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Systematic Review

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Signs of non-alcoholic fatty liver disease in indigenous Arctic populations – a systematic review

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ABSTRACT

INTRODUCTION. The increasing prevalence of obesity and type 2 diabetes mellitus has become a global healthcare concern spreading to indigenous Arctic populations. As non-alcoholic fatty liver disease (NAFLD) is strongly associated with the metabolic syndrome, it has become a leading cause of chronic liver disease. However, data are sparse on the prevalence of NAFLD in indigenous Arctic populations who may have a different risk profile for diabetes complications.

METHODS. We conducted a systematic review to estimate the prevalence of NAFLD or signs of NAFLD in indigenous Arctic people inhabiting Greenland, Alaska, Canadian territories and Eastern Russia. Also, we wanted to discuss how Arctic research in metabolic disease such as NAFLD may move forward.

RESULTS. Through the pre-specified search of Ovid MEDLINE and Embase, 3,070 unique references were identified and six studies including 5,487 persons qualified for data extraction. The prevalence of NAFLD or signs of NAFLD varied between 21% and 65%. The risk of bias was considerable particularly due to the inclusion of small and heterogeneous studies.

CONCLUSION. Only limited published research exists on NAFLD in indigenous Arctic populations. This review reports that the prevalence of NAFLD or signs of NAFLD in the indigenous Arctic populations residing in Arctic Regions may be similar to the global level, emphasising the need for further health research in indigenous Arctic populations.

KEY POINTS

- Obesity and type 2 diabetes mellitus have become major health concerns in Circumpolar areas.
- The burden of non-alcoholic fatty liver disease (NAFLD) in indigenous Arctic populations remains unknown.
- A systematic literature search identified only six, small and heterogeneous studies of NAFLD or signs of NAFLD.

Non-alcoholic fatty liver disease (NAFLD) is a leading cause of chronic liver disease affecting one-fourth of the World population [1]. NAFLD is the hepatic manifestation of the metabolic syndrome and is associated with obesity, insulin resistance and type 2 diabetes mellitus (T2DM) [2]. With the omnipresent, growing prevalence of obesity and T2DM, the ability to detect and treat NAFLD has increased [1, 3]. Among patients with T2DM, the prevalence of NAFLD is 40-55% with relative continental variations [4]. As the influence of Western culture has

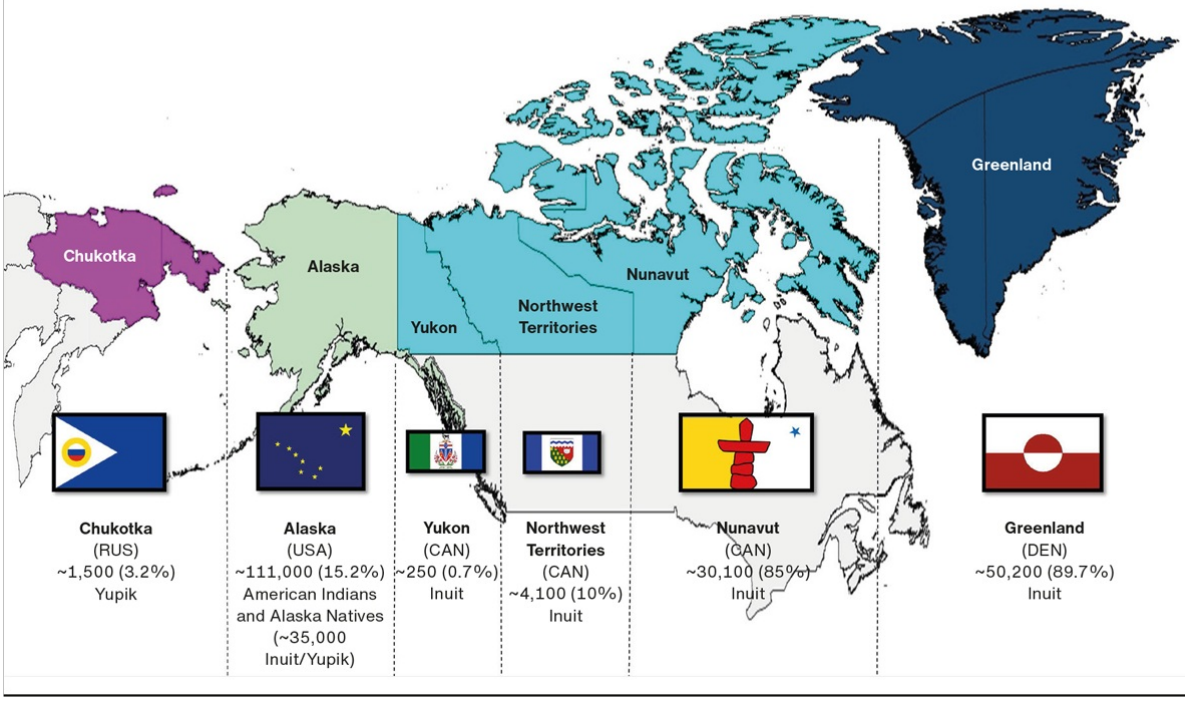
spread to indigenous Arctic populations, obesity and T2DM have been on the rise in Circumpolar areas [5, 6]. For example, individuals identifying as Alaska Native and Native American are 2.3 times more likely to develop T2DM than the general population of the United States [7]. Indigenous populations living in remote Circumpolar areas may not follow the global trend, and data on NAFLD prevalence in these Arctic populations are sparse [8]. For the indigenous Arctic peoples, identified predominantly as Inuit, Alaska Natives, Aleut, Inupiat and Yupik residing in Greenland, Northern Canada, Alaska and Eastern Russia, healthcare services are restricted to the larger towns or settlements. Therefore, clinical, biochemical, radiological and therapeutic tools for the diagnostics and monitoring of liver, cardiovascular and metabolic diseases are limited or unavailable. With the growing impact of NAFLD, it is important to estimate its prevalence and understand its risk factors in indigenous Arctic populations to prevent health inequity. Recently, it has been shown that genetic variants in Inuit may protect against diabetes complications. Furthermore, NAFLD may have a different phenotype in Inuit. Clarifications of such genotype-phenotype variations may potentially advance diagnostic and pharmaceutical measures of NAFLD in the global healthy community and in native circumpolar populations [9-11].

We aimed to estimate the prevalence of NAFLD or signs of NAFLD in indigenous Arctic populations. Therefore, we conducted a systematic review of the literature with a search strategy fine-tuned for an Arctic setting. Furthermore, we aimed to spread awareness of metabolic liver disease in indigenous populations across the Arctic areas of Greenland, Canada, Alaska and Eastern Russia.

METHODS

This systematic literature review adheres to the PRISMA guidelines and the Cochrane Handbook and a preregistration review protocol is available at Open Science Framework [12, 13]. We included trials estimating the prevalence of NAFLD or signs of NAFLD in the indigenous Arctic populations including Inuit, Alaska Native, Aleut, Inupiat and Yupik residing in Greenland and Alaska, as well as the Arctic Canadian territories and the Chukotka Okrug of Russia (Inuit Nunaat) (**Figure 1**). Inclusion was not restricted to specific cohort characteristics and studies were eligible for inclusion as long as indigenous Arctic populations were part of the cohorts. Moreover, studies were eligible for inclusion regardless of publication year, publication status or language. Ovid MEDLINE and Embase were searched for eligible publications on 23 December 2022 (**Supplementary Material** https://content.ugeskriftet.dk/sites/default/files/2023-04/a11220693-supplementary.pdf) with subsequent reference management in Covidence (systematic review software, Veritas Health Innovation, Melbourne, Australia). Google Scholar was used as a supplementary source for grey literature [18]. Conference reports from the triennial Greenlandic health conference NUNAMED were also screened for relevant abstracts (**Supplementary Material** https://content.ugeskriftet.dk/sites/default/files/2023-04/a11220693-supplementary.pdf). The screening and data extraction were performed by RHG and uncertainties in the process were resolved through internal discussions between RHG, MLP and HG. The primary outcome was the estimation of NAFLD prevalence. From all included studies, we extracted data on study design, size and duration. In addition, we extracted cohort characteristics including geographical location, ethnic group investigated, age, Body Mass Index and the measures and tools used for estimating the prevalence of NAFLD or signs of NAFLD.

FIGURE 1 Geographical overview of Arctic areas populated by indigenous Arctic peoples [14-17]: investigated areas and sizes of populations (Inuit Nunaat).

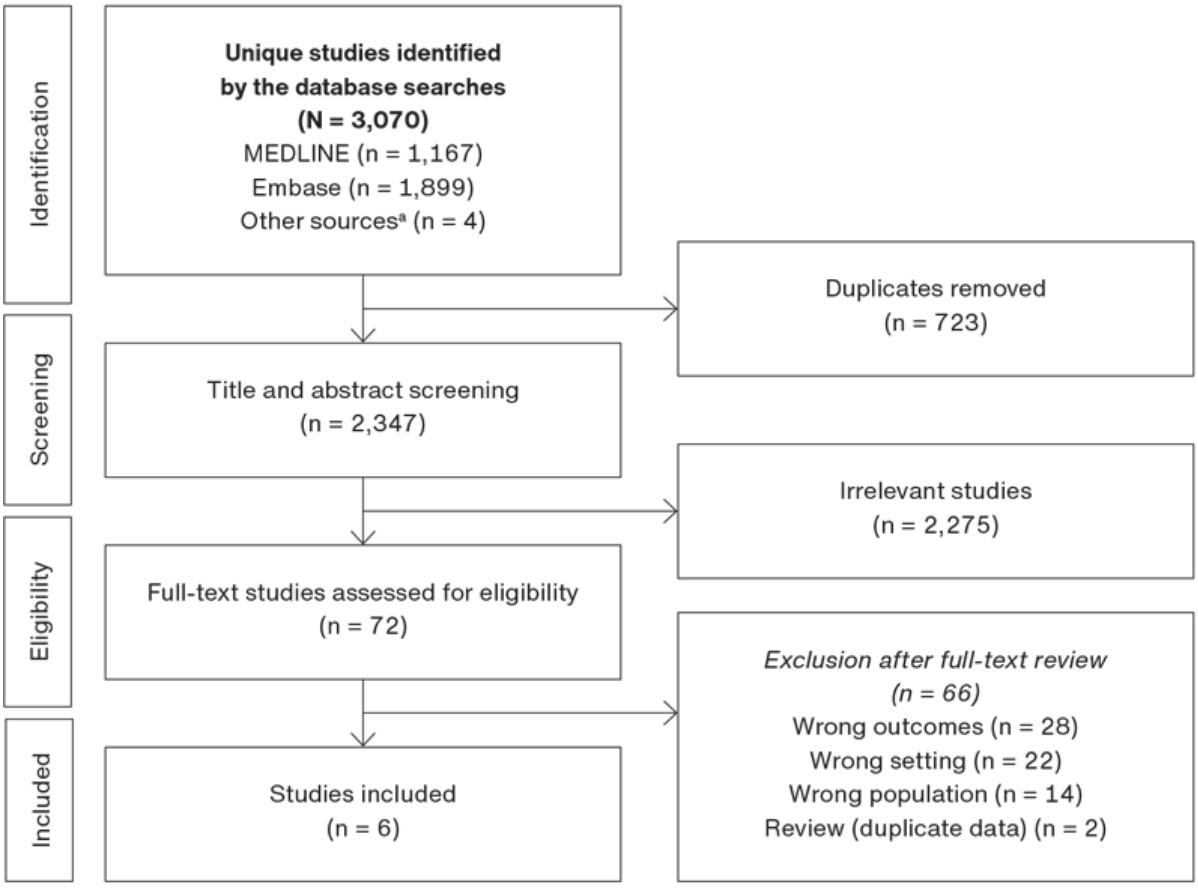


We used the modified risk of bias tool for all prevalence studies [19]. The tool includes ten items covering external and internal validity, where one point is given for each item with a negative evaluation. The risk of bias at study level was interpreted as low (≤ 4 points), intermediate (5-7 points) or high (≥ 8 points). The GRADE approach was used to assess the overall quality of evidence [20].

RESULTS

The predefined search strategy identified 3,070 unique references for screening (**Figure 2**). Five full-text articles and one conference abstract qualified for inclusion (**Table 1**). Five of the studies examined Alaska Natives either with self-identification as Inupiat, Yupik, Athabascan Indian, Southeast Alaska Indian or Aleut or in combination with other Native Americans [21-25]. Only one study examined NAFLD in Greenland Inuit [11]. No studies from Canada or Russia were identified. The cohorts were characterised by either having chronic hepatitis B virus (HBV) infection, chronic HCV infection, chronic liver disease, T2DM or elevated liver enzymes. All six studies were published within the past two decades. Three clinical studies estimated NAFLD or signs of NAFLD using liver histology examinations [21, 23], ultrasonography [23, 24], or clinical evaluations [21, 23, 24]. Two register-based studies used elevated plasma alanine aminotransferase as a marker for liver steatosis and one also included diagnosis codes [11, 22]. One study established a retrospective cohort from medical chart reviews [25]. The prevalence of NAFLD or signs of NAFLD varied between 21% and 65%, with a considerable risk of bias from other coexisting liver diseases. One study, using the non-invasive fibrosis (FIB)-4 score (> 1.45), estimated the prevalence of liver fibrosis to be 16% [11]. Regarding complications, one study reported that close to 40% with NAFLD also had steatohepatitis [25], whereas another study reported that 8% of patients with NAFLD had cirrhosis [22].

FIGURE 2 Flow chart of study identification.



a) Comprises reference list screening for all studies reaching the "Eligibility" assessment and screening of conference reports.

TABLE 1 Main characteristics of the six studies included in the literature review.

Reference	Study type	Indigenous population[a]	Cohort size, n	Cohort characteristics	Time period	NAFLD or signs of NAFLD prevalence, %	Age, mean, yrs	BMI ≥ 30 kg/m², %	Method for NAFLD detection	Quality assessment, RoB score[b]
Livingston et al, USA, 2006 [21]	Clinical	Alaska natives and American Indians	222	Chronic HCV infection	1994-2000's	53	41.3	45	Liver biopsy with steatosis	3 + 2
Fischer et al, USA, 2009 [22]	Register-based	Alaska natives: Inupiat, Yupik, Aleut, Athabascan Indian or Southeast Alaska Indians	1,664	Chronic liver disease	2003-2004	29	46.2	-	Diagnosis codes, transaminasaemia	3 + 3
Spradling et al, USA, 2014 [23]	Clinical	Alaska natives	634	Chronic HBV infection	2001-2010	25	39.2	63	Transaminasaemia with subsequent clinical, radiological or histopathological examination	3 + 2
Scott et al, USA, 2015 [24]	Clinical	Alaska natives and American Indians	26	Elevated ALAT	2011	65	50.4	56	Transaminasaemia with subsequent clinical, biochemical or radiological examination	4 + 2
Muhammad et al, Greenland, 2022 [11]	Register-based	Greenland Inuit	1,409	T2DM	2016-2021	21	63.0	63	ALAT elevation	3 + 2
Johnston et al, USA, 2022 [25]	Restrospective cohort	Alaska natives and American Indians	1,532	Chronic liver disease	1991-2021	25	-	-	Medical chart reviews	3 + 3

ALAT = alanine aminotransferase; HBV = hepatitis B virus; HCV = hepatitis C virus; NAFLD = non-alcoholic fatty liver disease; RoB = risk of bias; T2DM = type 2 diabetes mellitus.
a) To describe the indigenous population investigated we provide the terms used in the studies included. However, throughout the manuscript, we prefer the term native Americans instead of American Indians.
b) The RoB assessment consisted of 4 items concerning external validity and 6 items concerning internal validity (Supplementary Material https://www2.ugeskriftet.dk/files/a11220693_-_supplementary.pdf) and is provided in this table as e.g. 3 + 2 reflecting that 3 external validity items and 2 internal validity items achieved a negative RoB evaluation. All studies achieved a quality assessment of intermediate RoB.

The studies received intermediate risk of bias judgements, especially caused by external validity concerns. The quality of evidence for the prevalence of NAFLD or signs of NAFLD in Arctic indigenous populations derived from this review is judged as very low due to few, small and heterogeneous studies. Consequently, meta-analysis was not justified.

DISCUSSION

This systematic review is the first to compile results on the prevalence of NAFLD or signs of NAFLD in Arctic indigenous populations. As suspected, data are sparse concerning indigenous Arctic populations residing in Greenland and Alaska, and non-existing or unpublished for populations in Canadian territories and Eastern Russia. Although the six included studies are small, heterogeneous and investigate a spectrum of liver diseases, the reported 21-65% prevalence of NAFLD or signs of NAFLD indicates that NAFLD in indigenous Arctic populations may follow the global trend. Yet, the substantial variation in prevalence reported hinders sound conclusions from this work, and the true prevalence of NAFLD in Arctic regions remains unknown. Thus, most importantly this review reports a lack of knowledge on a growing health problem in hitherto unrecognised areas.

With growing populations and an increasing prevalence of obesity and T2DM in these remote Circumpolar areas, investigations of NAFLD prevalence and disease course are warranted to optimise regional and global health programmes.

Lower health standards are habitual for indigenous communities. However, with a transition from traditional to modern lifestyles, cardiovascular and metabolic diseases must be addressed urgently in indigenous and non-indigenous populations alike [26, 27]. Yet, population-specific differences in risk profiles exist from the complex interplay of environment, genetics and lifestyle. These differences influence the translatability of how metabolic risk factors impact the development and disease course of metabolic diseases such as T2DM and NAFLD in different populations. Clinical characteristics of Inuit and related indigenous Arctic people include a spherically shaped corpus that reduces heat loss and a subcutaneous fat deposition that favours survival in a cold climate [28]. Furthermore, a genetic mutation in the TBC1D4 gene, present in 17% of Greenland Inuit, affects insulin-stimulated glucose uptake in muscles predisposing to T2DM development [29]. As such, the management of NAFLD in Arctic indigenous populations requires an adaptable mindset to be able to interpret differences in unique cardiovascular and metabolic risk factors. Also, chronic infection with HBV is endemic in local populations across the Arctic regions, and HBV testing comprises an essential part of liver disease management especially in an Arctic context [30]. Furthermore, the indigenous knowledge and ways of living must be respected and integrated in all phases of planning, conducting and disseminating health research to ensure community-tailed implementation of healthcare strategies [31].

The majority of included studies originated from Alaska, USA, where mortality statistics have been collected systematically since the 1950s [32]. Although it is well documented that mortality from chronic liver diseases is more common in Alaska Natives than in the general US population, NAFLD has never been included in these reports [32]. The same applies to a Canadian report on mortality in First Nations people, including Inuit, who have a higher risk of death from T2DM, chronic liver disease and cirrhosis than the general population [33].

We were unable to identify any studies investigating NAFLD in Chukotka, Russia or in Arctic Canadian territories. However, a clinical study originating from Manitoba, Canada, showed a similar prevalence of NAFLD in Canadian First Nations and non-First Nations, whereas obesity and T2DM were more prevalent among First Nations [34]. This aligns with recent findings from our research group in Greenland, reporting a higher burden of steatosis but a lower degree of fibrosis in Greenland Inuit than in Danes with T2DM [11]. These results support the concept of a need for different risk profiles for metabolic disease progression among indigenous Arctic people.

Although multiple reviews exist that report the global and continental incidence rates and prevalence of NAFLD, we here used a search string tailored for a Circumpolar setting and allowed inclusion of studies without a strict definition for NAFLD [35, 36]. By this approach, we identified studies that are not otherwise included in NAFLD reviews.

The study limitations must also be addressed; first, we restricted our systematic review to indigenous Arctic populations residing in Artic countries, states or territories. Consequently, minorities in, e.g., Denmark and Quebec, Canada, were not evaluated. However, by restricting the cohort origins to Arctic areas, we more likely achieved results on isolated indigenous populations concerning genetics and environmental factors. Second, five out of six studies investigated fatty liver disease in Alaska Natives but only two studies did so unseparated from other Native Americans. This reduces the power of our results as these cohorts also consist of native people unrelated to Inuit, Yupik, Inupiat and Aleutians. Third, only selected cohorts were included, in turn reducing the generalisability of study results. Furthermore, the studies relying on liver biochemistry for the investigation of NAFLD or signs of NAFLD risk confounding from the Inuit genetic signature predisposing to higher levels of liver biochemistry variables than Caucasians. Fourth, even though we searched widely for relevant literature including conference reports, publications may have been overlooked as Arctic health-research remains a niche with only few international journals aiming to publish and disseminate research within this field.

CONCLUSION

This review is the first to compile information on the prevalence of NAFLD or signs of NAFLD in indigenous Arctic populations. Even though results were sparse and suffered from considerable risk of bias and a low quality of evidence, this compilation grossly emphasises the need for further health research in indigenous populations.

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