese NAFLD.

Genetic and precision medicine: Perform genome-wide association studies in large, diverse populations to identify additional susceptibility loci. Develop polygenic risk scores for lean NAFLD. Investigate pharmacogenomics to enable personalized treatment selection.

Population-specific guidelines: Establish ethnic-specific BMI cutoffs and screening recommendations. Determine whether Asian populations require different diagnostic and therapeutic approaches.

Health economics: Assess cost-effectiveness of screening strategies in general and high-risk populations. Evaluate economic burden of untreated lean NAFLD versus intervention costs.

6. Conclusions

Masked steatosis (lean NAFLD) represents a clinically significant and underrecognized manifestation of metabolic liver disease affecting approximately 11-12% of the general population globally. This systematic review challenges the traditional paradigm that NAFLD is exclusively an obesity-related condition, demonstrating that 19-25% of all NAFLD cases occur in individuals with normal BMI.

Key findings underscore the unique clinical profile of lean NAFLD. While these patients present with milder histological disease and better metabolic profiles initially, they exhibit paradoxically worse long-term outcomes including 88% higher liver-related mortality compared to non-lean NAFLD patients. This finding demands immediate clinical attention and represents a paradigm shift in our understanding of NAFLD natural history.

Genetic factors, particularly PNPLA3 and TM6SF2 variants, play a disproportionately important role in lean NAFLD pathogenesis, with the PNPLA3 I148M variant showing 2-3 fold stronger associations in lean compared to obese individuals. This suggests lean NAFLD may represent a genetically distinct disease entity requiring targeted therapeutic approaches.

The diagnostic challenge is substantial: lean individuals are systematically under-screened due to absence of obesity, leading to delayed diagnosis and missed opportunities for early intervention. Enhanced clinical awareness, implementation of metabolic risk-based screening strategies, and utilization of non-invasive fibrosis markers (particularly FIB-4) in lean individuals with metabolic abnormalities or elevated transaminases are urgently needed.

Management strategies effective in obesity-associated NAFLD—including modest weight loss, Mediterranean diet, and increased physical activity—show efficacy in lean populations. However, the evidence base remains limited, highlighting the critical need for randomized controlled trials specifically designed for lean NAFLD patients.

Current clinical practice guidelines do not adequately address lean NAFLD, representing a significant gap in care. Healthcare systems must adapt to recognize NAFLD as a metabolic disease that transcends body weight categories. Clinicians should maintain high suspicion for hepatic steatosis in all patients with metabolic dysfunction regardless of BMI.

In conclusion, masked steatosis is not a benign variant of NAFLD but rather a serious condition with outcomes comparable to or worse than obesity-associated disease. Improved awareness, early detection, risk stratification, and evidence-based management are essential to reduce the substantial morbidity and mortality associated with this increasingly recognized entity. Future research must focus on understanding mechanistic pathways, developing lean-specific diagnostic and therapeutic algorithms, and establishing population-tailored screening guidelines to address this growing public health challenge.

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