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## Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) of China in the past ten years: a scoping review protocol

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## ADMINISTRATIVE INFORMATION

**Support** - Novo Nordisk.

**Review Stage at time of this submission** - Piloting of the study selection process.

**Conflicts of interest** - Wei Lai consults for Abbvie, Bristol-Myers Squibb, Gilead, MSD, Novartis, Novo Nordisk, Pfizer, Roche and VirsiRNA and receives research grants from Abbvie, Bristol-Myers Squibb, Gilead, Pfizer and Sanofi. Cao Di, Qi Xuan and Wang Ying are employees of Novo Nordisk (China) Pharmaceuticals Co., Ltd. Nan Yuemin disclosed no conflicts of interest.

**INPLASY registration number:** INPLASY202380019

**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 04 August 2023 and was last updated on 04 August 2023.

## INTRODUCTION

**Review question / Objective** The objective of this scoping review is to examine and map the current evidence of NALFD, NASH or MAFLD in China in the recent 10 years.

The following research questions are formulated:

- 1) What is known from the existing literature about NAFLD, NASH and MAFLD in the Chinese population, including the following sub-questions: a) disease characteristics; b) disease diagnosis, intervention, and prognosis; c) population's knowledge and awareness;
- 2) What are the main gaps of evidence and research in terms of NAFLD, NASH and MAFLD in the context of China?

**Background** Over the past century, the increasing incidence of non-communicable diseases due to dramatic lifestyle changes has radically shifted the

health priorities in most regions of the world. Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease and the leading cause of liver-related morbidity and mortality worldwide. NAFLD is the spectrum of liver disease in which hepatic steatosis, the macrovascular accumulation of triglyceride in hepatocytes, develops in the absence of secondary causes (e.g., medications, excessive alcohol consumption, or certain heritable conditions). NAFLD can be divided into non-alcoholic fatty liver (NAFL, steatosis only) or non-alcoholic steatohepatitis (NASH). NASH is the inflammatory subtype and an advanced form of NAFLD, with steatosis as well as evidence of hepatocyte injury (e.g., ballooning) and inflammation, with or without any fibrosis. Over time, NASH can asymptotically progress to cirrhosis, end-stage liver disease, hepatocellular carcinoma (HCC) or the need for a liver transplant.

NAFLD is highly prevalent on all continents. The highest rates are reported from South America (31%) and the Middle East (32%), followed by Asia (27%), the USA (24%), and Europe (23%), whereas NAFLD is less common in Africa (14%). Globally, the prevalence of NAFLD in adults is estimated to be 25%, while the prevalence of NASH is estimated to be between 3% and 5%. NAFLD is one of the leading causes of chronic liver disease. Progression rates for simple steatosis are relatively low, with approximately 4% of patients going on to develop cirrhosis, while more than 20% of NASH patients develop cirrhosis during their lifetime. An increased prevalence of NAFLD and consequently of NASH could result in a rise in the cases of advanced liver disease, cirrhosis, and HCC, thus adding to the burden of disease and the overall cost of health care.

Once considered a common disease in the west, NAFLD and its complications now pose a major health threat in China. With the remarkable economic development of the past decades, the daily life patterns of Chinese people have been dramatically reshaped by westernized diets, increased consumption of alcoholic beverages, and sedentary lifestyles. The gradually growing prevalence of obesity, diabetes, dyslipidemia, and metabolic syndrome (MetS) has put the Chinese population at a higher risk of developing NAFLD. Over the past decade, the proportion of the Chinese population affected by NAFLD has increased from 18% to 29%, doubling the rate of increase in western countries. Predictably, China will have the highest global growth in total NAFLD cases, with 314.58 million cases by 2032. Moreover, China has the youngest median age of NAFLD in the world, suggesting that a significant increase in the disease burden of its advanced liver disease would occur in the coming decades as the population ages.

**Rationale** The prevalence of NAFLD in China is soaring at an unanticipated rate, and we now face tremendous challenges in containing this pandemic. Firstly, the global data indicate considerable heterogeneity in the prevalence and incidence of NAFLD across studies. There have been few epidemiological studies of NAFLD/NASH and its associated intra- and extra-hepatic complications nationwide. Second, inadequate diagnosis and treatment are also due to the lack of reliable and cost-effective diagnostic tools and medications for NAFLD. The substantial number of NAFLD patients with the potential for progressive liver disease presents a challenge for screening, as invasive liver biopsies are necessary for NASH diagnosis. There are no drugs specifically approved for the treatment of NAFLD. To date, the

most effective treatment strategies for NAFLD remain preventive measures through regular physical activity, low-calorie eating, and weight loss. Third, in contrast to the high prevalence of NAFLD in China, awareness of the disease in the population is relatively low. Reports of awareness of NAFLD are as low as 17% to 31% in the general population, and even among highly educated government employees, only 5% of participants have adequate knowledge of NAFLD. Therefore, the issues and challenges related to NAFLD or NASH should be taken seriously by the public, the health care system, pharmaceutical companies and policymakers in China. Understanding disease characteristics, clinical evidence, and addressing barriers in the management of NAFLD in China is urgent.

Considering the relatively broad subject and content of NAFLD and NASH research, scoping review is a helpful method for mapping the fundamental concepts of specific fields or topics of interest in literature and identifying potential evidence gaps. Unlike systematic reviews, which are usually used to solve specific problems, scope reviews are used for studies that have not been widely studied or have complex and heterogeneous topics. The current evidence on the disease characteristics, diagnosis, intervention, prognosis as well as the relevant population's knowledge and awareness of China, has not systematically investigated and summarized. In addition, research advances in the last five years, such as the discussion of metabolic associated fatty liver disease (MAFLD), have not been fully integrated. Therefore, this scoping review aims to summarize the status of NAFLD and NASH over the past 10 years, to identify and map the available evidence regarding the disease in Chinese population, as well as to identify any existing gaps in scientific knowledge.

## METHODS

**Strategy of data synthesis** A search strategy will be defined to identify published studies. A preliminary search in PubMed and CNKI will first be conducted, followed by an analysis of text words contained in the title and abstract for each article. A full secondary search will be performed across all included databases using keywords and search strategy identified from the preliminary search.

Specific search strategies will be formulated in six electronic databases. Electronic databases include three English databases (PubMed, Embase, and Cochrane) and three Chinese databases (CNKI, Wanfang, and VIP). Conference abstracts of the last two years are searched from Embase and

conference website (the European Association for the Study of the Liver (EASL) NAFLD Summit) for following the latest research progress.

**Eligibility criteria** The eligibility criteria studies will be based on the Population, Concept, Context (PCC) framework.

**Participants:** Patients diagnosed with NAFLD, NASH or MAFLD according to any of the standardized diagnostic criteria will be included. No restrictions on patient characteristics such as sex, ethnicity, age will be applied.

**Concept:** The concepts of this scoping review are disease epidemiological and clinical features, disease management as well as the relevant population' knowledge and awareness.

**Context:** The context of this review is limited in China, including Hongkong, Macau, and Taiwan.

No restrictions are being applied in terms of healthcare setting, or sociocultural.

### Source of evidence screening and selection

Study screening will be conducted by two independent reviewers through two phases: title and abstract review and full-text review. Any disagreement will be resolved by discussion between reviewers. If consensus cannot be reached, a third reviewer will be involved in the final decision.

**Title and abstract screening:** After the removal of duplicates, titles and abstracts will be screened before a full-text review by two independent reviewers who meet in regular intervals to resolve conflicts. Each study will be classified as: 'included' or 'excluded'. All studies marked as 'included' will be passed to full-text review. For excluded studies, the reason for exclusion will be standardized and documented.

**Full-text reviewing:** All available full-text will be screened for final inclusion by two independent reviewers who met in regular intervals to resolve conflicts. Each study will be classified as: 'included' or 'excluded' again. All studies marked as 'included' will be marked with different sub-objective of this study and passed to data charting. For excluded studies, the reason for exclusion will be documented. The search results and the screening process will be described in the final report and presented with a flow diagram.

**Data management** Two reviewers will independently collect data from all eligible articles. Any disagreement will be discussed, and a third reviewer will be involved if necessary.

The extracted data will include specific details regarding the population, concept, context, methods, and key results relevant to the review

objectives. Items to be collected for this scoping review may include:

(1) study characteristics; (2) disease characteristics; (3) disease diagnosis approaches and intervention; (4) disease prognosis and clinical outcome; and (5) population' knowledge and awareness.

A pre-designed data extraction sheet will be used to extract all data relevant to the research question. The information to be charted during the process may include the following information as required:

1) Study characteristics  
e.g., year, title, journal, study design, study duration, study population, sample size, study site.

2) Disease characteristics  
e.g., incidence rate, prevalence, mortality rate, case fatality rate, coexisting risk factors, comorbidity, disease burden and the course of the disease.

3) Disease diagnosis approaches and intervention  
e.g., diagnosis approaches like liver biopsy, noninvasive scoring (fibrosis-4 index (FIB-4), FibroScan, FibroTouch or Magnetic Resonance Elastography (MRE); interventions like lifestyle intervention (diet and exercise), medications (Vitamin E, Pioglitazone, statins and TCM).

4) Disease prognosis and clinical outcome  
e.g., disease progression likes nature history, prognosis; clinical outcomes like health-related quality of life (HRQL), other patient-reported outcomes (PRO) and corresponding measurement tools.

5) Population' knowledge and awareness  
e.g., population' knowledge about liver disease, patient satisfaction with liver disease care, patients' medical decision-making preference or attitudes toward the disease, and corresponding standardized measurement tools.

### Reporting results / Analysis of the evidence

A narrative summary of the findings will be presented regarding current disease characteristics in China, clinical evidence of disease management, and patient knowledge on liver disease care. The extracted results will be further organized to better reflect the questions of the study, such as current follow-up cohort or clinical study, potential diagnosis or therapy approaches and patients' concern about the disease depending on the variety and sufficiency of extracted data.

A flow diagram will be created to illustrate the progress of studies through the selection process and screening. A summary of the main characteristics of each included study will be presented, including author, year, study design, sample size, methodology, and main findings. Descriptive statistics will be used to summarize

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data extracted from included studies. Descriptive statistics including the mean, the median, the standard deviation (SD) and the interquartile range (IQR) will be extracted for outcomes described as continuous variables, while counts and proportions will be extracted for categorical outcomes as categorical variables. The reporting of this scoping review will be in accordance with the PRISMA-ScR[18]. Charting results will be summarized and/or presented in detail. The facts and gaps in knowledge identified from the results of this review will be identified to provide clear and specific suggestions for future research.

**Language restriction** Chinese and English.

**Country(ies) involved** China.

**Keywords** Non-alcoholic fatty liver disease; non-alcoholic steatohepatitis; China; scoping review.

**Dissemination plans** The results and interpretation will be disseminated through academic publications for the topics studied in this review.

**Contributions of each author**

Author 1 - Lai Wei.

Author 2 - Di Cao.

Author 3 - Xuan Qi.

Author 4 - Ying Wang.

Author 5 - Yuemin Nan.