Hepatology International (2020) 14:259–269
https://doi.org/10.1007/s12072-020-10023-3

ORIGINAL ARTICLE

The epidemiology of NAFLD in Mainland China with analysis by adjusted gross regional domestic product: a meta-analysis

Yuankai Wu[1,2] · Qi Zheng[1,3] · Biyao Zou[1] · Yee Hui Yeo[1] · Xiaohe Li[4] · Jie Li[5] · Xiaoyu Xie[6] · Yuemin Feng[6] · Christopher Donald Stave[7] · Qiang Zhu[6] · Ramsey Cheung[1,8] · Mindie H. Nguyen[1]

Received: 29 September 2019 / Accepted: 6 February 2020 / Published online: 4 March 2020

Abstract

Background Non-alcoholic fatty liver disease (NAFLD) is a leading cause of chronic liver disease worldwide. This study aimed to estimate the prevalence, incidence, and outcome of NAFLD in the large and diverse population of Mainland China.

Methods PubMed, Embase, and the Cochrane Library databases were searched to identify published studies with NAFLD epidemiology data in adult participants (≥ 18 years old) from Mainland China. Random effects models were used to determine pooled estimates.

Results We screened 1,328 studies and included 167 eligible studies (participant $n = 1{,}486{,}635$): 149 studies ($n = 1{,}350{,}819$) for prevalence, 18 studies ($n = 147{,}316$) for incidence, 7 studies ($n = 5446$) for evolution of hepatic steatosis, and 2 studies ($n = 647$) for mortality analysis. The NAFLD prevalence of the overall populations was 29.88%, with higher rates in males, increasing age and increasing gross regional domestic product (GRDP) per capita (all $p \leq 0.010$). The prevalence was the highest in North China (36.41%; higher in Uyghur and Hui Chinese 40.86% and 34.36% vs 28.11% in Han Chinese), higher in diabetics (51.83% vs. 30.76% in non-diabetics) and in obese participants (66.21% vs. 11.72% in lean). The NAFLD incidence was 56.7 (95% CI 47.4–66.8) per 1000 person-years, higher in males and with higher GRDP per capita. The overall mortality was 7.3 (3.3–12.7) per 1000 person-years.

Conclusions The overall prevalence of NAFLD in Mainland China is about 30%. The highest prevalences were found among regions with higher income, North China, the non-Han ethnic minorities, diabetics, and the obese. China's NAFLD prevalence is on par with Western countries.

Keywords GRDP · Lean · Obese · Ethnicity · Province · Region · Diabetes · Prevalence · Incidence · Mortality

Abbreviations

ALT	Alanine transaminase
AST	Aspartate transaminase
BMI	Body mass index
CI	Confidence interval
DBP	Diastolic blood pressure
FPG	Fasting plasma glucose concentration
GGT	Gamma-glutamyltransferase
GRDP	Gross regional domestic product

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12072-020-10023-3) contains supplementary material, which is available to authorized users.

✉ Mindie H. Nguyen
mindiehn@stanford.edu

1 Division of Gastroenterology and Hepatology, Stanford University Medical Center, 780 Welch Road, CJ250K, Palo Alto, CA 94304, USA

2 Department of Infectious Diseases, The Third Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China

3 Liver Center, 1st Affiliated Hospital of Fujian Medical University, Fuzhou, China

4 Division of Infectious Disease, The Third People's Hospital of Shenzhen, Shenzhen, China

5 Department of Infectious Disease, Shandong Provincial Hospital Affiliated to Shandong University, Jinan, China

6 Department of Gastroenterology, Shandong Provincial Hospital Affiliated to Shandong University, Jinan, China

7 Lane Medical Library, Stanford University School of Medicine, Stanford, USA

8 Division of Gastroenterology and Hepatology, Veterans Affairs Palo Alto Health Care, Palo Alto, USA

HbA1c	Glycated hemoglobin A1c
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
NAFLD	Nonalcoholic fatty liver disease
PROSPERO	International Prospective Register of Systematic Reviews
SBP	Systolic blood pressure
T2DM	Type 2 diabetes mellitus
TC	Total cholesterol
TG	Triglyceride
UA	Uric acid

Introduction

Non-alcoholic fatty liver disease (NAFLD) is currently the leading cause of chronic liver disease globally [1–5]. China is the largest country in Asia by land mass (9.6 million square kilometers) and population (1.33 billion people) encompassing 55 ethnic minorities [6]. This diversity has given rise to large differences in local customs, diet and socioeconomic levels that may affect the epidemiology of NAFLD in China.

A recent meta-analysis of NAFLD in China reported an overall NAFLD prevalence of 29.2% [7]. However, while the meta-analysis was comprehensive and examined additional outcomes such as risk factors and treatment, the study analysis lacked detailed subgroup analyses for NAFLD prevalence, included overlapping studies, included unpublished studies, with prevalence based on publication year rather than study year and using unadjusted gross regional domestic product (GRDP), rendering a less accurate reflection of temporal changes and local income levels [8]. Therefore, we aimed to address these gaps by performing an in-depth meta-analysis to determine Mainland China's prevalence of NAFLD with comprehensive subgroup analysis to include region/province level data and GRDP, to determine the incidence of NAFLD, the evolution of fatty liver (regression, progression, resolution), and mortality outcomes.

Methods

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for the conduct of meta-analyses of observational studies (http://www.prisma-statement.org/) and was registered on PROSPERO (Registration number: CRD42019137792).

Search strategy and selection criteria

We developed our search terms and strategy in collaboration with a medical librarian (details in Supplementary Methods). PubMed, Embase, and the Cochrane Library databases were searched to identify relevant published studies of adult data from inception to December 3, 2018 and without language restriction. We excluded studies that did not specify exclusions of other causes of chronic liver disease and studies that only enrolled highly selected population (except for type 2 diabetic, obese, or lean population). For published articles of overlapping cohorts, we chose the article with the largest and most updated data.

Study identification, data extraction and quality assessment

Two authors independently performed the literature search and extracted the data using a case report form designed specifically for this study. Discordances were resolved by consensus and/or by further discussion with a third author. Included studies are listed in Supplementary Tables 1–3. We rated the quality of the included studies using a quality assessment scale developed for this study based on the Newcastle–Ottawa scale, comprising three domains: selection, comparability, and outcome and a total score of 9 stars (details in Supplementary Methods). The scores are shown in Supplementary Tables 4 and 5.

Study definitions

NAFLD was defined by the presence of fatty liver on ultrasound and in the absence of excessive alcohol consumption [9] and other causes of chronic liver disease. For the purpose of this study, since many potential studies used BMI cutoff at 28 kg/m^2 or waist circumference > 90 cm in male or > 85 cm in female [10], we defined normal weight for body mass index (BMI) between 18.5 and 23 kg/m^2, overweight for BMI between 23 and 28 kg/m^2, obese with BMI ≥ 28 kg/m^2 or waist circumference > 90 cm in male or > 85 cm in female, and lean for BMI < 25 kg/m^2 [11, 12].

We defined general population as participants enrolled from a non-clinical community setting or from routine health check-up clinics. The high-risk population was defined as cohorts with specific risk factors for NAFLD (diabetes, obesity, or post-menopausal females). The low-risk population was defined as lean, non-diabetic, non-obese population, or populations from studies that excluded participants with other risk factors for NAFLD.

For geographic region, we analyzed by regions and provinces (details in Supplementary Methods). To more accurately reflect the time trend of NAFLD prevalence, we used median year of study period instead of year of publication to stratify studies [7].

To analyze NAFLD prevalence by economic levels, we used the GRDP per capita. To account for inflation and imbalance in economic development in different provinces at different time periods in Mainland China in the last decades [7], we calculated the adjusted GRDP based on the mean GRDP per capita during the study period and adjusted for inflation to 2019 dollars [13]. All included studies were divided into four groups by quartiles of GRDP (rounded to the closest hundred or thousand) (additional details in Supplementary Method).

Evolution and changes in degree of hepatic steatosis by ultrasound follow-up were defined as resolved (no detectable fatty liver), decreased (less hepatic steatosis), stable (no significant change), and increased (more hepatic steatosis).

Statistical analysis

We determined the pooled estimates for study outcomes using random effects model. We used the number of incident NAFLD cases among individuals without NAFLD at baseline and follow-up period (person-years) to estimate the pooled incidence of NAFLD and the number of deaths among NAFLD patients and follow-up period (person-years) to estimate the pooled mortality rates for persons with NAFLD. Cochran Q-statistic and I^2 statistic were used to assess heterogeneity. Estimates with p value of <0.05 in Q-statistic and $I^2 \geq 50\%$ are considered to have moderate to severe heterogeneity. We performed several subgroup analyses to determine the source of heterogeneity and sensitivity analysis excluding studies with extremely high or low prevalence (< 10% or > 50%). To identify factors influencing NAFLD prevalence, we performed a meta-regression by median study year, GRDP per capita (per $1000), age, BMI, SBP, DBP, total cholesterol, triglycerides, HDL-C, LDL-C, FPG, HbA1c, AST, ALT, GGT and uric acid. We utilized funnel plot and Egger's test to assess publication bias. All statistical analyses were conducted using the meta packages in R statistical software (version 3.5.1). This study is in compliance with the Declaration of Helsinki (1964).

Results

Study selection and characteristics

We screened 1328 studies and identified a total of 167 studies with 1,486,635 participants in the study analysis (Fig. 1): 149 studies (1,350,819 participants) for prevalence analysis, 18 studies (147,316 participants) for incidence analysis, 7 studies (5446 participants) for analysis of changes in the presence and degree of hepatic steatosis on follow-up ultrasound in NAFLD persons, and 2 studies (647 participants) for mortality outcome analysis (some studies presented both prevalence, incidence and/or outcome data, so the total number was not the same as the sum of subgroups). The year of publication ranged from 2003 to 2018, with the majority from 2010 or after. The study periods spanned from 1999 to 2017. The characteristics of included studies are shown in Supplementary Tables 1–3.

Prevalence of NAFLD

The pooled overall prevalence of NAFLD was 29.88% [95% confidence interval (95% CI) 27.59–32.27] (117 studies, 1,120,757 persons) (Table 1) and higher in male compared to female (35.45% vs. 24.48%, $p<0.001$). The pooled NAFLD prevalence for the general population (64 studies, 506,765 persons) was 28.83% (95% CI 26.47–31.31) (Table 1, Supplementary Fig. 1).

By geographic region and province

The prevalence varied with regions and provinces with highest prevalence in North China (35.78%, 95% CI 29.13–43.04) and lowest in Southeast China (21.52%, 95% CI 15.84–28.55) (Fig. 2a). Heilongjiang Province had the highest prevalence (50.48%) and Hainan had the lowest but there was only one study for each of these provinces (Fig. 2b). NAFLD prevalence was 30–35% for Xinjiang, Hebei, Anhui, Beijing Municipality, Guangdong and Zhejiang province; 24–30% for Jiangsu, Shanghai Municipality, Jilin, Yunnan, Shandong, Hubei, Hunan Province and about 20% for Chongqing Municipality and Sichuan Province. Generally, provinces in the North of China showed higher prevalence than those in the South.

By economic levels, study period and study year

The prevalence increased with increasing GRDP per capita, from 21.71% in GRDP per capita < $6500 to 32.43% in $9,500-$13,000, but this trend leveled off at ≥ $13,000 (32.02%) ($p=0.013$) (Figs. 2c, 3a).

NAFLD prevalence increased over the three study periods but was not statistically significant ($p=0.340$) (Fig. 3a). There was a significant association between NAFLD prevalence and individual study years on meta-regression noted below.

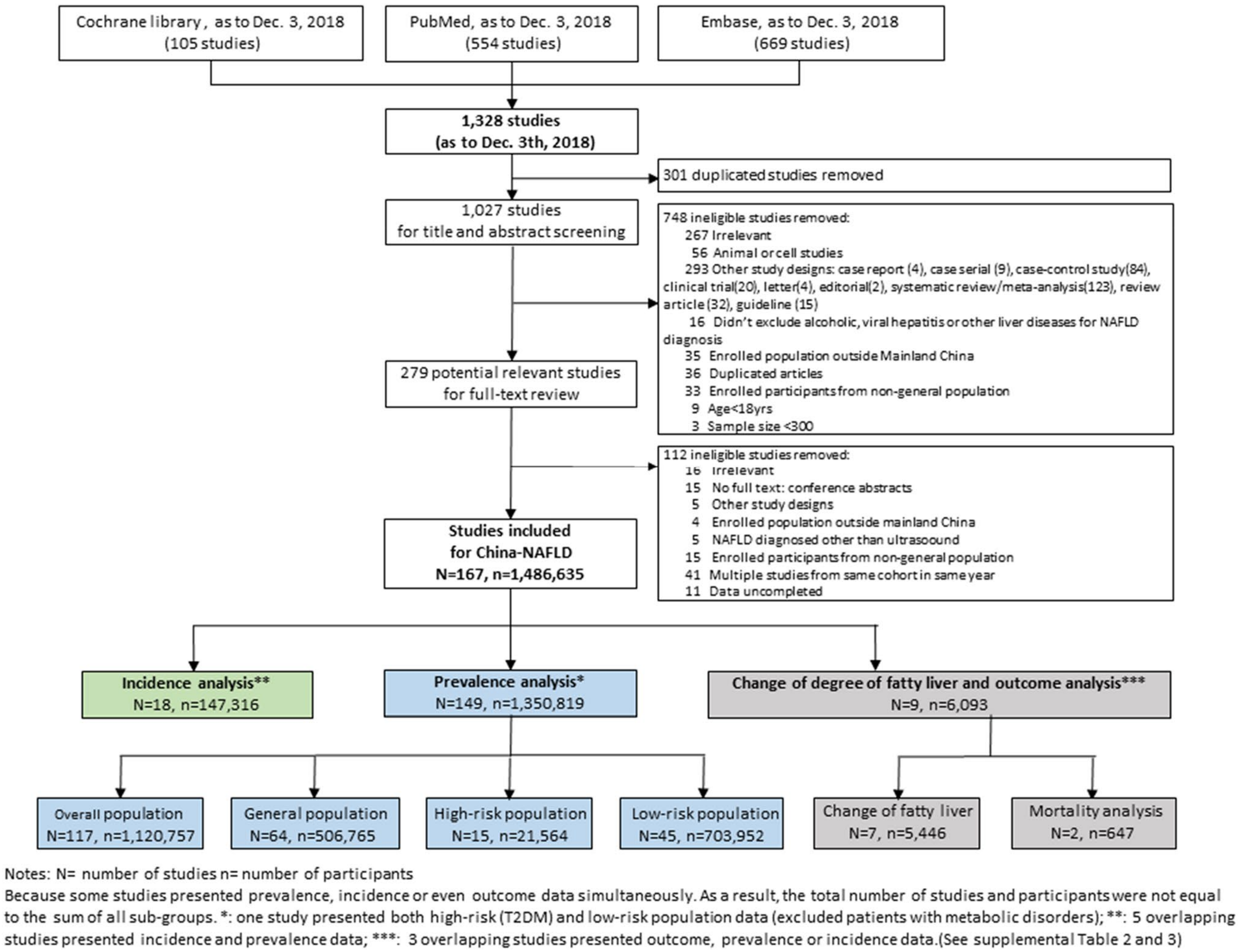

Fig. 1 Flow chart of systematic literature search and screening for NAFLD epidemiology in Mainland China

By sex, age, BMI

NAFLD prevalence was higher in males compared to females (34.75%, vs. 23.50%, $p < 0.001$) (Fig. 3b) and increased from 8.54% in 18–29-year-old group to 29.14% in 50–59-year-old group, but decreased after 70 years of age ($p = 0.004$) The prevalence in overweight persons was significantly higher than that in non-overweight persons (52.01% vs. 9.17%, $p < 0.001$) and even higher in obese (BMI $\geq$ 28 kg/m^2) compared to non-obese (BMI < 28 kg/m^2) participants (72.33% vs. 23.19%, $p < 0.001$) (Fig. 3b).

After performing meta-regression, we found median study year, GRDP per $1000, BMI, and GGT were positively associated with increasing NAFLD prevalence (all $p < 0.003$), while HDL-C showed a negative association ($p = 0.042$) (Supplementary Table 6).

High-risk and low-risk population

The prevalence was 46.04% in high-risk population and 27.08% in low-risk population ($p < 0.001$) (Table 1). Postmenopausal females showed a higher prevalence than female overall (34.52% vs. 23.96%, $p = 0.011$), and so did type 2 diabetics compared to non-diabetics (51.83% vs. 30.76%, $p < 0.001$) and in obese compared to lean participants (66.21% vs. 11.72%, $p < 0.001$).

Prevalence by ethnicity, education levels, physical activity, urban vs. rural population and presence of hyperuricemia

Several studies focused on selected ethnic groups: Han Chinese (4 studies, 30,442 participants), Uyghur (4 studies, 7035 participants) and Hui Chinese (2 studies, 136 participants).

Table 1 The prevalence of NAFLD in different populations in Mainland China

Population	Studies (*N*)	Participants (*n*)	NAFLD (*n*)	Prevalence (%, 95% CI)	I^2 (%)	*p* value
Total included studies and population	149	1,350,819	332,504	–	–	
Overall population*	117	1,120,757	265,844	29.88% (27.59–32.27)	99.8	
With or without other liver diseases						0.384
With other liver diseases*	35	124,374	31,228	28.01% (23.70–32.78)	99.6	
Without other liver diseases*	85	999,478	233,847	30.41% (27.71–33.25)	99.9	
Sex						< 0.001
Male	87	444,039	128,773	35.45% (32.60–38.41)	99.7	
Female	85	374,601	61,891	24.48% (21.07–28.24)	99.8	
General population**	64	506,765	136,893	28.83% (26.47–31.31)	99.7	
With or without other liver diseases						0.087
With other liver diseases	24	87,485	21,069	25.43% (20.34–31.29)	99.7	
Without other liver diseases	44	426,913	117,875	30.99% (28.34–33.77)	99.7	
High-risk population[#]	15	21,564	10,198	46.04% (40.53–51.65)	98.2	
T2DM population	13	19,462	9549	51.83% (47.03–56.59)	97.1	
Obese population	9	4438	2800	66.21% (57.82–73.68)	96.0	
Postmenopausal females	7	10,627	3861	34.52% (26.93–42.99)	98.6	
Low-risk population[#]	45	703,952	151,802	27.08% (23.58–30.89)	99.9	
Non-DM population	13	113,935	33,118	30.76% (26.58–35.28)	99.5	
Lean population	18	334,908	39,594	11.72% (9.64–14.19)	99.6	
Excluded ≥ 2 metabolic diseases[##]	19	388,040	79,586	25.94% (21.19–31.35)	99.9	

Because some studies could be enrolled in certain sub-analysis when excluded from another sub-analysis, so some were repeatedly used in different subgroups. As a result, the total number of articles and participants was not equal to the sum of all the subgroups

*One and two studies in group with and without other liver diseases were further excluded when estimating pooled prevalence in overall population, because study population overlapped (studies from same cohort of same study period)

**Four overlapping studies in group without other liver disease were further excluded when estimating pooled prevalence in the whole general population. Prevalence in general population with other liver disease vs. that without other liver disease, $p = 0.087$

[#]One overlapped study in high- and low-risk population. High risk vs. low risk, high risk vs. general population, $p < 0.0001$, low risk vs. general population, $p = 0.44$; T2DM vs. non-DM, Obese vs lean population, $p < 0.0001$; postmenopausal females vs. general females, $p = 0.010$

[##]Population from studies that excluded participants with T2DM and/or other metabolic disorders

Other liver diseases, including alcoholic liver diseases, viral hepatitis, autoimmune hepatitis, hemochromatosis, Wilson's disease, non-NAFLD-related liver cirrhosis or liver cancer, other secondary causes of fatty liver (drugs or hereditary disorders), etc.; T2DM, type 2 diabetes mellitus; non-DM, non-diabetic; general population: participants from community-based investigation or participants went to the hospital for routine health check-up, without exclusion or inclusion of some specific participants; obese population: BMI > 28 kg/m^2 or waist circumference > 90 cm in male or > 80 cm in female; lean population: BMI < 25 kg/m^2

The prevalence in Uyghur (40.86%, 95% CI 32.29–50.02) and Hui Chinese (34.36%, 95% CI 6.24–80.47) was higher than Han Chinese (28.11%, 95% CI 22.66–34.29), but without reaching statistical significance ($p = 0.060$) (Fig. 3c). NAFLD prevalence was higher in urban than rural population setting (30.43% vs. 17.01%, $p = 0.128$), but only two studies included rural population (7656 participants).

Incidence of NAFLD

The average age of the study population without NAFLD at baseline was 44.7 ± 7.3 years. With a 564,220.5 person-year total follow-up, there were 29,848 cases of newly diagnosed NAFLD, yielding NAFLD incidence of 56.7 (95% CI 47.4–66.8) per 1000 person-years (Table 2, Supplementary Table 2, and Supplementary Fig. 2). NAFLD incidence was higher in males than in females (33.8 vs. 22.1 per 1000 person-years, $p = 0.044$). There was also a trend of increased incidence with GRDP per capita, from 49.7 (95% CI 38.8–62.0) (< $6500) to 71.6 (95% CI 37.3–117.1) per 1000 person-years ($9500–13,000) ($p = 0.19$). NAFLD incidence varied by geographic region and provinces, but data from some of these regions were limited with only one study for some.

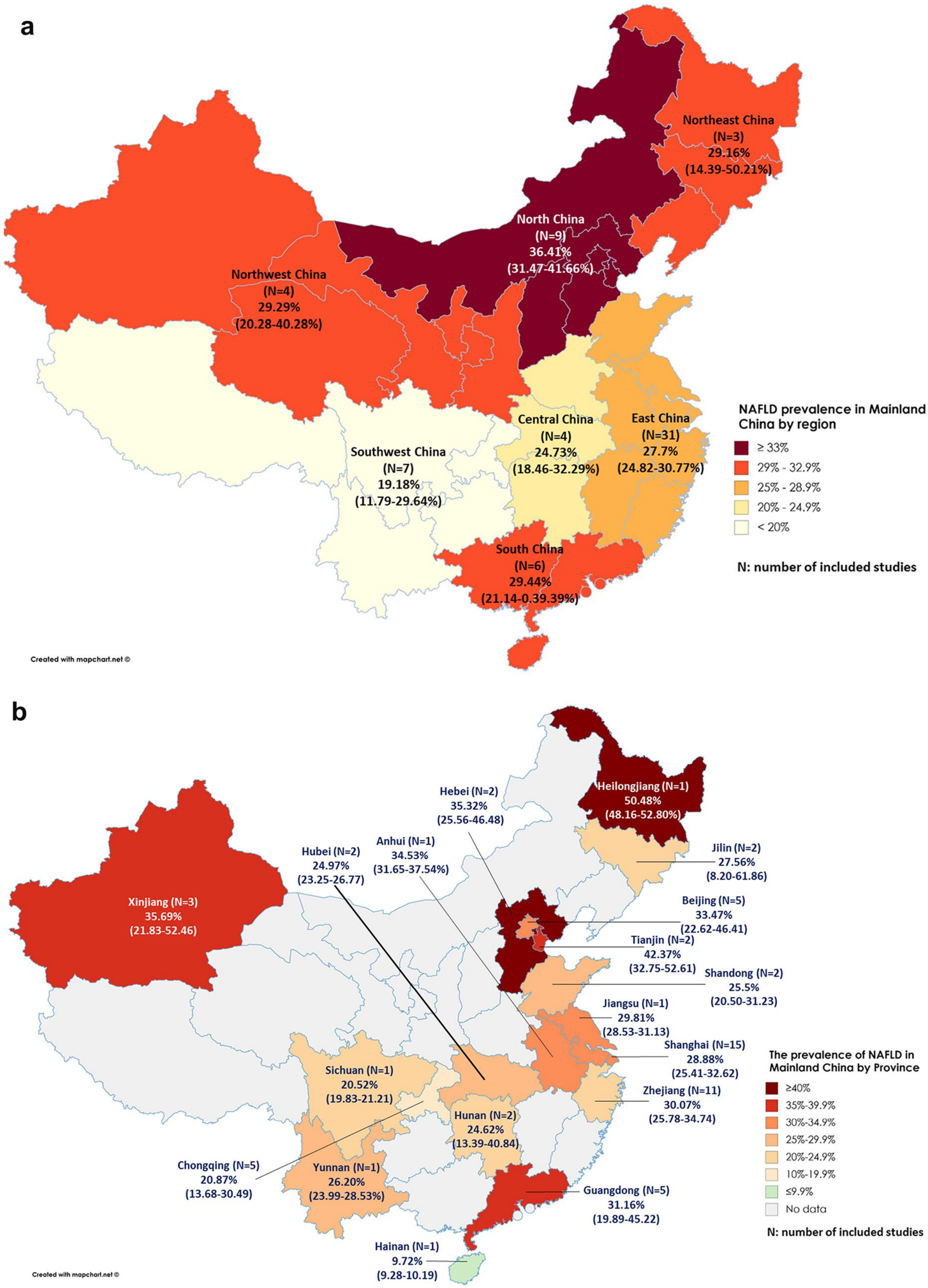

Fig. 2 The prevalence of NAFLD in Mainland China by geographic region, province, and gross regional domestic product (GRDP). **a** NAFLD prevalence in Mainland China by region. **b** NAFLD prevalence in Mainland China by province. **c** NAFLD prevalence in Mainland China by unadjusted GRDP in 2017 of each province

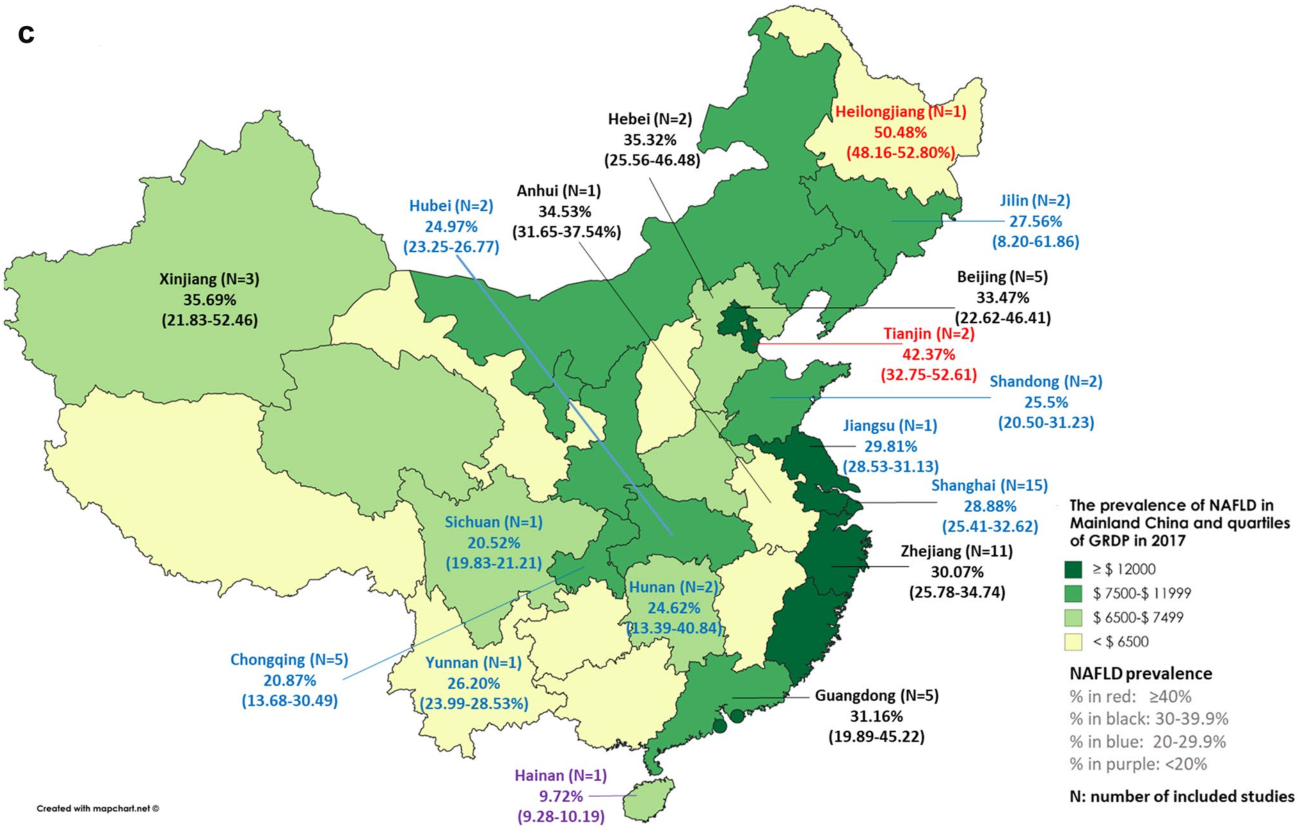

Fig. 2 (continued)

Changes in the presence and degree of liver fat in persons with NAFLD

Seven longitudinal, non-interventional cohort studies (n = 5,446, follow-up years = 3.1–8.0 years) provided data for the evolution of hepatic steatosis by follow-up ultrasound. Most studies came from coastal provinces or cities in the eastern and southern part of China. Changes in the presence and degree of fatty liver by ultrasonography follow-up were common. The rates of remission (resolved) (no more steatosis on follow-up), decrease, remaining stable, and increase in hepatic steatosis were 41.3, 56.0, 145.2 and 39.0 per 1000 person-years, respectively (Table 3 and Supplementary Table 3). The cumulative rates of resolved, decreased, stable and increased rate varied in the range of 18–25%, 21–34%, 62–87%, 17–22% respectively, among the studies.

Clinical outcomes of NAFLD

Only two studies (n = 647) reported 22 deaths among 647 participants during a follow-up of 3056 person-years, resulting in an overall all-cause mortality of 7.3 (95% CI 3.3–12.7) per 1000 person-years (Table 3 and Supplementary Table 3). The causes of death were liver-related events in 2 cases, extrahepatic malignances (one each: pancreas, colon, lung, breast, bile duct), cardiovascular disease in 14 and 1 pneumonia.

Sensitivity analysis

We performed sensitivity analysis for prevalence of general population by excluding studies with quality assessment score < 7 points, sample size less than 1000, non-population-based, non-academic center-based studies, as well as studies with extremely low (< 10%) or high (> 50%) prevalence and studies from provinces with only one study, which did not show significant changes (all $p > 0.05$) (Supplementary Table 7). We also performed sensitivity for the different alcohol criteria used by primary studies (52 studies used Chinese or Asia-Pacific criteria: > 140/week for males, > 70 g/week for females; 4 studies used AASLD or EASL criteria : > 210/week for males, > 140 g/week for females; 2 studies used criteria of > 280 g/d for males, > 140 g/week for females; and 6 studies used other criteria) and did not find significant differences (Supplementary Table 7). Similar findings were found in sensitivity analysis for incidence after excluding

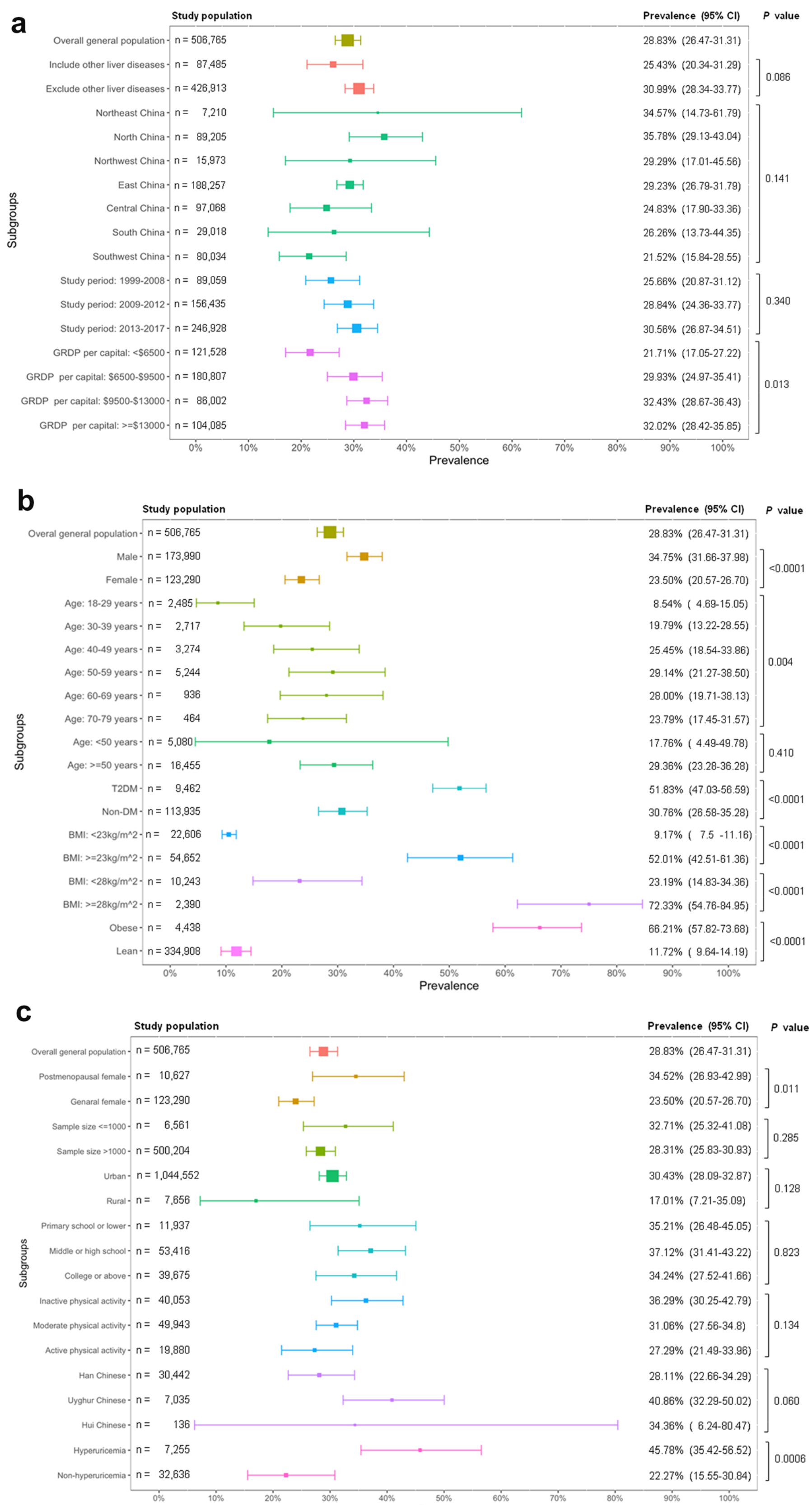

Fig. 3 NAFLD prevalence in general population in Mainland China: subgroup analysis by including/excluding other liver diseases, region, study period, gross regional domestic product (GRDP) (**a**), sex, age, body mass index (BMI), obese vs. lean population (**b**), sample size, urban vs. rural population, education level, physical activity, ethnicity, presence of hyperuricemia and diabetes (**c**)

Table 2 The incidence of NAFLD in Mainland China

	Studies (*n*)	Non-NAFLD participants at baseline (*n*)	Incident NAFLD patients (*n*)	Follow-up (person-years)	Incidence (per 1000 person-years, 95% CI)	I^2 (%)	*p* value
Overall incidence	18	147,316	29,848	564,220.5	56.7 (47.4–66.8)	99.5	
By sex							0.044
Male	13	108,672	15,079	445,689.0	33.8 (24.3–11.7)	99.7	
Female	12	106,305	7853	438,588.0	22.1 (16.7–28.4)	99.3	
By median year of study period							0.570
1999–2008	4	28,635	5255	85,334.0	56.2 (32.8–85.8)	99.5	
2009–2012	10	89,449	19,222	392,584.2	52.3 (40.4–65.8)	99.6	
2013–2017	4	29,232	5371	86,302.4	66.0 (45.7–90.0)	98.7	
By gross regional domestic product (GRDP) per capita							0.198
< $6500	6	67,762	14,863	307,308.1	49.7 (38.8–62.0)	99.4	
$6500–9500	5	22,509	2745	79,611.4	46.6 (33.7–61.5)	98.5	
$9500–13000	3	24,955	6047	73,470.8	71.6 (37.3–117.1)	99.6	
>=$13000	4	32,090	6193	103,830.2	67.7(50.2–87.8)	98.9	
By region							<0.001
South China	1	552	202	2208.0	91.5 (79.3–104.6)	–	
North China	4	57,968	13,080	257,254.0	61.8 (47.1–78.5)	99.5	
Northeast China	1	512	188	3072.0	61.2 (52.8–70.3)	–	
East China	9	70,749	13,054	218,781.2	53.6 (36.9–73.4)	99.7	
Central China	2	15,152	2961	73,373.4	48.9 (30.2–72.0)	97.4	
Southwest China	1	2383	363	9532.0	38.1 (34.3–42.1)	–	
By province							<0.001
Guangdong	1	552	202	2208.0	91.5 (79.3–104.6)	–	
Shandong	1	15,791	3913	51,652.0	75.8 (73.4–78.1)	–	
Tianjin	3	32,690	6400	105,586.0	68.5 (47.9–92.8)	99.3	
Shanghai	3	7169	859	16,149.2	62.7 (18.7–132.5)	99.4	
Jilin	1	512	188	3072.0	61.2 (52.8–70.3)	–	
Hubei	2	15,152	2961	73,373.4	48.9 (30.2–72.0)	97.4	
Jiangxi	1	11,363	1022	22,385.1	45.7 (42.9–48.5)	–	
Zhejiang	4	36,426	7260	128,594.8	44.5 (19.3–80.2)	99.8	
Hebei	1	25,278	6680	151,668.0	44.0 (43.0–45.1)	–	
Sichuan	1	2383	363	9532.0	38.1 (34.3–42.1)	–	

Table 3 The change of degrees of fatty liver and mortality of NAFLD in Mainland China

	Studies (*n*)	NAFLD patients at baseline (*n*)	Transitions (*n*)	Follow-up (person-years)	Incidence (per 1000 person-years, 95% CI)	I^2 (%)
Changes in degree of hepatic steatosis by ultrasound follow-up[a]						
Resolved	5	2615	486	14,222.3	41.3 (25.4–61.0)	95.8
Decreased	2	2831	605	16,698.0	56.0 (17.1–117)	96.1
Stable	7	5446	3860	30,920.3	145.2 (113.3–181.1)	97.9
Increased	2	2831	495	16,698.0	39.0 (18.1–67.7)	89.1
	Studies (*n*)	NAFLD patients at baseline (*n*)	Death (*n*)	Follow-up (person-years)	Mortality (per 1000 person-years, 95% CI)	I^2 (%)
Mortality	2	647	22	3056.0	7.3 (3.3–12.7)	54.8

[a]Resolved, with fatty liver at baseline, but resolved (no detectable fatty liver under US) during follow-up; decreased, with fatty liver at baseline, but degree of fatty liver decreased or score decreased during follow-up; stable: no significant change of degree or score of fatty liver during follow-up; increased: deteriorated degree or score of fatty liver during follow-up

studies with quality assessment score < 7 points, sample size less than 1000, non-population-based, and non-academic center-based studies (all $p > 0.05$) (Supplementary Table 7).

Heterogeneity and publication bias

The heterogeneity between NAFLD prevalence studies was significant (Tables 1, 2, 3). Egger's test and funnel plot did not show significant publication bias in the prevalence analysis of general population ($p = 0.38$) and high-risk population ($p = 0.49$), as well as overall incidence analysis ($p = 0.63$), though there was bias in prevalence analysis of the low-risk population ($p = 0.036$), which could be due to studies that only enrolled lean people in low-risk population analysis (Supplementary Fig. 3).

Discussion

This study estimated the pooled prevalence in the general population of NAFLD in Mainland China to be 28.83%, higher than the global level (25.24%) [3]. There were also large geographic differences, with higher prevalence in the north, which could be due to dietary factor [14, 15], larger body size and colder weather [16], and more ethnic minorities with higher NAFLD prevalence such as the Uyghur [17] and the Hui [18] groups. These findings are important to inform public health efforts in both disease prevention and monitoring.

We also found increasing NAFLD prevalence and incidence of NAFLD with increasing GRDP per capita, but plateaued in areas with highest GRDP per capita (≥ $13,000). Increased (red) meat consumption [15, 19], popularization of fast food [20] and western diet [21], and less physical activity [22, 23] can all contribute to higher NAFLD prevalence in areas with higher economic prosperity. Interestingly, prior studies from China have found lower physical activity level in higher income population in rural areas [24], but relatively higher or comparable physical activity in higher income urban population which could explain the plateauing of prevalence in areas with highest GRDP per capita [25]. Contrary to our finding with adjusted GRDP, Zhou et al. [7] found a U-shaped change between NAFLD and GRDP per capita using unadjusted values which likely is an artifact of unadjusted values. We did not observe a dramatic increase in NAFLD prevalence as the Zhou et al.'s study, but we analyzed different cutoffs for time periods and our time analysis was based on by median study year rather publication year (as used by Zhou et al. [7]), which can lag behind considerably. However, we did find an association between increasing (more recent) study year with increasing NAFLD prevalence on meta-regression.

Another important finding in present study was the dynamic evolution of the presence and degree of fatty liver by ultrasonography follow-up in real-world settings, as also reported by a prior study from Japan [26].

This study has many strengths. Unlike the recent meta-analysis [7], we reported the prevalence based on the study period instead of the year of publication and used adjusted instead of unadjusted GRDP, both made the pooled estimates for NAFLD in the current study more accurate as well as providing additional detailed analyses not available in the prior meta-analysis. Given great variation in economic development in the last decades in Mainland China, analysis by GRDP per capita should be performed according to GRDP during the study period instead of that of a specific year (e.g., 2019), and should take currency inflation into account to more accurately reflect the association, which is what we did in the present study. Our study also covered the majority of population and areas in Mainland China (22 out of 31 provinces, these province covers 81.36% populations of Mainland China) [6] and we only included studies using abdominal ultrasound for the diagnosis of NAFLD, which is the most common diagnostic modality.

Limitations of this study included high heterogeneity among studies, which is not uncommon in a meta-analysis of percentage and of this size. There could also be selection bias in some of the analyses due to the small number of published studies such as in analysis of studies from rural areas and publication bias for populations perceived to be low risk. As there are more than 30 provinces or municipalities in Mainland China, only 1–2 studies were enrolled in some provinces in general population analysis. Outcome data were also limited.

In conclusion, NAFLD is a common liver disease affecting almost one in three in the general population of Mainland China, higher in North China, in areas with higher GRDP per capita, and among the non-Han ethnic minority groups. At the prevalence of 28.8% observed in this study and with a 1.33 billion population [6], Mainland China has an estimated NAFLD disease burden of over 388 million people, a number that almost certainly will rise in the coming decade with continued economic development and rising GRPD per capita across Mainland China. More researches are needed to investigate the long-term outcomes of NAFLD in Mainland China; and even more importantly, additional research and better health education and public policy are urgently needed to prevent and curtail the obesity epidemic and related metabolic diseases that contribute to NAFLD development and progression.

Acknowledgements We specially acknowledge http://www.mapchart.net for the generous sharing of the map tools used to generate all maps in this article.

Author contributions Guarantor of article: MHN. Specific author contributions: Study design: YKW, YHY, QZhu, RC, MHN. Data collection: YKW, QZheng, BYZ, XHL, JL, XYX, YMF, CDS. Data analysis: YKW, BYZ, YHY, MHN. Drafting of the article: YKW, RC, MHN. Data interpretation, review and/or revision of the manuscript: All authors. Study concept and study supervision: MHN.

Funding No external funding to disclose

Compliance with ethical standards

Conflict of interest Ramsey Cheung: Research grant from Gilead; Mindie Nguyen: Research grants from Gilead, Pfizer; Consultation and/or advisory board with Gilead, Intercept. Yuankai Wu, Qi Zheng, Biyao Zou, Yee Hui Yeo, Xiaohe Li, Jie Li, Xiaoyu Xie, Yuemin Feng, Christopher Donald Stave, Qiang Zhu have nothing to disclose.

Ethical approval The study was performed according to the 1964 Declaration of Helsinki. This study is not a human subject research. The study only utilizes publically available published aggregated anonymous data.

References

1. Younossi Z, Stepanova M, Ong JP, et al. Nonalcoholic steatohepatitis is the fastest growing cause of hepatocellular carcinoma in liver transplant candidates. Clin Gastroenterol Hepatol 2018;17(4), 748 e743–755 e743
2. Goldberg D, Ditah IC, Saeian K, et al. Changes in the prevalence of hepatitis C virus infection, nonalcoholic steatohepatitis, and alcoholic liver disease among patients with cirrhosis or liver failure on the waitlist for liver transplantation. Gastroenterology 2017;152(5):1090 e1091–1099 e1091
3. Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of nonalcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64(1):73–84
4. Li J, Zou B, Yeo YH, et al. Prevalence, incidence, and outcome of non-alcoholic fatty liver disease in Asia, 1999–2019: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2019;4(5):389–398
5. Calzadilla-Bertot L, Jeffrey GP, Jacques B, et al. Increasing incidence of nonalcoholic steatohepatitis as an indication for liver transplantation in Australia and New Zealand. Liver Transpl 2019;25(1):25–34
6. The 6th national population census data of China in 2010. http://www.stats.gov.cn/tjsj/pcsj/rkpc/6rp/indexch.htm. Accessed 11 Mar 2019
7. Zhou F, Zhou J, Wang W, et al. Unexpected rapid increase in the burden of nonalcoholic fatty liver disease in China from 2008 to 2018: a systematic review and meta-analysis. Hepatology 2019;70(4):1119–1133
8. Wu Y, Yeo YH, Nguyen MH, Cheung RC. Prevalence of NAFLD in China: what did we learn from the recent meta-analysis? Hepatology 2019
9. Gao X, Fan JG, Study Group of Liver Metabolism Chinese Society of Endocrinology. Diagnosis and management of non-alcoholic fatty liver disease and related metabolic disorders: consensus statement from the Study Group of Liver and Metabolism, Chinese Society of Endocrinology. J Diabetes 2013;5(4):406–415
10. Zhang HJ, Zhang XF, Ma ZM, et al. Irisin is inversely associated with intrahepatic triglyceride contents in obese adults. J Hepatol 2013;59(3):557–562
11. WHO expert consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet (London, England) 2004;363(9403:157–163
12. Zhou BF. Predictive values of body mass index and waist circumference for risk factors of certain related diseases in Chinese adults–study on optimal cut-off points of body mass index and waist circumference in Chinese adults. Biomed Environ Sci 2002;15(1:83–96
13. Gross regional domestic product. http://data.stats.gov.cn/easyquery.htm?cn=E0103. Accessed 5 Ma 2019
14. Zhang JG, Wang ZH, Du WW, et al. Dietary sodium intake of adult residents in 15 provinces of China in 2015. Chin J Prevent Med 2019;53(5):455–458
15. Shi L, Liu ZW, Li Y, et al. The prevalence of nonalcoholic fatty liver disease and its association with lifestyle/dietary habits among university faculty and staff in Chengdu. BES 2012;25(4):383–391
16. Reitman ML. Of mice and men—environmental temperature, body temperature, and treatment of obesity. FEBS Lett 2018;592(12):2098–2107
17. Cai W, Wu X, Zhang B, et al. Serum uric acid levels and nonalcoholic fatty liver disease in Uyghur and Han ethnic groups in northwestern China. Arquivos brasileiros de endocrinologia e metabologia 2013;57(8):617–622
18. Lin S, Xian Y, Liu Y, et al. Risk factors and community intervention for nonalcoholic fatty liver disease in community residents of Urumqi, China. Medicine 2018;97(9):e0021
19. Zelber-Sagi S, Nitzan-Kaluski D, Goldsmith R, et al. Long term nutritional intake and the risk for non-alcoholic fatty liver disease (NAFLD): a population based study. J Hepatol 2007;47(5):711–717
20. Pereira MA, Kartashov AI, Ebbeling CB, et al. Fast-food habits, weight gain, and insulin resistance (the CARDIA study): 15-year prospective analysis. Lancet (London, England) 2005;365(9453):36–42
21. Oddy WH, Herbison CE, Jacoby P, et al. The Western dietary pattern is prospectively associated with nonalcoholic fatty liver disease in adolescence. Am J Gastroenterol 2013;108(5):778–785
22. Qiu S, Cai X, Sun Z, et al. Association between physical activity and risk of nonalcoholic fatty liver disease: a meta-analysis. Ther Adv Gastroenterol 2017;10(9):701–713
23. Wang S, Song J, Shang X, et al. Physical activity and sedentary behavior can modulate the effect of the PNPLA3 variant on childhood NAFLD: a case–control study in a Chinese population. BMC Med Genet 2016;17(1):90
24. Zhao YF, Ma JX, Li JH, et al. Study on prevalence of physical activity in rural residents in four counties (districts) of Shanxi and Chongqing. Zhonghua liu xing bing xue za zhi 2018;39(3):302–307
25. Attard SM, Howard AG, Herring AH, et al. Differential associations of urbanicity and income with physical activity in adults in urbanizing China: findings from the population-based China Health and Nutrition Survey 1991–2009. Int J Behav Nutr Phys Act 2015;12:152
26. Fukuda, T., Hamaguchi, M., Kojima, T. et al. Transient remission of nonalcoholic fatty liver disease decreases the risk of incident type 2 diabetes mellitus in Japanese men. Eur J Gastroenterol Hepatol 2016;28(12):1443–1449