

# BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email [info.bmjopen@bmj.com](mailto:info.bmjopen@bmj.com)

# BMJ Open

## Prevalence and risk factors of metabolic fatty liver disease during 2014-2018 from three cities of Liaoning province

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-047588
Article Type:	Original research
Date Submitted by the Author:	02-Dec-2020
Complete List of Authors:	Guan, Lin; The First Hospital of China Medical University, Gastroenterology Department Zhang, Xinhe; The First Hospital of China Medical University, Gastroenterology Department Tian, Haoyu; China Medical University, the 3rd Clinical Department Jin, Xing; The First Hospital of China Medical University, Gastroenterology Department Fan, Hang; Neusoft Xikang Healthcare Technology Co., Ltd., Data Operation & Management Department Wang, Ningning; The First Hospital of China Medical University, Gastroenterology Department Sun, Jing; The First Hospital of China Medical University, Gastroenterology Department Li, Dan; The First Hospital of China Medical University, Gastroenterology Department Li, Jia; Neusoft Xikang Healthcare Technology Co., Ltd., Data Operation & Management Department Wang, Xue ; The First Hospital of China Medical University, Gastroenterology Department Zeng, Zilu; The First Hospital of China Medical University, Gastroenterology Department Li, Yiling; The First Hospital of China Medical University, Gastroenterology Department
Keywords:	Hepatology < INTERNAL MEDICINE, DIABETES & ENDOCRINOLOGY, General endocrinology < DIABETES & ENDOCRINOLOGY

SCHOLARONE™  
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

# Prevalence and risk factors of metabolic fatty liver disease during 2014-2018 from three cities of Liaoning province

**Running title:** Prevalence of MAFLD in Liaoning, China

Lin Guan<sup>1¶</sup>, Xinhe Zhang<sup>1¶</sup>, Haoyu Tian<sup>2</sup>, Xing Jin<sup>1</sup>, Hang Fan<sup>3</sup>, Ningning Wang<sup>1</sup>,  
Jing Sun<sup>1</sup>, Dan Li<sup>1</sup>, Jia Li<sup>3</sup>, Xue Wang<sup>1</sup>, Zilu Zeng<sup>1</sup>, Yiling Li<sup>1\*</sup>

<sup>1</sup>Gastroenterology Department, the First Hospital of China Medical University,  
No.155 North Nanjing Street, Heping District, Shenyang 110001, Liaoning, China

<sup>2</sup>the 3rd Clinical Department, China Medical University, No.77 Puhe Road, Shenyang  
North New Area, Shenyang 110122, Liaoning, China

<sup>3</sup>Data Operation & Management Department, Neusoft Xikang Healthcare Technology  
Co., Ltd., No.175 Chuangxin Road, Hunnan New District, Shenyang 110179,  
Liaoning, China

¶**These authors contributed equally to this work.**

**\*Corresponding author**

Yiling Li, Gastroenterology Department, the First Hospital of China Medical  
University, No.155 North Nanjing Street, Heping District, Shenyang 110001,  
Liaoning, China

E-mail: lyl-72@163.com

Tel: +86 13998841476

**Word count:** 2466

**ABSTRACT**

**Objectives:** To investigate the incidence and disease characteristics of metabolic fatty liver disease (MAFLD) in physical examination populations in Liaoning (China).

**Design:** Retrospective study

**Setting:** Single center.

**Participants:** Adults who underwent routine health examination at Xikang Medical Center in Liaoning Province (Shenyang, Dandong, and Dalian) between 01/2014 and 12/2018.

**Interventions:** Not applicable.

**Primary And Secondary Outcome Measures:** Not applicable.

**Results:** Among the 204,394 included subjects, 71,756 were diagnosed with MAFLD, accounting for 35.28%. The total prevalence of MAFLD in Shenyang, Dandong, and Dalian in the past five years is 35.8%, 40.41%, and 31.7%, respectively. Men had a prevalence of 46.12%, which is higher than in women (21.80%). The percentage of MAFLD in BMI <23 and  $\geq 23$  kg/m<sup>2</sup> is 6.49 % and 53.23%, respectively. In all subjects, BMI, SBP, DBP, FBG, TG, TC, LDL-C, HDL-C, ALT, AST, ALP, GGT, BUN, Scr, SUA, HCT, MCV, and UPRO are independently associated with MAFLD (all P<0.001). In lean subjects, DBP, FBG, TG, TC, LDL-C, HDL-C, AST, ALP, GGT, Scr, SUA, HCT, and MCV are independently associated with MAFLD (all P<0.001).

**Conclusions:** The prevalence of MAFLD in Liaoning is related to sex, cities with

1  
2  
3  
4  
5 different economic statuses, BMI, and multiple metabolic indicators.  
6

7 **Key words:** metabolic fatty liver disease; prevalence; risk factors; body mass index;  
8  
9 lean.  
10  
11  
12  
13  
14

### 15 **Strengths and limitations of this study**

- 16
- 17
- 18 1. Among the 204,394 included subjects, 71,756 were diagnosed with MAFLD.
- 19
- 20 2. Men had a prevalence of 46.12%, which is higher than in women (21.80%).
- 21
- 22
- 23 3. The prevalence of MAFLD in Liaoning is related to sex, cities with different  
24 economic statuses, BMI, and multiple metabolic indicators.
- 25
- 26
- 27
- 28 4. This cross-sectional study cannot provide any causal relationship between  
29 MAFLD and the associated factors.  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease and is defined as the presence of  $\geq 5\%$  of hepatic steatosis (HS) (1, 2). Recently, it was recommended to rename NAFLD as metabolic (dysfunction) associated fatty liver disease (MAFLD), which might increase the awareness of the disease and decrease its stigma (3, 4). NAFLD is associated with chronic diseases like insulin resistance and/or type 2 diabetes (T2DM), dyslipidemia, hypertriglyceridemia, and hypertension (5-8). The reported prevalence of MAFLD is reported to be 24%-45%, with an estimated prevalence of 76% in patients with T2DM (9). For non-obese patients, MAFLD is associated with elevated triglyceride (TG) levels, increased waist circumference, and insulin resistance (10).

Chinese individuals have substantially higher risks of MAFLD, even at much lower BMI levels, compared with the US population (11). Factors like waist circumference, T2DM, increased TG, low high - density lipoprotein (HDL)-cholesterol, and metabolic syndrome are known to be predictive factors for MAFLD in adults, and the metabolic syndrome is considered as a strong predictive factor (12, 13). MAFLD is also associated with dyslipidemia characterized by high TG, high low-density lipoprotein (LDL), and low HDL-cholesterol levels (14). Determining the risk factors associated with a worse prognosis is essential for improving the therapeutic strategies.

Since the 21st century, the prevalence of MAFLD in China has increased

1  
2  
3  
4  
5 significantly to reach about one in three mainland Chinese residents (12). A recent  
6  
7 meta-analysis showed that the incidence of MAFLD is higher in northern China  
8  
9 (35.78%) and lower in northwestern China (21.52%) (15). Among the provinces in  
10  
11 northern China, Heilongjiang has the highest incidence, with up to 50.48% (15).  
12  
13 Nevertheless, the results might be biased due to the small number of studies, yet  
14  
15 MAFLD incidence in northern China is significantly higher than that in the southern  
16  
17 provinces. In addition, the risk of MAFLD-related mortality has also increased  
18  
19 significantly, mainly due to diseases associated with liver fibrosis (16). MAFLD has  
20  
21 become an important health issue affecting the Chinese population, increasing the  
22  
23 socioeconomic burden (11, 12, 15). Therefore, Chinese medical professionals and  
24  
25 stakeholders urgently need to carry out early scientific prevention and control of  
26  
27 MAFLD. Multiple studies have shown that MAFLD is a heterogeneous entity and that  
28  
29 its development is related to sex, age, race, mild-to-moderate alcohol consumption,  
30  
31 dietary intake, lifestyle, obesity, metabolism, genetic variation, and education (11, 12,  
32  
33 15, 16). With uneven economic development and diverse lifestyles among the  
34  
35 different provinces, the epidemiology of MAFLD in China has marked regional  
36  
37 differences. By understanding the epidemiology of MAFLD in Liaoning Province, we  
38  
39 can conduct targeted education and clinical research for precise prevention and  
40  
41 control of MAFLD.  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53

54 There have been no data from large-scale epidemiological investigations of  
55  
56 MAFLD in Liaoning province in northern China in the past ten years. Therefore, this  
57  
58  
59  
60



1  
2  
3  
4  
5 retrospective study aims to investigate the incidence and disease characteristics of  
6  
7 MAFLD in physical examination populations in Liaoning. The study uses physical  
8  
9 examination data of residents collected from 2014 to 2018 in three cities with  
10  
11  
12 different economic levels in Liaoning (Shenyang, Dandong, and Dalian).  
13  
14  
15  
16  
17

## 18 **METHODS**

### 19 **Study subjects**

20  
21  
22  
23 This is a retrospective study of adults who underwent routine health examination  
24  
25 at Xikang Medical Center in Liaoning Province (which has clinics in Shenyang,  
26  
27 Dandong, and Dalian) between January 2014 and December 2018. The study was  
28  
29 conducted in accordance with Declaration Helsinki, and the protocol was approved by  
30  
31 the Ethics Committee of the First Hospital of China Medical University  
32  
33 ([2020]2020-257-2). The ethics committee waived the requirement for informed  
34  
35 consent because of the retrospective nature of the study.  
36  
37  
38  
39

40  
41 The three cities are from different parts of the province (North, South, and East  
42  
43 (Figure 1), and they have different economic levels. Shenyang, situated in North  
44  
45 Liaoning Province, is a highly developed inland city, while Dalian in South Liaoning  
46  
47 is a developed coastal city. Dandong, in the east of Liaoning Province, is a poorly  
48  
49 developed city bordering North Korea.  
50  
51  
52  
53

54 The inclusion criteria are 1) >18 years of age; 2) have been living in Shenyang,  
55  
56 Dalian, or Dandong for at least 5 years; 3) participate in the annual physical  
57  
58  
59  
60

1  
2  
3  
4  
5 examination; and 4) no missing data (as listed in Table 1). The exclusion criteria are  
6  
7 1) liver cirrhosis; 2) liver cancer; 3) any liver ultrasound lesions; or 4) no ultrasound  
8  
9 examination. For individuals with more than one examination during the study period,  
10  
11 only the first examination is included in this study.  
12  
13

14  
15 The selected patients are divided into the MAFLD group and the non-MAFLD  
16  
17 group based on ultrasound features (17). All study subjects are classified as lean (BMI  
18  
19  $<23 \text{ kg/m}^2$ ) or overweight-obese (BMI  $\geq 23 \text{ kg/m}^2$ ), according to the standards  
20  
21 recommended by the World Health Organization for Asians (18).  
22  
23  
24  
25

### 26 27 28 **Physical examination**

29  
30 All physical examinations included in this study are part of the routine  
31  
32 examination. Blood pressure measurements, including systolic blood pressure (SBP)  
33  
34 and diastolic blood pressure (DBP), are taken twice after the participants have been  
35  
36 sitting, in a calm state, for at least 5 min, using an electronic sphygmomanometer  
37  
38 (HEM-7200, OMRON Healthcare, Kyoto, Japan). Height and weight are measured in  
39  
40 the morning on an empty stomach, and body mass index (BMI) is as  $\text{kg/m}^2$ .  
41  
42  
43  
44  
45  
46  
47

### 48 49 **Laboratory examination**

50  
51 All physical blood tests included in this study are part of the routine examination.  
52  
53 Anterior cubital vein blood is drawn in the fasting state (at least 8 h). A midcourse  
54  
55 morning urine specimen is also taken. Routine blood panel, liver function, kidney  
56  
57  
58  
59  
60

1  
2  
3  
4  
5 function, serum uric acid (SUA), fasting blood glucose (FBG), blood lipids, and  
6  
7 routine urine analysis are assessed using a 7600 autoanalyzer (Hitachi, Tokyo, Japan).  
8  
9

### 10 11 12 **Color Doppler ultrasound of the liver and gallbladder**

13  
14  
15 A liver ultrasound is part of the routine examination. It is performed by two  
16  
17 experienced ultrasound radiologists with at least 5 years of experience and using an  
18  
19 IU 22 system (Philips, Best, The Netherlands). An individual is diagnosed with  
20  
21 MAFLD when the ultrasound examination shows that the liver has fatty liver changes  
22  
23 (hyperechogenicity due to increased acoustic interface caused by the intracellular  
24  
25 accumulation of lipid vesicles, blurring of vascular margins, increased liver size, and  
26  
27 increased acoustic attenuation (10, 17)) and after excluding other causes of liver fatty  
28  
29 disease (such as excessive alcohol consumption) (17).  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40

### 41 42 **Statistical analysis**

43  
44 R 3.5.3 and R Commander 2.5-3 were used for statistical analysis. The  
45  
46 categorical data are expressed as n (%) and were analyzed using the chi-square test.  
47  
48 The continuous variables conforming to the normal distribution (according to the  
49  
50 Kolmogorov-Smirnov test) are expressed as means  $\pm$  standard deviations and were  
51  
52 analyzed using Student's t-test. Non-normally distributed continuous variables are  
53  
54 presented as medians (interquartile range (IQR)) and were analyzed using the  
55  
56 Mann-Whitney U-test. The factors associated with MAFLD were identified using  
57  
58  
59  
60

1  
2  
3  
4  
5 univariable analyses. Variables with P-values <0.05 were included in a multivariable  
6  
7 logistic regression model. P-values <0.05 were considered statistically significant.  
8  
9

## 10 11 12 **RESULTS**

### 13 14 15 **Characteristics of the subjects**

16  
17  
18 A total of 284,129 subjects were examined during the study period, and 204,394  
19  
20 met the inclusion criteria. Table 1 presents the characteristics of the subjects. The  
21  
22 mean age is 39.6±13.6 years. The numbers of men and women are 111,782 and  
23  
24 92,612, respectively. The mean age of the men is 38.8±13.7 years, and that of women  
25  
26 is 40.5±13.3 years. Shenyang includes 78,329 subjects, who were 39.3±12.7 years of  
27  
28 age. The clinic in Dandong did not perform routine health examinations in 2014.  
29  
30 Dandong includes 42,039 subjects, who were 47.8±14.1 years. Finally, Dalian has  
31  
32 84,026 subjects; they were 36.3±12.7 years.  
33  
34  
35  
36  
37  
38  
39  
40

### 41 42 **MAFLD in the healthy population**

43  
44 Among the 204,394 included subjects, 71,756 were diagnosed with MAFLD,  
45  
46 accounting for 35.28% (Table 1). The prevalence of MAFLD increases with the age  
47  
48 groups (P<0.001), is higher in males than in females (P<0.001), is higher in  
49  
50 overweight/obese subjects than in lean ones (P<0.001), and is higher in Dandong,  
51  
52 followed by Shenyang and Dalian (P<0.001) (Table 1). The prevalence of MAFLD in  
53  
54 Shenyang, Dandong, and Dalian in the past five years was 36.83%, 40.42%, and  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5 31.78%, respectively.  
6  
7  
8  
9

### 10 **MAFLD over time**

11  
12 The total prevalence of MAFLD from 2014 to 2018 is 30.01%, 30.11%, 33.22%,  
13  
14 34.58%, and 32.19%, respectively. The prevalence of MAFLD over the 5 years  
15  
16 mainly increased in the 30-39 groups ( $P=0.006$ ), and both in males ( $P=0.029$ ) and in  
17  
18 females ( $P=0.035$ ) (Table 2). The prevalence of MAFLD in Shenyang in the past 5  
19  
20 years was basically consistent with the general trend in Liaoning. The MAFLD  
21  
22 prevalence in Dandong showed a significant increase annually in the past 4 years. The  
23  
24 MAFLD prevalence in Dalian increased substantially in 2016, but it declined annually  
25  
26 in 2017 and 2018 (Figure 2). The prevalence rate in men and women in the past five  
27  
28 years is basically consistent with the general trend of MAFLD in Liaoning (Figure 3).  
29  
30  
31  
32  
33  
34  
35  
36 As age increases, MAFLD prevalence in Liaoning increases.  
37  
38  
39  
40

### 41 **Biomarkers and MAFLD**

42  
43 Table 3 presents the biomarkers in all subjects and according to  
44  
45 lean/overweight-obese. Compared with the non-MAFLD group, the subjects with  
46  
47 MAFLD have higher SBP, DBP, FBG, TG, TC, LDL-C, ALT, AST, ALP, GGT,  
48  
49 BUN, Scr, and SUA, higher frequencies of UPRO and GBp, lower HDL-C, HCT, and  
50  
51 MCV, and lower frequency of UOB (all  $P<0.001$ ). The same tendencies are observed  
52  
53  
54  
55  
56  
57 in lean subjects, except that there is no difference in UPRO ( $P=0.86$ ).  
58  
59  
60

## Factors associated with MAFLD

Table 4 presents the univariable and multivariable analyses of the factors associated with MAFLD. In all subjects, BMI, SBP, DBP, FBG, TG, TC, LDL-C, HDL-C, ALT, AST, ALP, GGT, BUN, Scr, SUA, HCT, MCV, and UPRO are independently associated with MAFLD (all  $P < 0.001$ ), while UOB ( $P = 0.47$ ) and GBp ( $P = 0.21$ ) are not. In lean subjects, DBP, FBG, TG, TC, LDL-C, HDL-C, AST, ALP, GGT, Scr, SUA, HCT, and MCV are independently associated with MAFLD (all  $P < 0.001$ ), while SBP ( $P = 0.51$ ), ALT ( $P = 0.27$ ), BUN ( $P = 0.16$ ), UPRO ( $P = 0.57$ ), UOB ( $P = 0.06$ ), and GBp ( $P = 0.06$ ) are not.

## DISCUSSION

The present study shows that the prevalence of MAFLD in Shenyang, Dandong, and Dalian varied and that higher BMI and age play significant roles in the development of the disease. In addition, biomarkers like DBP, FBG, TG, LDL-C, ALT, GGT, BUN, SUA, HCT, UPRO, GBs, and GBp are independently and positively correlated with the prevalence of MAFLD, whereas HDL-C and MCV are negatively correlated. Therefore, the prevalence of MAFLD in Liaoning is related to sex, cities with different economic statuses, BMI, and multiple metabolic indicators.

The increasing trend in the prevalence of MAFLD follows the level of industrialization and urbanization. At present, China is the fastest-growing major

1  
2  
3  
4  
5 economy in the world and displays the problems associated with a westernized diet,  
6  
7 sedentary lifestyle, and population aging, which are associated with MAFLD. Studies  
8  
9 have shown that the increase in the total annual MAFLD prevalence in China is  
10  
11 consistent with the improvement in the per capita GDP (19). An increase in morbidity  
12  
13 in various regions of mainland China is related to the increase in per capita GDP, but  
14  
15 the area with the highest per capita GDP ( $\geq$ \$13,000) does not exhibit an increased  
16  
17 incidence of MAFLD (20). According to the National Bureau of Statistics of China,  
18  
19 the per capita GDP of Liaoning Province has been ranking first in Northeast China in  
20  
21 the past five years, but it is still in the lower-middle level nationally. This study shows  
22  
23 that the prevalence of MAFLD in Liaoning (35.1%) is slightly higher than the overall  
24  
25 prevalence of MAFLD in China (29.2%) (12). This study selected two economically  
26  
27 developed cities (Dalian and Shenyang) and one city with moderate development  
28  
29 (Dandong). The prevalence of MAFLD in these three cities is inversely proportional  
30  
31 to the level of urban economic development. The prevalence of MAFLD in Dalian is  
32  
33 lower than that in Shenyang. A reason might be that Dalian is a coastal city, with  
34  
35 dietary habits different from that of inland cities.  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45

46 Differences in age are also involved. The prevalence of MAFLD in the 20-29  
47  
48 years group is 17.9%, while the prevalence in the >60 years group is 45.6%, which is  
49  
50 in alignment with previous studies that show that age plays a crucial factor in  
51  
52 MAFLD (11, 12, 15).  
53  
54  
55

56 This study found that the overall prevalence of MAFLD in men is higher than  
57  
58  
59  
60

1  
2  
3  
4  
5 that in women, which is basically consistent with the findings in other regions in  
6  
7 China (21). The prevalence of MAFLD in middle-aged men is highest and peaks at  
8  
9 40-49 years of age (50.27%). This high prevalence might be related to high stress,  
10  
11 irregular work and rest, and decreased metabolism among middle-aged men. The  
12  
13 prevalence of MAFLD in women over 50 years of age is significantly higher, which  
14  
15 relates to the age range of menopause.  
16  
17  
18  
19

20  
21 Obesity is closely related to metabolic-related diseases such as MAFLD. This  
22  
23 study confirmed that BMI  $\geq 23$  kg/m<sup>2</sup> is an independent risk factor for MAFLD in  
24  
25 Liaoning. Therefore, for overweight and obese people, it is necessary to improve diet  
26  
27 and exercise management, even with the help of drugs or surgery if needed. It has  
28  
29 been reported that the global prevalence of lean-MAFLD is 5%-26% (22). In the  
30  
31 study, the prevalence of lean-MAFLD is 10.75%, which is similar to previous results  
32  
33 (23).  
34  
35  
36  
37  
38

39  
40 In this study, both lean-MAFLD and non-lean-MAFLD were closely related to  
41  
42 metabolic indicators. Those metabolic indicators are also associated with T2DM,  
43  
44 metabolic syndrome, obesity, and liver diseases, as supported by previous studies (11,  
45  
46 12, 15, 21-23). In addition to obesity, the variation in the prevalence of MAFLD  
47  
48 follows the epidemic trends of T2DM and MetS. The prevalence of MAFLD in  
49  
50 hyperlipidemia and T2DM patients is higher, reaching 27%-92% and 28%-70%,  
51  
52 respectively. Patients with MAFLD also often have hyperlipidemia, hypertension,  
53  
54 T2DM, and metabolic syndrome (24). In this study, logistic regression analysis found  
55  
56  
57  
58  
59  
60



1  
2  
3  
4  
5 that DBP, TG, LDL-C, FBG, and SUA were independent risk factors for MAFLD, but  
6  
7 HDL-C is independently associated with MAFLD. Therefore, paying attention to  
8  
9  
10 hyperlipidemia, hypertension, and T2DM should have important effects on the  
11  
12 prevention and treatment of MAFLD. Regarding the correlation between SUA and  
13  
14  
15 MAFLD, SUA elevation is one of the risk factors for MAFLD (25).  
16

17  
18 Although it was not examined in this study, genetic susceptibility is involved  
19  
20 in MAFLD. Polymorphisms in PNPLA3 (26), SREBF-2 (27), CETP (27, 28), and  
21  
22 APOC3 (29) have been found to be associated with lean-MAFLD. In addition to  
23  
24 genetic polymorphisms, lean-MAFLD people have increased bile acid and FXR  
25  
26 activity due to metabolic abnormalities and changes in intestinal microbial  
27  
28 composition (30, 31). Those factors should be examined in future studies.  
29  
30  
31

32  
33 This study has limitations. Even if the examinations were performed at the same  
34  
35 clinical company, they were performed at three different physical locations and over 5  
36  
37 years. Biases due to the different locations and changes in practice over time cannot  
38  
39 be excluded. In addition, ultrasound is operator-dependent, and a bias in the diagnosis  
40  
41 of MAFLD cannot be excluded. Finally, this was a cross-sectional study that cannot  
42  
43 provide any causal relationship between MAFLD and the associated factors.  
44  
45  
46  
47

48  
49 In conclusion, the prevalence of MAFLD in Liaoning is related to sex, cities with  
50  
51 different economic statuses, BMI, and multiple metabolic indicators. Longitudinal  
52  
53 studies are necessary to determine the factors associated with the development of  
54  
55  
56  
57 MAFLD.  
58  
59  
60

## Acknowledgment

No applicable.

**Funding:** No applicable

**Conflict of interest:** The authors declare that they have no conflict of interest.

**Data Sharing Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Ethical statement:** The study was conducted in accordance with Declaration Helsinki, and the protocol was approved by the Ethics Committee of the First Hospital of China Medical University ([2020]2020-257-2). The ethics committee waived the requirement for informed consent because of the retrospective nature of the study.

## Author contributions

(I) Conception and design: LG, XHZ, YLL

(II) Administrative support: JS, DL, YLL

(III) Provision of study materials or patients: LG, XJ, NNW

(IV) Collection and assembly of data: HYT, XW, ZLZ

(V) Data analysis and interpretation: HF, JL

(VI) Manuscript writing: All authors

(VII) Final approval of manuscript: All authors

## REFERENCES

- 1  
2  
3  
4  
5 1. Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of  
6  
7 nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence,  
8  
9 and outcomes. *Hepatology*. 2016;64:73-84.
- 10  
11  
12 2. Stal P. Liver fibrosis in non-alcoholic fatty liver disease - diagnostic challenge  
13  
14 with prognostic significance. *World J Gastroenterol*. 2015;21:11077-87.
- 15  
16  
17 3. Eslam M, Sanyal AJ, George J, et al. MAFLD: A Consensus-Driven Proposed  
18  
19 Nomenclature for Metabolic Associated Fatty Liver Disease. *Gastroenterology*.  
20  
21 2020;158:1999-2014 e1.
- 22  
23  
24 4. Fouad Y, Waked I, Bollipo S, et al. What's in a name? Renaming 'NAFLD' to  
25  
26 'MAFLD'. *Liver Int*. 2020;40:1254-61.
- 27  
28  
29 5. Pai RK. NAFLD Histology: a Critical Review and Comparison of Scoring  
30  
31 Systems. *Curr Hepatol Rep*. 2019;18:473-81.
- 32  
33  
34 6. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and  
35  
36 natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in  
37  
38 adults. *Aliment Pharmacol Ther*. 2011;34:274-85.
- 39  
40  
41 7. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of  
42  
43 non-alcoholic fatty liver disease: practice guideline by the American  
44  
45 Gastroenterological Association, American Association for the Study of Liver  
46  
47 Diseases, and American College of Gastroenterology. *Gastroenterology*.  
48  
49 2012;142:1592-609.
- 50  
51  
52 8. Non-Alcoholic Fatty Liver Disease: Assessment and Management. National  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5 Institute for Health and Care Excellence: Guidance. London 2016.  
6

7 9. Rinella ME. Nonalcoholic fatty liver disease: a systematic review. JAMA.  
8  
9 2015;313:2263-73.  
10

11  
12 10. Shen FF, Lu LG. Advances in noninvasive methods for diagnosing nonalcoholic  
13  
14 fatty liver disease. J Dig Dis. 2016;17:565-71.  
15

16  
17 11. Zhou J, Zhou F, Wang W, et al. Epidemiological Features of NAFLD From 1999  
18  
19 to 2018 in China. Hepatology. 2020;71:1851-64.  
20

21  
22 12. Zhou F, Zhou J, Wang W, et al. Unexpected Rapid Increase in the Burden of  
23  
24 NAFLD in China From 2008 to 2018: A Systematic Review and Meta-Analysis.  
25  
26 Hepatology. 2019;70:1119-33.  
27

28  
29 13. Caballeria L, Auladell MA, Toran P, et al. Risk factors associated with  
30  
31 non-alcoholic fatty liver disease in subjects from primary care units. A case-control  
32  
33 study. BMC Gastroenterol. 2008;8:44.  
34  
35

36  
37 14. Hartmann P, Schnabl B. Risk factors for progression of and treatment options for  
38  
39 NAFLD in children. Clin Liver Dis (Hoboken). 2018;11:11-5.  
40

41  
42 15. Wu Y, Zheng Q, Zou B, et al. The epidemiology of NAFLD in Mainland China  
43  
44 with analysis by adjusted gross regional domestic product: a meta-analysis. Hepatol  
45  
46 Int. 2020;14:259-69.  
47

48  
49 16. Dulai PS, Singh S, Patel J, et al. Increased risk of mortality by fibrosis stage in  
50  
51 nonalcoholic fatty liver disease: Systematic review and meta-analysis. Hepatology.  
52  
53 2017;65:1557-65.  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3  
4  
5 17. Mahale AR, Prabhu SD, Nachiappan M, et al. Clinical relevance of reporting  
6 fatty liver on ultrasound in asymptomatic patients during routine health checkups. *J*  
7  
8  
9  
10 Int Med Res. 2018;46:4447-54.  
11
- 12 18. Consultation WHOE. Appropriate body-mass index for Asian populations and its  
13 implications for policy and intervention strategies. *Lancet*. 2004;363:157-63.  
14
- 15 19. Cai J, Zhang XJ, Li H. Progress and challenges in the prevention and control of  
16 nonalcoholic fatty liver disease. *Med Res Rev*. 2019;39:328-48.  
17
- 18 20. Fan JG, Kim SU, Wong VW. New trends on obesity and NAFLD in Asia. *J*  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
20. Fan JG, Kim SU, Wong VW. New trends on obesity and NAFLD in Asia. *J*  
Hepatol. 2017;67:862-73.
21. Zhu JZ, Zhou QY, Wang YM, et al. Prevalence of fatty liver disease and the  
economy in China: A systematic review. *World J Gastroenterol*. 2015;21:5695-706.
22. Wang AY, Dhaliwal J, Mouzaki M. Lean non-alcoholic fatty liver disease. *Clin*  
*Nutr*. 2019;38:975-81.
23. Shi Y, Wang Q, Sun Y, et al. The Prevalence of Lean/Nonobese Nonalcoholic  
Fatty Liver Disease: A Systematic Review and Meta-Analysis. *J Clin Gastroenterol*.  
2020;54:378-87.
24. Fan JG, Wei L, Zhuang H, et al. Guidelines of prevention and treatment of  
nonalcoholic fatty liver disease (2018, China). *J Dig Dis*. 2019;20:163-73.
25. Ma Z, Xu C, Kang X, et al. Changing trajectories of serum uric acid and risk of  
non-alcoholic fatty liver disease: a prospective cohort study. *J Transl Med*.  
2020;18:133.

- 1  
2  
3  
4  
5 26. Musso G, Cassader M, Bo S, et al. Sterol regulatory element-binding factor 2  
6  
7 (SREBF-2) predicts 7-year NAFLD incidence and severity of liver disease and  
8  
9 lipoprotein and glucose dysmetabolism. *Diabetes*. 2013;62:1109-20.
- 10  
11  
12 27. Adams LA, Marsh JA, Ayonrinde OT, et al. Cholesteryl ester transfer protein  
13  
14 gene polymorphisms increase the risk of fatty liver in females independent of  
15  
16 adiposity. *J Gastroenterol Hepatol*. 2012;27:1520-7.
- 17  
18 28. Petersen KF, Dufour S, Hariri A, et al. Apolipoprotein C3 gene variants in  
19  
20 nonalcoholic fatty liver disease. *N Engl J Med*. 2010;362:1082-9.
- 21  
22 29. Li C, Guo P, Okekunle AP, et al. Lean non-alcoholic fatty liver disease patients  
23  
24 had comparable total caloric, carbohydrate, protein, fat, iron, sleep duration and  
25  
26 overtime work as obese non-alcoholic fatty liver disease patients. *J Gastroenterol*  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
30. Safari Z, Gerard P. The links between the gut microbiome and non-alcoholic fatty liver disease (NAFLD). *Cell Mol Life Sci*. 2019;76:1541-58.
31. Suk KT, Kim DJ. Gut microbiota: novel therapeutic target for nonalcoholic fatty liver disease. *Expert Rev Gastroenterol Hepatol*. 2019;13:193-204.

**Table 1.** Characteristics of the patients with non-MAFLD and MAFLD

Subgroups	Age (years), Mean±SD	All N=204,3 94	Non-MAFLD n=132,638	MAFLD n=71,7 56	Prevalence (%)	P
Age						<0.001
20-29		22,822	18,728	4094	17.94	
30-39		80,227	54,671	25,556	31.85	
40-49		44,464	27,913	16,551	37.22	
50-59		30,861	17,173	13,688	44.35	
≥60		26,020	14,153	11,867		
Sex						<0.001
Male	38.8±13.7	111,782	60,222	51,560	46.13	
Female	40.5±13.3	92,612	72,416	20,196	21.81	
BMI (kg/m <sup>2</sup> )						<0.001
<23		79,271	74,124	5147	6.49	
≥23		125,123	58,514	66,609	53.23	
City						<0.001

---

01

Shenya	39.3±12.7	78,329	50,265	28,064	36.83
ng					
Dando	47.8±14.1	42,039	25,048	16,991	40.42
ng					
Dalian	36.3±12.7	84,026	57,325	26,701	31.78
Overall	39.6±13.6	204,394	132,638	71,756	35.11

---

MAFLD: metabolic-associated fatty liver disease; BMI: body mass index.



**Table 2.** Changes in the prevalence of MAFLD over time (2014-2018)

Subgroups	Year, %					P
	2014	2015	2016	2017	2018	
<b>Age (years)</b>						
20-29	16.43	17.20	17.30	18.82	18.18	0.081
30-39	29.24	28.60	31.05	33.37	34.33	0.006
40-49	35.65	34.50	35.40	39.04	38.69	0.200
50-59	46.32	39.40	41.67	46.96	45.44	0.636
≥60	44.83	40.65	45.34	48.39	46.50	0.234
<b>Sex</b>						
Male	42.60	42.63	44.36	48.12	48.45	0.029
Female	14.85	19.33	21.49	24.63	22.67	0.035
<b>BMI (kg/m<sup>2</sup>)</b>						
<23	5.08	5.35	6.68	7.36	6.80	0.058
≥23	54.93	50.37	52.15	55.08	53.76	0.510
<b>City</b>						
Shenyang	34.89	34.80	34.27	37.36	36.92	0.182
Dandong	-	30.06	34.29	42.66	44.17	0.039
Dalian	26.36	29.00	33.20	32.36	32.98	0.048
Overall	30.01	30.11	33.22	34.58	32.19	<0.001

BMI: body mass index.

**Table 3.** Comparison of the metabolic tests between non-MAFLD and MAFLD

Variables	Overall			Lean (BMI<23)			Overweight (BMI >=23)		
	Non-MAFLD	MAFLD	P	Non-MAFLD	MAFLD	P	Non-MAFLD	MAFLD	P
SBP, mmHg	118±18	129±19	<0.001	114±16	122±19	<0.001	123±18	129±19	<0.001
DBP, mmHg	70±11	77±13	<0.001	67±10	73±12	<0.001	72±12	77±13	<0.001
FBG, mmol/L	5.15±1.30	5.82±1.63	<0.001	5.04±1.22	5.63±1.65	<0.001	5.3±1.18	5.83±1.63	<0.001
TG, mmol/L	1.07±0.85	2.12±1.73	<0.001	0.91±0.64	1.79±1.46	<0.001	1.28±1.01	2.14±1.75	<0.001
TC, mmol/L	4.41±1.43	4.96±1.34	<0.001	4.29±1.41	4.94±1.36	<0.001	4.55±1.43	4.97±1.34	<0.001
LDL-C, mmol/L	1.99±1.34	2.42±1.43	<0.001	1.9±1.28	2.46±1.38	<0.001	2.09±1.40	2.42±1.43	<0.001
HDL-C, mmol/L	1.01±0.71	0.9±0.60	<0.001	1.06±0.73	0.99±0.64	<0.001	0.93±0.67	0.9±0.60	<0.001
ALT, U/L	19.37±17.28	36.58±27.98	<0.001	17.09±14.34	27.89±21.40	<0.001	22.19±19.98	37.2±28.29	<0.001
AST, U/L	19.59±11.18	25.85±13.56	<0.001	18.76±10.03	23.55±13.08	<0.001	20.62±12.38	26.02±13.57	<0.001
ALP, U/L	7.01±22.44	9.62±25.91	<0.001	5.51±20.85	8.48±24.35	<0.001	8.98±24.13	9.7±26.02	<0.001

GGT, U/L	18.42±24.10	39.36±42.82	<0.001	15.54±20.76	31.41±48.78	<0.001	21.99±27.27	37.71±42.34	<0.001
BUN, mmol/L	4.32±1.97	4.8±1.80	<0.001	4.17±1.90	4.65±1.77	<0.001	4.51±2.04	4.81±1.80	<0.001
Scr, µmol/L	58.57±26.43	66.63±24.76	<0.001	56.12±25.14	62.05±22.61	<0.001	61.62±27.66	66.96±24.88	<0.001
SUA, µmol/L	283.17±125.06	369.05±135.06	<0.001	263.87±116.14	330.07±123.40	<0.001	307.09±131.43	371.84±135.42	<0.001
HCT, %	21.57±21.35	20.32±22.42	<0.001	21.95±20.97	20.36±21.90	<0.001	21.1±21.80	20.32±22.46	<0.001
MCV, fl	47.2±44.74	41.66±44.42	<0.001	48.78±44.68	42.74±44.70	<0.001	45.23±44.74	41.58±44.40	<0.001
UPRO, n (%)	6.70%	9.20%	<0.001	6.30%	6.20%	0.86	7.30%	9.40%	<0.001
UOB, n (%)	11.10%	8.80%	<0.001	11.20%	9.40%	0.00	10.80%	8.80%	<0.001
GBp, n (%)	7.40%	8.90%	<0.001	6.20%	8.60%	<0.001	8.90%	9.70%	<0.001

SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting plasma glucose; TG: triglycerides; TC: total cholesterol;

LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; ALT: alanine aminotransferase; AST:

aspartate aminotransferase; ALP: alkaline phosphatase; GGT:  $\gamma$ -glutamyl transpeptidase; BUN: blood urea nitrogen; Scr: serum

creatinine; SUA: serum uric acid; HCT: hematocrit; MCV: mean corpuscular volume; UPRO: urine protein; UOB: urine occult blood;

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

GBp: gallbladder polyps.

For peer review only

**Table 4.** Multivariable analyses of the factors associated with MAFLD

Variables	Univariable logistical regression			Multivariable logistical regression				
	OR	OR (95% CI)	P	OR	OR (95% CI)	P		
<b>MAFLD</b>								
BMI (kg/m <sup>2</sup> )								
<23	0.057	0.056	0.060	<0.001	0.125	0.119	0.130	<0.001
≥23								
SBP, mmHg	1.033	1.033	1.034	<0.001	1.003	1.003	1.005	<0.001
DBP, mmHg	1.053	1.052	1.054	<0.001	1.014	1.012	1.016	<0.001
FBG, mmol/L	1.541	1.520	1.559	<0.001	1.122	1.104	1.131	<0.001
TG, mmol/L	2.899	2.854	2.953	<0.001	1.651	1.627	1.691	<0.001
TC, mmol/L	1.378	1.365	1.392	<0.001	0.879	0.866	0.893	<0.001
LDL-C, mmol/L	1.267	1.255	1.277	<0.001	1.231	1.216	1.259	<0.001

1									
2									
3									
4									
5	HDL-C, mmol/L	0.799	0.785	0.813	<0.001	0.717	0.690	0.740	<0.001
6									
7	ALT, U/L	1.040	1.038	1.040	<0.001	1.036	1.035	1.038	<0.001
8									
9									
10	AST, U/L	1.055	1.054	1.057	<0.001	0.979	0.977	0.981	<0.001
11									
12									
13	ALP, U/L	1.004	1.004	1.005	<0.001	0.998	0.998	1.000	<0.001
14									
15	GGT, U/L	1.025	1.025	1.026	<0.001	1.002	1.002	1.002	<0.001
16									
17									
18	BUN, mmol/L	1.145	1.139	1.154	<0.001	1.019	1.007	1.032	<0.001
19									
20									
21	Scr, µmol/L	1.014	1.013	1.014	<0.001	0.995	0.994	0.996	<0.001
22									
23									
24	SUA, µmol/L	1.005	1.005	1.006	<0.001	1.003	1.002	1.003	<0.001
25									
26	HCT, %	0.998	0.997	0.998	<0.001	1.006	1.003	1.008	<0.001
27									
28									
29	MCV, fl	0.997	0.997	0.997	<0.001	0.994	0.993	0.995	<0.001
30									
31									
32	UPRO, n (%)	1.407	1.342	1.462	<0.001	1.112	1.069	1.198	<0.001
33									
34	UOB, n (%)	0.762	0.749	0.811	<0.001	1.000	0.933	1.033	0.47
35									
36									
37	GBp, n (%)	1.233	1.176	1.280	<0.001	1.026	0.981	1.090	0.21
38									
39									
40									
41									
42									
43									
44									
45									
46									

**Lean (BMI<23), MAFLD**

SBP, mmHg	1.027	1.025	1.029	<0.001	1.999	0.995	1.002	0.51
DBP, mmHg	1.046	1.042	1.048	<0.001	1.018	1.012	1.024	<0.001
FBG, mmol/L	1.393	1.346	1.424	<0.001	1.098	1.064	1.133	<0.001
TG, mmol/L	2.771	2.642	2.891	<0.001	1.878	1.781	1.968	<0.001
TC, mmol/L	1.498	1.465	1.565	<0.001	0.891	0.860	0.941	<0.001
LDL-C, mmol/L	1.455	1.393	1.485	<0.001	1.372	1.301	1.430	<0.001
HDL-C, mmol/L	1.890	0.831	0.920	<0.001	0.695	0.631	0.741	<0.001
ALT, U/L	1.028	1.026	1.030	<0.001	1.025	1.024	1.030	0.27
AST, U/L	1.028	1.026	1.030	<0.001	0.971	0.969	0.980	<0.001
ALP, U/L	1.006	1.004	1.007	<0.001	1.000	0.998	1.001	<0.001
GGT, U/L	1.016	1.016	1.018	<0.001	1.001	1.001	1.004	<0.001
BUN, mmol/L	1.150	1.133	1.182	<0.001	1.022	0.990	1.059	0.16

Scr, $\mu\text{mol/L}$	1.010	1.008	1.012	<0.001	0.898	0.987	0.993	<0.001
SUA, $\mu\text{mol/L}$	1.005	1.005	1.006	<0.001	1.004	1.004	1.004	<0.001
HCT, %	0.996	0.995	0.998	<0.001	1.016	1.005	1.023	<0.001
MCV, fl	0.997	0.996	0.998	<0.001	0.993	0.986	0.995	<0.001
UPRO, n (%)	1.000	0.841	1.149	<0.001	0.995	0.795	1.130	0.57
UOB, n (%)	0.802	0.716	0.926	<0.001	0.947	0.757	1.004	0.06
GBp, n (%)	1.444	1.242	1.629	<0.001	1.221	0.992	1.337	0.06

MAFLD: metabolic associated fatty liver disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting plasma glucose; TG: triglyceride; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT:  $\gamma$ -glutamyl transpeptidase; BUN: blood urea nitrogen; Scr: serum creatinine; SUA: serum uric acid; HCT: hematocrit; MCV: mean corpuscular volume; UPRO: urine protein; UOB: urine occult blood; GBp: gallbladder polyps.



## FIGURE LEHENDS

**Figure 1.** The location of the three study cities in Liaoning Province.

**Figure 2.** The prevalence of MAFLD in different cities from 2014 to 2018. The data for Dandong City in 2014 are lacking.

**Figure 3.** The prevalence of MAFLD in males is significantly higher than that in females (2014-2018). \*\*\* $P < 0.001$ .



Figure 1. The location of the three study cities in Liaoning Province.

80x71mm (300 x 300 DPI)

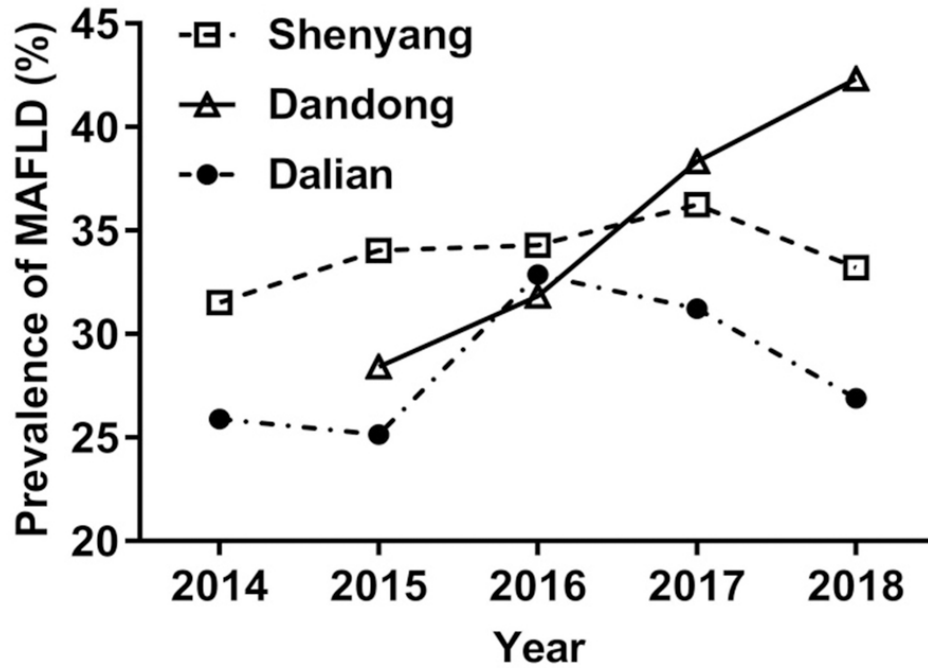


Figure 2. The prevalence of MAFLD in different cities from 2014 to 2018. The data for Dandong City in 2014 are lacking.

80x61mm (300 x 300 DPI)

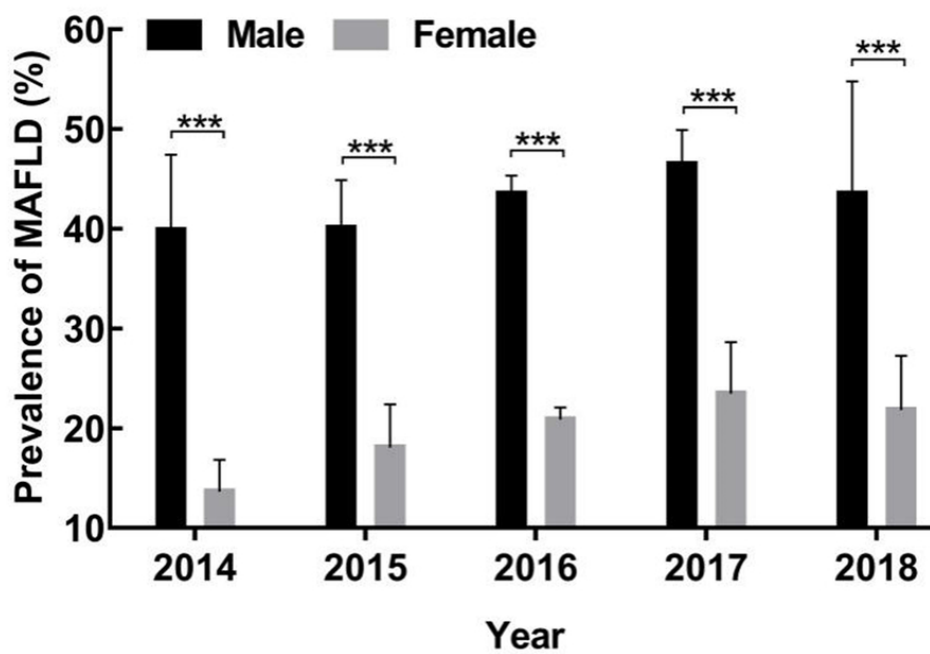


Figure 3. The prevalence of MAFLD in males is significantly higher than that in females (2014-2018).  
\*\*\*P<0.001.

79x55mm (300 x 300 DPI)

## STROBE Statement—checklist of items that should be included in reports of observational studies

Section/item	Item No	Recommendation	Reported on Page Number/Line Number	Reported on Section/Paragraph
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract		
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found		
<b>Introduction</b>				
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported		
Objectives	3	State specific objectives, including any prespecified hypotheses		
<b>Methods</b>				
Study design	4	Present key elements of study design early in the paper		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection		
Participants	6	(a) <b>Cohort study</b> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <b>Case-control study</b> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <b>Cross-sectional study</b> —Give the eligibility criteria, and the sources and methods of selection of participants		
		(b) <b>Cohort study</b> —For matched studies, give matching criteria and number of exposed and unexposed <b>Case-control study</b> —For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable		
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		
Bias	9	Describe any efforts to address potential sources of bias		
Study size	10	Explain how the study size was arrived at		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why		

bmjopen-2020-047588 on 17 February 2022. Downloaded from <http://bmjopen.bmj.com/> on April 19, 2024 by guest. Protected by copyright.

Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	
		(b) Describe any methods used to examine subgroups and interactions	
		(c) Explain how missing data were addressed	
		(d) <b>Cohort study</b> —If applicable, explain how loss to follow-up was addressed <b>Case-control study</b> —If applicable, explain how matching of cases and controls was addressed <b>Cross-sectional study</b> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) <b>Cohort study</b> —Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	<b>Cohort study</b> —Report numbers of outcome events or summary measures over time	
		<b>Case-control study</b> —Report numbers in each exposure category, or summary measures of exposure	
		<b>Cross-sectional study</b> —Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence		
Generalisability	21	Discuss the generalisability (external validity) of the study results		
<b>Other information</b>				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based		

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

For peer review only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

# BMJ Open

## Prevalence and risk factors of metabolic fatty liver disease during 2014-2018 from three cities of Liaoning province: An epidemiological survey

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-047588.R1
Article Type:	Original research
Date Submitted by the Author:	19-Oct-2021
Complete List of Authors:	Guan, Lin; The First Hospital of China Medical University, Gastroenterology Department Zhang, Xinhe; The First Hospital of China Medical University, Gastroenterology Department Tian, Haoyu; China Medical University, the 3rd Clinical Department Jin, Xing; The First Hospital of China Medical University, Gastroenterology Department Fan, Hang; Neusoft Xikang Healthcare Technology Co., Ltd., Data Operation & Management Department Wang, Ningning; The First Hospital of China Medical University, Gastroenterology Department Sun, Jing; The First Hospital of China Medical University, Gastroenterology Department Li, Dan; The First Hospital of China Medical University, Gastroenterology Department Li, Jia; Neusoft Xikang Healthcare Technology Co., Ltd., Data Operation & Management Department Wang, Xue ; The First Hospital of China Medical University, Gastroenterology Department Zeng, Zilu; The First Hospital of China Medical University, Gastroenterology Department Li, Yiling; The First Hospital of China Medical University, Gastroenterology Department
<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Public health
Keywords:	Hepatology < INTERNAL MEDICINE, DIABETES & ENDOCRINOLOGY, General endocrinology < DIABETES & ENDOCRINOLOGY

SCHOLARONE™  
Manuscripts





I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1  
2  
3  
4  
5 **Prevalence and risk factors of metabolic fatty liver disease**  
6  
7 **during 2014-2018 from three cities of Liaoning province: An**  
8  
9 **epidemiological survey**  
10  
11

12 **Running title:** Prevalence of MAFLD in Liaoning, China  
13  
14  
15  
16

17  
18 Lin Guan<sup>1¶</sup>, Xinhe Zhang<sup>1¶</sup>, Haoyu Tian<sup>2</sup>, Xing Jin<sup>1</sup>, Hang Fan<sup>3</sup>, Ningning Wang<sup>1</sup>,  
19  
20 Jing Sun<sup>1</sup>, Dan Li<sup>1</sup>, Jia Li<sup>3</sup>, Xue Wang<sup>1</sup>, Zilu Zeng<sup>1</sup>, Yiling Li<sup>1\*</sup>  
21  
22

23 <sup>1</sup>Gastroenterology Department, the First Hospital of China Medical University,  
24  
25 No.155 North Nanjing Street, Heping District, Shenyang 110001, Liaoning, China  
26  
27

28 <sup>2</sup>the 3rd Clinical Department, China Medical University, No.77 Puhe Road, Shenyang  
29  
30 North New Area, Shenyang 110122, Liaoning, China  
31  
32

33 <sup>3</sup>Data Operation & Management Department, Neusoft Xikang Healthcare Technology  
34  
35 Co., Ltd., No.175 Chuangxin Road, Hunnan New District, Shenyang 110179,  
36  
37 Liaoning, China  
38  
39

40  
41 ¶**These authors contributed equally to this work.**  
42  
43

44 **\*Corresponding author**  
45

46 Yiling Li, Gastroenterology Department, the First Hospital of China Medical  
47  
48 University, No.155 North Nanjing Street, Heping District, Shenyang 110001,  
49  
50 Liaoning, China  
51  
52

53  
54 E-mail: lyl-72@163.com  
55  
56

57 Tel: +86 13998841476  
58  
59  
60

1  
2  
3  
4  
5 **Word count:** 5203  
6

7 **Acknowledgment**  
8

9  
10 No applicable.  
11

12 **Funding:** No applicable  
13

14  
15 **Conflict of interest:** The authors declare that they have no conflict of interest.  
16

17 **Data Sharing Statement:** The data that support the findings of this study are  
18 available from the corresponding author upon reasonable request.  
19  
20  
21

22  
23 **Ethical statement:** The study was conducted in accordance with Declaration  
24 Helsinki, and the protocol was approved by the Ethics Committee of the First Hospital  
25 of China Medical University ([2020]2020-257-2). The ethics committee waived the  
26 requirement for informed consent because of the retrospective nature of the study.  
27  
28  
29  
30  
31  
32

33  
34 **Author contributions**  
35

36  
37 (I) Conception and design: LG, XHZ, YLL  
38

39 (II) Administrative support: JS, DL, YLL  
40

41 (III) Provision of study materials or patients: LG, XJ, NNW  
42

43 (IV) Collection and assembly of data: HYT, XW, ZLZ  
44

45 (V) Data analysis and interpretation: HF, JL  
46

47 (VI) Manuscript writing: All authors  
48

49 (VII) Final approval of manuscript: All authors  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## ABSTRACT

**Objectives:** To investigate the incidence and disease characteristics of metabolic fatty liver disease (MAFLD) in physical examination populations in Liaoning (China).

**Design:** Retrospective study

**Setting:** Single center.

**Participants:** Adults who underwent routine health examination at Xikang Medical Center in Liaoning Province (Shenyang, Dandong, and Dalian) between 01/2014 and 12/2018.

**Interventions:** Not applicable.

**Primary And Secondary Outcome Measures:** Not applicable.

**Results:** Among the 204,394 included subjects, 71,756 were diagnosed with MAFLD, accounting for 35.28%. The total prevalence of MAFLD in Shenyang, Dandong, and Dalian in the past five years is 35.8%, 40.41%, and 31.7%, respectively. Men had a prevalence of 46.12%, which is higher than in women (21.80%). The percentage of MAFLD in BMI <23 and  $\geq 23$  kg/m<sup>2</sup> is 6.49 % and 53.23%, respectively. In all subjects, BMI, SBP, DBP, FBG, TG, TC, LDL-C, HDL-C, ALT, AST, ALP, GGT, BUN, Scr, SUA, HCT, MCV, and UPRO are independently associated with MAFLD (all P<0.001). In lean subjects, DBP, FBG, TG, TC, LDL-C, HDL-C, AST, ALP, GGT, Scr, SUA, HCT, and MCV are independently associated with MAFLD (all P<0.001).

**Conclusions:** The prevalence of MAFLD in Liaoning is related to sex, cities with

1  
2  
3  
4  
5 different economic statuses, BMI, and multiple metabolic indicators.  
6

7 **Key words:** metabolic fatty liver disease; prevalence; risk factors; body mass index;  
8  
9 lean.  
10  
11  
12  
13  
14

### 15 **Strengths and limitations of this study**

- 16  
17 1. The study is a large-scale epidemiological survey.
- 18  
19 2. It is one of the first epidemiological articles after NAFLD renamed as MAFLD.
- 20  
21 3. The study provides time trends from three cities in China of varying economic  
22  
23 development.  
24  
25 4. The data of MAFLD with T2DM is lacking in the study.
- 26  
27 5. Although most of the metabolic risk factors have been discussed in the study, it is  
28  
29 still not comprehensive enough.  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease and is defined as the presence of  $\geq 5\%$  of hepatic steatosis (HS) (1, 2). Recently, it was recommended to rename NAFLD as metabolic (dysfunction) associated fatty liver disease (MAFLD), which might increase the awareness of the disease and decrease its stigma (3, 4). NAFLD is associated with chronic diseases like insulin resistance and/or type 2 diabetes (T2DM), dyslipidemia, hypertriglyceridemia, and hypertension (5-8). The reported prevalence of MAFLD is reported to be 24%-45%, with an estimated prevalence of 76% in patients with T2DM (9). For non-obese patients, MAFLD is associated with elevated triglyceride (TG) levels, increased waist circumference, and insulin resistance (10).

Chinese individuals have substantially higher risks of MAFLD, even at much lower BMI levels, compared with the US population (11). Factors like waist circumference, T2DM, increased TG, low high-density lipoprotein (HDL)-cholesterol, and metabolic syndrome are known to be predictive factors for MAFLD in adults, and the metabolic syndrome is considered as a strong predictive factor (12, 13). MAFLD is also associated with dyslipidemia characterized by high TG, high low-density lipoprotein (LDL), and low HDL-cholesterol levels (14). Determining the risk factors associated with a worse prognosis is essential for improving the therapeutic strategies.

1  
2  
3  
4  
5 Since the 21st century, the prevalence of MAFLD in China has increased  
6  
7 significantly to reach about one in three mainland Chinese residents (12). A recent  
8  
9 meta-analysis showed that the incidence of MAFLD is higher in northern China  
10  
11 (35.78%) and lower in northwestern China (21.52%) (15). Among the provinces in  
12  
13 northern China, Heilongjiang has the highest incidence, with up to 50.48% (15).  
14  
15 Nevertheless, the results might be biased due to the small number of studies, yet  
16  
17 MAFLD incidence in northern China is significantly higher than that in the southern  
18  
19 provinces. In addition, the risk of MAFLD-related mortality has also increased  
20  
21 significantly, mainly due to diseases associated with liver fibrosis (16). MAFLD has  
22  
23 become an important health issue affecting the Chinese population, increasing the  
24  
25 socioeconomic burden (11, 12, 15). Therefore, Chinese medical professionals and  
26  
27 stakeholders urgently need to carry out early scientific prevention and control of  
28  
29 MAFLD. Multiple studies have shown that MAFLD is a heterogeneous entity and that  
30  
31 its development is related to sex, age, race, mild-to-moderate alcohol consumption,  
32  
33 dietary intake, lifestyle, obesity, metabolism, genetic variation, and education (11, 12,  
34  
35 15, 16). With uneven economic development and diverse lifestyles among the  
36  
37 different provinces, the epidemiology of MAFLD in China has marked regional  
38  
39 differences. By understanding the epidemiology of MAFLD in Liaoning Province, we  
40  
41 can conduct targeted education and clinical research for precise prevention and  
42  
43 control of MAFLD.  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55

56 There have been no data from large-scale epidemiological investigations of  
57  
58  
59  
60

1  
2  
3  
4  
5 MAFLD in Liaoning province in northern China in the past ten years. Therefore, this  
6  
7 retrospective study aims to investigate the incidence and disease characteristics of  
8  
9  
10 MAFLD in physical examination populations in Liaoning. The study uses physical  
11  
12 examination data of residents collected from 2014 to 2018 in three cities with  
13  
14 different economic levels in Liaoning (Shenyang, Dandong, and Dalian).  
15  
16  
17  
18  
19

## 20 **METHODS**

### 21 **Study subjects**

22  
23 This is a retrospective study of adults who underwent routine health examination  
24  
25 at Xikang Medical Center in Liaoning Province (which has clinics in Shenyang,  
26  
27 Dandong, and Dalian) between January 2014 and December 2018. The study was  
28  
29 conducted in accordance with Declaration Helsinki, and the protocol was approved by  
30  
31 the Ethics Committee of the First Hospital of China Medical University  
32  
33 ([2020]2020-257-2). The ethics committee waived the requirement for informed  
34  
35 consent because of the retrospective nature of the study.  
36  
37  
38  
39  
40  
41  
42

43  
44 The three cities are from different parts of the province (North, South, and East  
45  
46 (Figure 1), and they have different economic levels. Shenyang, situated in North  
47  
48 Liaoning Province, is a highly developed inland city, while Dalian in South Liaoning  
49  
50 is a developed coastal city. Dandong, in the east of Liaoning Province, is a poorly  
51  
52 developed city bordering North Korea.  
53  
54  
55

56  
57 The inclusion criteria are 1) >18 years of age; 2) have been living in Shenyang,  
58  
59  
60



1  
2  
3  
4  
5 Dalian, or Dandong for at least 5 years; 3) participate in the annual physical  
6  
7 examination; and 4) no missing data (as listed in Table 1). The exclusion criteria are  
8  
9  
10 1) liver cirrhosis; 2) liver cancer; 3) any liver ultrasound lesions; or 4) no ultrasound  
11  
12 examination. For individuals with more than one examination during the study period,  
13  
14  
15 only the first examination is included in this study.  
16

17  
18 The selected patients are divided into MAFLD group and non-MAFLD group  
19  
20 based on the ultrasound evidence of hepatic steatosis in addition to one of the  
21  
22 following two criteria, namely overweight/obesity ( $\text{BMI} \geq 23 \text{ kg/m}^2$ , according to the  
23  
24 standards recommended by the World Health Organization for Asians (18) ) or  $\text{BMI}$   
25  
26  $< 23 \text{ kg/m}^2$  with at least two evidence of metabolic dysregulation, such as Blood  
27  
28 pressure  $\geq 130/85 \text{ mmHg}$ ,  $\text{TG} \geq 1.70 \text{ mmol/L}$ ,  $\text{HDL-cholesterol} < 1.0 \text{ mmol/L}$  for  
29  
30 men and  $< 1.3 \text{ mmol/L}$  for women, or prediabetes (fasting blood glucose levels 5.6 to  
31  
32 6.9 mmol/L) (19). Unfortunately, patients with presence of T2DM who received  
33  
34 medical intervention were not included in this study, due to serious incomplete  
35  
36 records of medical history.  
37  
38  
39  
40  
41  
42

### 43 **Patient and Public Involvement**

44  
45 No patient involved  
46  
47

### 48 **Physical examination**

49  
50 All physical examinations included in this study are part of the routine  
51  
52 examination. Blood pressure measurements, including systolic blood pressure (SBP)  
53  
54 and diastolic blood pressure (DBP), are taken twice after the participants have been  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5 sitting, in a calm state, for at least 5 min, using an electronic sphygmomanometer  
6  
7 (HEM-7200, OMRON Healthcare, Kyoto, Japan). Height and weight are measured in  
8  
9  
10 the morning on an empty stomach, and body mass index (BMI) is as kg/m<sup>2</sup>.  
11  
12  
13  
14

### 15 **Laboratory examination**

16  
17 All physical blood tests included in this study are part of the routine examination.  
18  
19 Anterior cubital vein blood is drawn in the fasting state (at least 8 h). A midcourse  
20  
21 morning urine specimen is also taken. Routine blood panel, liver function, kidney  
22  
23 function, serum uric acid (SUA), fasting blood glucose (FBG), blood lipids, and  
24  
25 routine urine analysis are assessed using a 7600 autoanalyzer (Hitachi, Tokyo, Japan).  
26  
27  
28  
29  
30  
31  
32

### 33 **Color Doppler ultrasound of the liver and gallbladder**

34  
35 A liver ultrasound is part of the routine examination. It is performed by two  
36  
37 experienced ultrasound radiologists with at least 5 years of experience and using an  
38  
39 IU 22 system (Philips, Best, The Netherlands). An individual is diagnosed with  
40  
41 hepatic steatosis when the ultrasound examination shows that the liver has fatty liver  
42  
43 changes (hyperechogenicity due to increased acoustic interface caused by the  
44  
45 intracellular accumulation of lipid vesicles, blurring of vascular margins, increased  
46  
47 liver size, and increased acoustic attenuation (10, 17)).  
48  
49  
50  
51  
52  
53  
54  
55  
56

### 57 **Statistical analysis**

1  
2  
3  
4  
5 R 3.5.3 and R Commander 2.5-3 were used for statistical analysis. The  
6  
7 categorical data are expressed as n (%) and were analyzed using the chi-square test.  
8  
9  
10 The continuous variables conforming to the normal distribution (according to the  
11  
12 Kolmogorov-Smirnov test) are expressed as means  $\pm$  standard deviations and were  
13  
14 analyzed using Student's t-test. Non-normally distributed continuous variables are  
15  
16 presented as medians (interquartile range (IQR)) and were analyzed using the  
17  
18 Mann-Whitney U-test. The factors associated with MAFLD were identified using  
19  
20 univariable analyses. Variables with P-values  $<0.05$  were included in a multivariable  
21  
22 logistic regression model. P-values  $<0.05$  were considered statistically significant.  
23  
24  
25  
26  
27  
28  
29

## 30 RESULTS

### 31 Characteristics of the subjects

32  
33 A total of 284,129 subjects were examined during the study period, and 204,394  
34  
35 met the inclusion criteria. Table 1 presents the characteristics of the subjects. The  
36  
37 mean age is  $39.6 \pm 13.6$  years. The numbers of men and women are 111,782 and  
38  
39 92,612, respectively. The mean age of the men is  $38.8 \pm 13.7$  years, and that of women  
40  
41 is  $40.5 \pm 13.3$  years. Shenyang includes 78,329 subjects, who were  $39.3 \pm 12.7$  years of  
42  
43 age. The clinic in Dandong did not perform routine health examinations in 2014.  
44  
45 Dandong includes 42,039 subjects, who were  $47.8 \pm 14.1$  years. Finally, Dalian has  
46  
47 84,026 subjects; they were  $36.3 \pm 12.7$  years.  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

### MAFLD in the healthy population

Among the 204,394 included subjects, 71,756 were diagnosed with MAFLD, accounting for 35.28% (Table 1). The prevalence of MAFLD increases with the age groups ( $P<0.001$ ), is higher in males than in females ( $P<0.001$ ), is higher in overweight/obese subjects than in lean ones ( $P<0.001$ ), and is higher in Dandong, followed by Shenyang and Dalian ( $P<0.001$ ) (Table 1). The prevalence of MAFLD in Shenyang, Dandong, and Dalian in the past five years was 36.83%, 40.42%, and 31.78%, respectively.

### MAFLD over time

The total prevalence of MAFLD from 2014 to 2018 is 30.01%, 30.11%, 33.22%, 34.58%, and 32.19%, respectively. The prevalence of MAFLD over the 5 years mainly increased in the 30-39 groups ( $P=0.006$ ), and both in males ( $P=0.029$ ) and in females ( $P=0.035$ ) (Table 2). The prevalence of MAFLD in Shenyang in the past 5 years was basically consistent with the general trend in Liaoning. The MAFLD prevalence in Dandong showed a significant increase annually in the past 4 years. The MAFLD prevalence in Dalian increased substantially in 2016, but it declined annually in 2017 and 2018 (Figure 2). The prevalence rate in men and women in the past five years is basically consistent with the general trend of MAFLD in Liaoning (Figure 3). As age increases, MAFLD prevalence in Liaoning increases.

## **Biomarkers and MAFLD**

Table 3 presents the biomarkers in all subjects and according to lean/overweight-obese. Compared with the non-MAFLD group, the subjects with MAFLD have higher SBP, DBP, FBG, TG, TC, LDL-C, ALT, AST, ALP, GGT, BUN, Scr, and SUA, higher frequencies of UPRO and GBp, lower HDL-C, HCT, and MCV, and lower frequency of UOB (all  $P<0.001$ ). The same tendencies are observed in lean subjects, except that there is no difference in UPRO ( $P=0.86$ ).

## **Factors associated with MAFLD**

Table 4 presents the univariable and multivariable analyses of the factors associated with MAFLD. In all subjects, BMI, SBP, DBP, FBG, TG, TC, LDL-C, HDL-C, ALT, AST, ALP, GGT, BUN, Scr, SUA, HCT, MCV, and UPRO are independently associated with MAFLD (all  $P<0.001$ ), while UOB ( $P=0.47$ ) and GBp ( $P=0.21$ ) are not. In lean subjects, DBP, FBG, TG, TC, LDL-C, HDL-C, AST, ALP, GGT, Scr, SUA, HCT, and MCV are independently associated with MAFLD (all  $P<0.001$ ), while SBP ( $P=0.51$ ), ALT ( $P=0.27$ ), BUN ( $P=0.16$ ), UPRO ( $P=0.57$ ), UOB ( $P=0.06$ ), and GBp ( $P=0.06$ ) are not.

## **DISCUSSION**

The present study shows that the prevalence of MAFLD in Shenyang, Dandong, and Dalian varied and that higher BMI and age play significant roles in the

1  
2  
3  
4  
5 development of the disease. In addition, biomarkers like DBP, FBG, TG, LDL-C,  
6  
7 ALT, GGT, BUN, SUA, HCT, UPRO, GBs, and GBp are independently and  
8  
9 positively correlated with the prevalence of MAFLD, whereas HDL-C and MCV are  
10  
11 negatively correlated. Therefore, the prevalence of MAFLD in Liaoning is related to  
12  
13 sex, cities with different economic statuses, BMI, and multiple metabolic indicators.  
14  
15

16  
17  
18 The increasing trend in the prevalence of MAFLD follows the level of  
19  
20 industrialization and urbanization. At present, China is the fastest-growing major  
21  
22 economy in the world and displays the problems associated with a westernized diet,  
23  
24 sedentary lifestyle, and population aging, which are associated with MAFLD. Studies  
25  
26 have shown that the increase in the total annual MAFLD prevalence in China is  
27  
28 consistent with the improvement in the per capita GDP (20). An increase in morbidity  
29  
30 in various regions of mainland China is related to the increase in per capita GDP, but  
31  
32 the area with the highest per capita GDP ( $\geq$ \$13,000) does not exhibit an increased  
33  
34 incidence of MAFLD (21). According to the National Bureau of Statistics of China,  
35  
36 the per capita GDP of Liaoning Province has been ranking first in Northeast China in  
37  
38 the past five years, but it is still in the lower-middle level nationally. This study shows  
39  
40 that the prevalence of MAFLD in Liaoning (35.1%) is slightly higher than the overall  
41  
42 prevalence of MAFLD in China (29.2%) (12). This study selected two economically  
43  
44 developed cities (Dalian and Shenyang) and one city with moderate development  
45  
46 (Dandong). The prevalence of MAFLD in these three cities is inversely proportional  
47  
48 to the level of urban economic development. The prevalence of MAFLD in Dalian is  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5 lower than that in Shenyang. A reason might be that Dalian is a coastal city, with  
6  
7 dietary habits different from that of inland cities.  
8  
9

10 Differences in age are also involved. The prevalence of MAFLD in the 20-29  
11  
12 years group is 17.9%, while the prevalence in the >60 years group is 45.6%, which is  
13  
14 in alignment with previous studies that show that age plays a crucial factor in  
15  
16 MAFLD (11, 12, 15).  
17  
18

19  
20 This study found that the overall prevalence of MAFLD in men is higher than  
21  
22 that in women, which is basically consistent with the findings in other regions in  
23  
24 China (22). The prevalence of MAFLD in middle-aged men is highest and peaks at  
25  
26 40-49 years of age (50.27%). This high prevalence might be related to high stress,  
27  
28 irregular work and rest, and decreased metabolism among middle-aged men. The  
29  
30 prevalence of MAFLD in women over 50 years of age is significantly higher, which  
31  
32 relates to the age range of menopause.  
33  
34  
35  
36  
37

38 Obesity is closely related to metabolic-related diseases such as MAFLD. This  
39  
40 study confirmed that  $BMI \geq 23 \text{ kg/m}^2$  is an independent risk factor for MAFLD in  
41  
42 Liaoning. Therefore, for overweight and obese people, it is necessary to improve diet  
43  
44 and exercise management, even with the help of drugs or surgery if needed. It has  
45  
46 been reported that the global prevalence of lean-MAFLD is 5%-26% (23). In the  
47  
48 study, the prevalence of lean-MAFLD is 10.75%, which is similar to previous results  
49  
50  
51  
52  
53  
54 (24).  
55  
56

57 In this study, both lean-MAFLD and non-lean-MAFLD were closely related to  
58  
59  
60

1  
2  
3  
4  
5 metabolic indicators. Those metabolic indicators are also associated with T2DM,  
6  
7 metabolic syndrome, obesity, and liver diseases, as supported by previous studies (11,  
8  
9 12, 15, 22-24). In addition to obesity, the variation in the prevalence of MAFLD  
10  
11 follows the epidemic trends of T2DM and MetS. The prevalence of MAFLD in  
12  
13 hyperlipidemia and T2DM patients is higher, reaching 27%-92% and 28%-70%,  
14  
15 respectively. Patients with MAFLD also often have hyperlipidemia, hypertension,  
16  
17 T2DM, and metabolic syndrome (25). In this study, logistic regression analysis found  
18  
19 that DBP, TG, LDL-C, FBG, and SUA were independent risk factors for MAFLD, but  
20  
21 HDL-C is independently associated with MAFLD. Therefore, paying attention to  
22  
23 hyperlipidemia, hypertension, and T2DM should have important effects on the  
24  
25 prevention and treatment of MAFLD. Regarding the correlation between SUA and  
26  
27 MAFLD, SUA elevation is one of the risk factors for MAFLD (26).

28  
29  
30  
31  
32  
33  
34  
35  
36 Although it was not examined in this study, genetic susceptibility is involved  
37  
38 in MAFLD. Polymorphisms in PNPLA3 (27), SREBF-2 (28), CETP (28, 29), and  
39  
40 APOC3 (30) have been found to be associated with lean-MAFLD. In addition to  
41  
42 genetic polymorphisms, lean-MAFLD people have increased bile acid and FXR  
43  
44 activity due to metabolic abnormalities and changes in intestinal microbial  
45  
46 composition (31, 32). Those factors should be examined in future studies.

47  
48  
49  
50  
51 This study has limitations. Even if the examinations were performed at the same  
52  
53 clinical company, they were performed at three different physical locations and over 5  
54  
55 years. Biases due to the different locations and changes in practice over time cannot  
56  
57  
58  
59  
60



1  
2  
3  
4  
5 be excluded. In addition, ultrasound is operator-dependent, and a bias in the diagnosis  
6  
7 of MAFLD cannot be excluded. Finally, this was a cross-sectional study that cannot  
8  
9 provide any causal relationship between MAFLD and the associated factors.  
10  
11

12 In conclusion, the prevalence of MAFLD in Liaoning is related to sex, cities with  
13  
14 different economic statuses, BMI, and multiple metabolic indicators. Longitudinal  
15  
16 studies are necessary to determine the factors associated with the development of  
17  
18 MAFLD.  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30

## 31 REFERENCES

- 32  
33 1. Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of  
34  
35 nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence,  
36  
37 and outcomes. *Hepatology*. 2016;64:73-84.  
38  
39
- 40  
41 2. Stal P. Liver fibrosis in non-alcoholic fatty liver disease - diagnostic challenge  
42  
43 with prognostic significance. *World J Gastroenterol*. 2015;21:11077-87.  
44  
45
- 46  
47 3. Eslam M, Sanyal AJ, George J, et al. MAFLD: A Consensus-Driven Proposed  
48  
49 Nomenclature for Metabolic Associated Fatty Liver Disease. *Gastroenterology*.  
50  
51 2020;158:1999-2014 e1.  
52  
53
- 54  
55 4. Fouad Y, Waked I, Bollipo S, et al. What's in a name? Renaming 'NAFLD' to  
56  
57 'MAFLD'. *Liver Int*. 2020;40:1254-61.  
58  
59  
60

- 1  
2  
3  
4  
5 5. Pai RK. NAFLD Histology: a Critical Review and Comparison of Scoring  
6  
7 Systems. *Curr Hepatol Rep.* 2019;18:473-81.  
8  
9
- 10 6. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and  
11  
12 natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in  
13  
14 adults. *Aliment Pharmacol Ther.* 2011;34:274-85.  
15  
16
- 17 7. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of  
18  
19 non-alcoholic fatty liver disease: practice guideline by the American  
20  
21 Gastroenterological Association, American Association for the Study of Liver  
22  
23 Diseases, and American College of Gastroenterology. *Gastroenterology.*  
24  
25 2012;142:1592-609.  
26  
27
- 28 8. Non-Alcoholic Fatty Liver Disease: Assessment and Management. National  
29  
30 Institute for Health and Care Excellence: Guidance. London 2016.  
31  
32
- 33 9. Rinella ME. Nonalcoholic fatty liver disease: a systematic review. *JAMA.*  
34  
35 2015;313:2263-73.  
36  
37
- 38 10. Shen FF, Lu LG. Advances in noninvasive methods for diagnosing nonalcoholic  
39  
40 fatty liver disease. *J Dig Dis.* 2016;17:565-71.  
41  
42
- 43 11. Zhou J, Zhou F, Wang W, et al. Epidemiological Features of NAFLD From 1999  
44  
45 to 2018 in China. *Hepatology.* 2020;71:1851-64.  
46  
47
- 48 12. Zhou F, Zhou J, Wang W, et al. Unexpected Rapid Increase in the Burden of  
49  
50 NAFLD in China From 2008 to 2018: A Systematic Review and Meta-Analysis.  
51  
52 *Hepatology.* 2019;70:1119-33.  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3  
4  
5 13. Caballeria L, Auladell MA, Toran P, et al. Risk factors associated with  
6 non-alcoholic fatty liver disease in subjects from primary care units. A case-control  
7 study. *BMC Gastroenterol.* 2008;8:44.  
8  
9  
10  
11  
12 14. Hartmann P, Schnabl B. Risk factors for progression of and treatment options for  
13 NAFLD in children. *Clin Liver Dis (Hoboken).* 2018;11:11-5.  
14  
15 15. Wu Y, Zheng Q, Zou B, et al. The epidemiology of NAFLD in Mainland China  
16 with analysis by adjusted gross regional domestic product: a meta-analysis. *Hepatol*  
17 *Int.* 2020;14:259-69.  
18  
19  
20  
21 16. Dulai PS, Singh S, Patel J, et al. Increased risk of mortality by fibrosis stage in  
22 nonalcoholic fatty liver disease: Systematic review and meta-analysis. *Hepatology.*  
23 2017;65:1557-65.  
24  
25 17. Mahale AR, Prabhu SD, Nachiappan M, et al. Clinical relevance of reporting  
26 fatty liver on ultrasound in asymptomatic patients during routine health checkups. *J*  
27 *Int Med Res.* 2018;46:4447-54.  
28  
29  
30  
31 18. Consultation WHOE. Appropriate body-mass index for Asian populations and its  
32 implications for policy and intervention strategies. *Lancet.* 2004;363:157-63.  
33  
34 19. Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic  
35 associated fatty liver disease: an international expert consensus statement. *Journal of*  
36 *Hepatology.* 2020;73(1):202-209.  
37  
38  
39  
40  
41 20. Cai J, Zhang XJ, Li H. Progress and challenges in the prevention and control of  
42 nonalcoholic fatty liver disease. *Med Res Rev.* 2019;39:328-48.  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3  
4  
5 21. Fan JG, Kim SU, Wong VW. New trends on obesity and NAFLD in Asia. *J*  
6  
7 *Hepatol.* 2017;67:862-73.  
8  
9  
10 22. Zhu JZ, Zhou QY, Wang YM, et al. Prevalence of fatty liver disease and the  
11  
12 economy in China: A systematic review. *World J Gastroenterol.* 2015;21:5695-706.  
13  
14  
15 23. Wang AY, Dhaliwal J, Mouzaki M. Lean non-alcoholic fatty liver disease. *Clin*  
16  
17 *Nutr.* 2019;38:975-81.  
18  
19  
20 24. Shi Y, Wang Q, Sun Y, et al. The Prevalence of Lean/Nonobese Nonalcoholic  
21  
22 Fatty Liver Disease: A Systematic Review and Meta-Analysis. *J Clin Gastroenterol.*  
23  
24 2020;54:378-87.  
25  
26  
27  
28 25. Fan JG, Wei L, Zhuang H, et al. Guidelines of prevention and treatment of  
29  
30 nonalcoholic fatty liver disease (2018, China). *J Dig Dis.* 2019;20:163-73.  
31  
32  
33 26. Ma Z, Xu C, Kang X, et al. Changing trajectories of serum uric acid and risk of  
34  
35 non-alcoholic fatty liver disease: a prospective cohort study. *J Transl Med.*  
36  
37 2020;18:133.  
38  
39  
40  
41 27. Musso G, Cassader M, Bo S, et al. Sterol regulatory element-binding factor 2  
42  
43 (SREBF-2) predicts 7-year NAFLD incidence and severity of liver disease and  
44  
45 lipoprotein and glucose dysmetabolism. *Diabetes.* 2013;62:1109-20.  
46  
47  
48  
49 28. Adams LA, Marsh JA, Ayonrinde OT, et al. Cholesteryl ester transfer protein  
50  
51 gene polymorphisms increase the risk of fatty liver in females independent of  
52  
53 adiposity. *J Gastroenterol Hepatol.* 2012;27:1520-7.  
54  
55  
56  
57 29. Petersen KF, Dufour S, Hariri A, et al. Apolipoprotein C3 gene variants in  
58  
59  
60

1  
2  
3  
4  
5 nonalcoholic fatty liver disease. *N Engl J Med.* 2010;362:1082-9.  
6

7  
8 30. Li C, Guo P, Okekunle AP, et al. Lean non-alcoholic fatty liver disease patients  
9  
10 had comparable total caloric, carbohydrate, protein, fat, iron, sleep duration and  
11  
12 overtime work as obese non-alcoholic fatty liver disease patients. *J Gastroenterol*  
13  
14  
15 *Hepatol.* 2019;34:256-62.  
16

17  
18 31. Safari Z, Gerard P. The links between the gut microbiome and non-alcoholic fatty  
19  
20 liver disease (NAFLD). *Cell Mol Life Sci.* 2019;76:1541-58.  
21

22  
23 32. Suk KT, Kim DJ. Gut microbiota: novel therapeutic target for nonalcoholic fatty  
24  
25 liver disease. *Expert Rev Gastroenterol Hepatol.* 2019;13:193-204.  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**Table 1.** Characteristics of the patients with non-MAFLD and MAFLD

Subgroups	Age (years), Mean±SD	All N=204,3 94	Non-MAFLD n=132,638	MAFLD n=71,7 56	Prevalence (%)	P
Age						<0.001
20-29		22,822	18,728	4094	17.94	
30-39		80,227	54,671	25,556	31.85	
40-49		44,464	27,913	16,551	37.22	
50-59		30,861	17,173	13,688	44.35	
≥60		26,020	14,153	11,867		
Sex						<0.001
Male	38.8±13.7	111,782	60,222	51,560	46.13	
Female	40.5±13.3	92,612	72,416	20,196	21.81	
BMI (kg/m <sup>2</sup> )						<0.001
<23		79,271	74,124	5147	6.49	
≥23		125,123	58,514	66,609	53.23	
City						<0.001

---

01

Shenya	39.3±12.7	78,329	50,265	28,064	36.83
ng					
Dando	47.8±14.1	42,039	25,048	16,991	40.42
ng					
Dalian	36.3±12.7	84,026	57,325	26,701	31.78
Overall	39.6±13.6	204,394	132,638	71,756	35.11

---

MAFLD: metabolic-associated fatty liver disease; BMI: body mass index.

**Table 2.** Changes in the prevalence of MAFLD over time (2014-2018)

Subgroups	Year, %					P
	2014	2015	2016	2017	2018	
<b>Age (years)</b>						
20-29	16.43	17.20	17.30	18.82	18.18	0.081
30-39	29.24	28.60	31.05	33.37	34.33	0.006
40-49	35.65	34.50	35.40	39.04	38.69	0.200
50-59	46.32	39.40	41.67	46.96	45.44	0.636
≥60	44.83	40.65	45.34	48.39	46.50	0.234
<b>Sex</b>						
Male	42.60	42.63	44.36	48.12	48.45	0.029
Female	14.85	19.33	21.49	24.63	22.67	0.035
<b>BMI (kg/m<sup>2</sup>)</b>						
<23	5.08	5.35	6.68	7.36	6.80	0.058
≥23	54.93	50.37	52.15	55.08	53.76	0.510
<b>City</b>						
Shenyang	34.89	34.80	34.27	37.36	36.92	0.182
Dandong	-	30.06	34.29	42.66	44.17	0.039
Dalian	26.36	29.00	33.20	32.36	32.98	0.048
Overall	30.01	30.11	33.22	34.58	32.19	<0.001

BMI: body mass index.



**Table 3.** Comparison of the metabolic tests between non-MAFLD and MAFLD

Variables	Overall			Lean (BMI<23)			Overweight (BMI >=23)		
	Non-MAFLD	MAFLD	P	Non-MAFLD	MAFLD	P	Non-MAFLD	MAFLD	P
SBP, mmHg	118±18	129±19	<0.001	114±16	122±19	<0.001	123±18	129±19	<0.001
DBP, mmHg	70±11	77±13	<0.001	67±10	73±12	<0.001	72±12	77±13	<0.001
FBG, mmol/L	5.15±1.30	5.82±1.63	<0.001	5.04±1.22	5.63±1.65	<0.001	5.3±1.18	5.83±1.63	<0.001
TG, mmol/L	1.07±0.85	2.12±1.73	<0.001	0.91±0.64	1.79±1.46	<0.001	1.28±1.01	2.14±1.75	<0.001
TC, mmol/L	4.41±1.43	4.96±1.34	<0.001	4.29±1.41	4.94±1.36	<0.001	4.55±1.43	4.97±1.34	<0.001
LDL-C, mmol/L	1.99±1.34	2.42±1.43	<0.001	1.9±1.28	2.46±1.38	<0.001	2.09±1.40	2.42±1.43	<0.001
HDL-C, mmol/L	1.01±0.71	0.9±0.60	<0.001	1.06±0.73	0.99±0.64	<0.001	0.93±0.67	0.9±0.60	<0.001
ALT, U/L	19.37±17.28	36.58±27.98	<0.001	17.09±14.34	27.89±21.40	<0.001	22.19±19.98	37.2±28.29	<0.001
AST, U/L	19.59±11.18	25.85±13.56	<0.001	18.76±10.03	23.55±13.08	<0.001	20.62±12.38	26.02±13.57	<0.001
ALP, U/L	7.01±22.44	9.62±25.91	<0.001	5.51±20.85	8.48±24.35	<0.001	8.98±24.13	9.7±26.02	<0.001

GGT, U/L	18.42±24.10	39.36±42.82	<0.001	15.54±20.76	31.41±48.78	<0.001	21.99±27.27	37.71±42.34	<0.001
BUN, mmol/L	4.32±1.97	4.8±1.80	<0.001	4.17±1.90	4.65±1.77	<0.001	4.51±2.04	4.81±1.80	<0.001
Scr, µmol/L	58.57±26.43	66.63±24.76	<0.001	56.12±25.14	62.05±22.61	<0.001	61.62±27.66	66.96±24.88	<0.001
SUA, µmol/L	283.17±125.06	369.05±135.06	<0.001	263.87±116.14	330.07±123.40	<0.001	307.09±131.43	371.84±135.42	<0.001
HCT, %	21.57±21.35	20.32±22.42	<0.001	21.95±20.97	20.36±21.90	<0.001	21.1±21.80	20.32±22.46	<0.001
MCV, fl	47.2±44.74	41.66±44.42	<0.001	48.78±44.68	42.74±44.70	<0.001	45.23±44.74	41.58±44.40	<0.001
UPRO, n (%)	6.70%	9.20%	<0.001	6.30%	6.20%	0.86	7.30%	9.40%	<0.001
UOB, n (%)	11.10%	8.80%	<0.001	11.20%	9.40%	0.00	10.80%	8.80%	<0.001
GBp, n (%)	7.40%	8.90%	<0.001	6.20%	8.60%	<0.001	8.90%	9.70%	<0.001

SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting plasma glucose; TG: triglycerides; TC: total cholesterol;

LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; ALT: alanine aminotransferase; AST:

aspartate aminotransferase; ALP: alkaline phosphatase; GGT:  $\gamma$ -glutamyl transpeptidase; BUN: blood urea nitrogen; Scr: serum

creatinine; SUA: serum uric acid; HCT: hematocrit; MCV: mean corpuscular volume; UPRO: urine protein; UOB: urine occult blood;

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

GBp: gallbladder polyps.

For peer review only

**Table 4.** Multivariable analyses of the factors associated with MAFLD

Variables	Univariable logistical regression			Multivariable logistical regression				
	OR	OR (95% CI)	P	OR	OR (95% CI)	P		
<b>MAFLD</b>								
BMI (kg/m <sup>2</sup> )								
<23	0.057	0.056	0.060	<0.001	0.125	0.119	0.130	<0.001
≥23								
SBP, mmHg	1.033	1.033	1.034	<0.001	1.003	1.003	1.005	<0.001
DBP, mmHg	1.053	1.052	1.054	<0.001	1.014	1.012	1.016	<0.001
FBG, mmol/L	1.541	1.520	1.559	<0.001	1.122	1.104	1.131	<0.001
TG, mmol/L	2.899	2.854	2.953	<0.001	1.651	1.627	1.691	<0.001
TC, mmol/L	1.378	1.365	1.392	<0.001	0.879	0.866	0.893	<0.001
LDL-C, mmol/L	1.267	1.255	1.277	<0.001	1.231	1.216	1.259	<0.001

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

HDL-C, mmol/L	0.799	0.785	0.813	<0.001	0.717	0.690	0.740	<0.001
ALT, U/L	1.040	1.038	1.040	<0.001	1.036	1.035	1.038	<0.001
AST, U/L	1.055	1.054	1.057	<0.001	0.979	0.977	0.981	<0.001
ALP, U/L	1.004	1.004	1.005	<0.001	0.998	0.998	1.000	<0.001
GGT, U/L	1.025	1.025	1.026	<0.001	1.002	1.002	1.002	<0.001
BUN, mmol/L	1.145	1.139	1.154	<0.001	1.019	1.007	1.032	<0.001
Scr, µmol/L	1.014	1.013	1.014	<0.001	0.995	0.994	0.996	<0.001
SUA, µmol/L	1.005	1.005	1.006	<0.001	1.003	1.002	1.003	<0.001
HCT, %	0.998	0.997	0.998	<0.001	1.006	1.003	1.008	<0.001
MCV, fl	0.997	0.997	0.997	<0.001	0.994	0.993	0.995	<0.001
UPRO, n (%)	1.407	1.342	1.462	<0.001	1.112	1.069	1.198	<0.001
UOB, n (%)	0.762	0.749	0.811	<0.001	1.000	0.933	1.033	0.47
GBp, n (%)	1.233	1.176	1.280	<0.001	1.026	0.981	1.090	0.21

**Lean (BMI<23), MAFLD**

SBP, mmHg	1.027	1.025	1.029	<0.001	1.999	0.995	1.002	0.51
DBP, mmHg	1.046	1.042	1.048	<0.001	1.018	1.012	1.024	<0.001
FBG, mmol/L	1.393	1.346	1.424	<0.001	1.098	1.064	1.133	<0.001
TG, mmol/L	2.771	2.642	2.891	<0.001	1.878	1.781	1.968	<0.001
TC, mmol/L	1.498	1.465	1.565	<0.001	0.891	0.860	0.941	<0.001
LDL-C, mmol/L	1.455	1.393	1.485	<0.001	1.372	1.301	1.430	<0.001
HDL-C, mmol/L	1.890	0.831	0.920	<0.001	0.695	0.631	0.741	<0.001
ALT, U/L	1.028	1.026	1.030	<0.001	1.025	1.024	1.030	0.27
AST, U/L	1.028	1.026	1.030	<0.001	0.971	0.969	0.980	<0.001
ALP, U/L	1.006	1.004	1.007	<0.001	1.000	0.998	1.001	<0.001
GGT, U/L	1.016	1.016	1.018	<0.001	1.001	1.001	1.004	<0.001
BUN, mmol/L	1.150	1.133	1.182	<0.001	1.022	0.990	1.059	0.16

Scr, $\mu\text{mol/L}$	1.010	1.008	1.012	<0.001	0.898	0.987	0.993	<0.001
SUA, $\mu\text{mol/L}$	1.005	1.005	1.006	<0.001	1.004	1.004	1.004	<0.001
HCT, %	0.996	0.995	0.998	<0.001	1.016	1.005	1.023	<0.001
MCV, fl	0.997	0.996	0.998	<0.001	0.993	0.986	0.995	<0.001
UPRO, n (%)	1.000	0.841	1.149	<0.001	0.995	0.795	1.130	0.57
UOB, n (%)	0.802	0.716	0.926	<0.001	0.947	0.757	1.004	0.06
GBp, n (%)	1.444	1.242	1.629	<0.001	1.221	0.992	1.337	0.06

MAFLD: metabolic associated fatty liver disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting plasma glucose; TG: triglyceride; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT:  $\gamma$ -glutamyl transpeptidase; BUN: blood urea nitrogen; Scr: serum creatinine; SUA: serum uric acid; HCT: hematocrit; MCV: mean corpuscular volume; UPRO: urine protein; UOB: urine occult blood; GBp: gallbladder polyps.

## FIGURE LEHENDS

**Figure 1.** The location of the three study cities in Liaoning Province.

**Figure 2.** The prevalence of MAFLD in different cities from 2014 to 2018. The data for Dandong City in 2014 are lacking.

**Figure 3.** The prevalence of MAFLD in males is significantly higher than that in females (2014-2018). \*\*\* $P < 0.001$ .



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



Figure 1. The location of the three study cities in Liaoning Province.  
80x71mm (600 x 600 DPI)

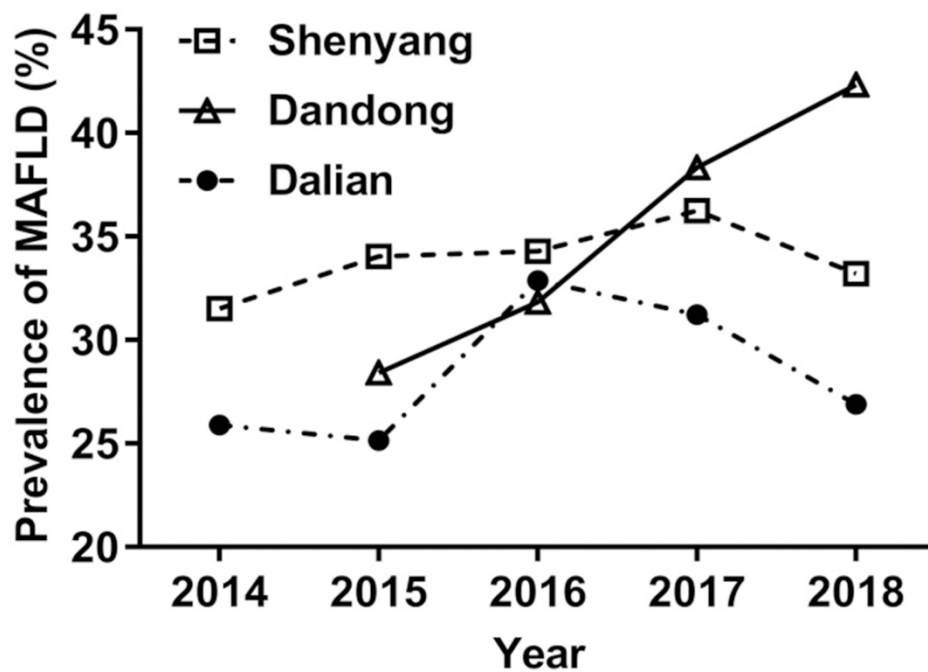


Figure 2. The prevalence of MAFLD in different cities from 2014 to 2018. The data for Dandong City in 2014 are lacking.

80x61mm (600 x 600 DPI)

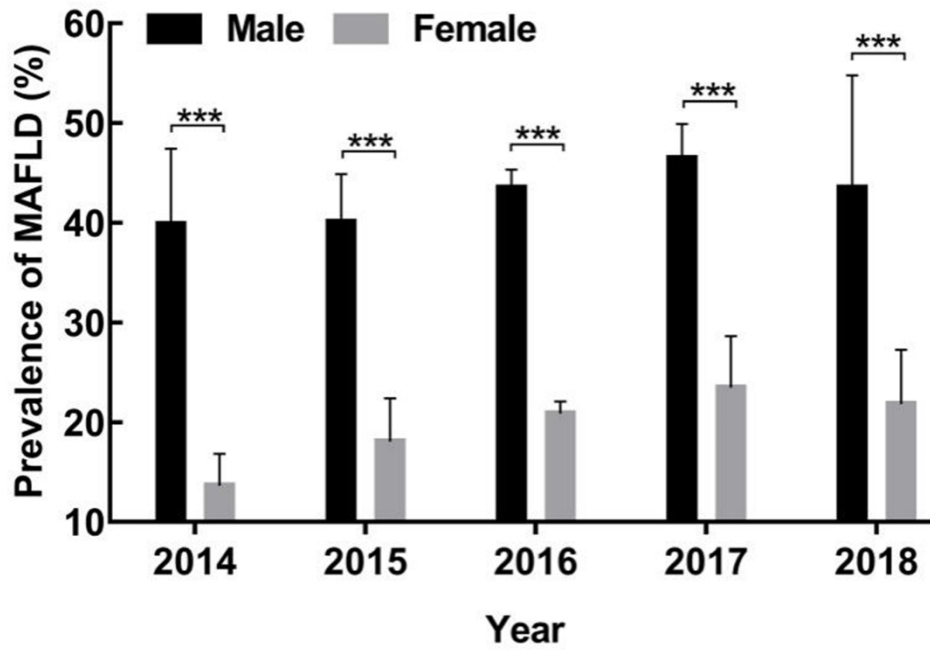


Figure 3. The prevalence of MAFLD in males is significantly higher than that in females (2014-2018).  
\*\*\*P<0.001.

80x55mm (600 x 600 DPI)

## STROBE Statement—checklist of items that should be included in reports of observational studies

Section/item	Item No	Recommendation	Reported on Page Number/Line Number	Reported on Section/Paragraph
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract		
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found		
<b>Introduction</b>				
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported		
Objectives	3	State specific objectives, including any prespecified hypotheses		
<b>Methods</b>				
Study design	4	Present key elements of study design early in the paper		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection		
Participants	6	(a) <b>Cohort study</b> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <b>Case-control study</b> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <b>Cross-sectional study</b> —Give the eligibility criteria, and the sources and methods of selection of participants		
		(b) <b>Cohort study</b> —For matched studies, give matching criteria and number of exposed and unexposed <b>Case-control study</b> —For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable		
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		
Bias	9	Describe any efforts to address potential sources of bias		
Study size	10	Explain how the study size was arrived at		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why		

Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	
		(b) Describe any methods used to examine subgroups and interactions	
		(c) Explain how missing data were addressed	
		(d) <b>Cohort study</b> —If applicable, explain how loss to follow-up was addressed <b>Case-control study</b> —If applicable, explain how matching of cases and controls was addressed <b>Cross-sectional study</b> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) <b>Cohort study</b> —Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	<b>Cohort study</b> —Report numbers of outcome events or summary measures over time	
		<b>Case-control study</b> —Report numbers in each exposure category, or summary measures of exposure	
		<b>Cross-sectional study</b> —Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence		
Generalisability	21	Discuss the generalisability (external validity) of the study results		
<b>Other information</b>				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based		

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

For peer review only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

# BMJ Open

## Prevalence and risk factors of metabolic associated fatty liver disease during 2014-2018 from three cities of Liaoning province: An epidemiological survey

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-047588.R2
Article Type:	Original research
Date Submitted by the Author:	24-Jan-2022
Complete List of Authors:	Guan, Lin; The First Hospital of China Medical University, Gastroenterology Department Zhang, Xinhe; The First Hospital of China Medical University, Gastroenterology Department Tian, Haoyu; China Medical University, the 3rd Clinical Department Jin, Xing; The First Hospital of China Medical University, Gastroenterology Department Fan, Hang; Neusoft Corporation, Data Operation & Management Department Wang, Ningning; The First Hospital of China Medical University, Gastroenterology Department Sun, Jing; The First Hospital of China Medical University, Gastroenterology Department Li, Dan; The First Hospital of China Medical University, Gastroenterology Department Li, Jia; Neusoft Corporation, Data Operation & Management Department Wang, Xue ; The First Hospital of China Medical University, Gastroenterology Department Zeng, Zilu; The First Hospital of China Medical University, Gastroenterology Department Li, Yiling; The First Hospital of China Medical University, Gastroenterology Department
<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Public health
Keywords:	Hepatology < INTERNAL MEDICINE, DIABETES & ENDOCRINOLOGY, General endocrinology < DIABETES & ENDOCRINOLOGY

SCHOLARONE™  
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.



1  
2  
3  
4  
5 **Prevalence and risk factors of metabolic associated fatty**  
6  
7 **liver disease during 2014-2018 from three cities of Liaoning**  
8  
9 **province: An epidemiological survey**  
10  
11

12 **Running title:** Prevalence of MAFLD in Liaoning, China  
13  
14  
15  
16

17  
18 Lin Guan<sup>1¶</sup>, Xinhe Zhang<sup>1¶</sup>, Haoyu Tian<sup>2</sup>, Xing Jin<sup>1</sup>, Hang Fan<sup>3</sup>, Ningning Wang<sup>1</sup>,  
19  
20 Jing Sun<sup>1</sup>, Dan Li<sup>1</sup>, Jia Li<sup>3</sup>, Xue Wang<sup>1</sup>, Zilu Zeng<sup>1</sup>, Yiling Li<sup>1\*</sup>  
21  
22

23 <sup>1</sup>Gastroenterology Department, the First Hospital of China Medical University,  
24  
25 No.155 North Nanjing Street, Heping District, Shenyang 110001, Liaoning, China  
26  
27

28 <sup>2</sup>the 3rd Clinical Department, China Medical University, No.77 Puhe Road, Shenyang  
29  
30 North New Area, Shenyang 110122, Liaoning, China  
31  
32

33 <sup>3</sup>Data Operation & Management Department, Neusoft Xikang Healthcare Technology  
34  
35 Co., Ltd., No.175 Chuangxin Road, Hunnan New District, Shenyang 110179,  
36  
37 Liaoning, China  
38  
39

40  
41 ¶**These authors contributed equally to this work.**  
42  
43

44 **\*Corresponding author**  
45

46 Yiling Li, Gastroenterology Department, the First Hospital of China Medical  
47  
48 University, No.155 North Nanjing Street, Heping District, Shenyang 110001,  
49  
50

51 Liaoning, China  
52

53  
54 E-mail: lyl-72@163.com  
55

56  
57 Tel: +86 13998841476  
58  
59  
60

1  
2  
3  
4  
5 **Word count:** 5203  
6

7 **Acknowledgment**  
8

9  
10 No applicable.  
11

12 **Funding:** No applicable  
13

14  
15 **Conflict of interest:** The authors declare that they have no conflict of interest.  
16

17 **Data Sharing Statement:** The data that support the findings of this study are  
18 available from the corresponding author upon reasonable request.  
19  
20  
21

22  
23 **Ethical statement:** The study was conducted in accordance with Declaration  
24 Helsinki, and the protocol was approved by the Ethics Committee of the First Hospital  
25 of China Medical University ([2020]2020-257-2). The ethics committee waived the  
26 requirement for informed consent because of the retrospective nature of the study.  
27  
28  
29  
30  
31  
32

33  
34 **Author contributions**  
35

36  
37 (I) Conception and design: LG, XHZ, YLL  
38

39 (II) Administrative support: JS, DL, YLL  
40

41 (III) Provision of study materials or patients: LG, XJ, NNW  
42

43 (IV) Collection and assembly of data: HYT, XW, ZLZ  
44

45 (V) Data analysis and interpretation: HF, JL  
46

47 (VI) Manuscript writing: All authors  
48

49 (VII) Final approval of manuscript: All authors  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## ABSTRACT

**Objectives:** To investigate the incidence and characteristics of metabolic associated fatty liver disease (MAFLD) in individuals undergoing physical examinations in Liaoning province (China).

**Design:** Retrospective study

**Setting:** Single-center.

**Participants:** Adults who underwent routine health examination at Xikang Medical Center in Liaoning province (Shenyang, Dandong, and Dalian cities) between January 2014 and December 2018.

**Interventions:** Not applicable.

**Primary And Secondary Outcome Measures:** Not applicable.

**Results:** Among the 204,394 included subjects, 71,756 were diagnosed with MAFLD, accounting for 35.28%. The total prevalence of MAFLD in Shenyang, Dandong, and Dalian cities over the past 5 years was 35.8%, 40.41%, and 31.7%, respectively. Men had a prevalence of 46.12%, which was higher than in women (21.80%). The percentage of MAFLD in body mass index (BMI)  $<23$  and  $\geq 23$  kg/m<sup>2</sup> was 6.49 % and 53.23%, respectively. In all subjects, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood glucose (FBG), triglyceride (TG), total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), total cholesterol (TC), alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP),  $\gamma$ -glutamyl transferase

(GGT), blood urea nitrogen (BUN), serum creatinine (sCr), and serum uric acid (SUA), hematocrit (HCT), mean corpuscular volume (MCV), and urine protein (UPRO) were independently associated with MAFLD (all  $P < 0.001$ ). In lean subjects, DBP, FBG, TG, TC, LDL-C, HDL-C, AST, ALP, GGT, sCr, SUA, HCT, and MCV were independently associated with MAFLD (all  $P < 0.001$ ).

**Conclusion:** The prevalence of MAFLD in Liaoning province was found to be associated with sex, cities with different economic statuses, BMI, and multiple metabolic indicators.

**Key words:** metabolic associated fatty liver disease; prevalence; risk factors; body mass index; lean.

#### **Strengths and limitations of this study**

1. The study is a large-scale epidemiological survey.
2. It is one of the first epidemiological articles after NAFLD renamed as MAFLD.
3. The study provides time trends from three cities in China with varying economic development.
4. The data of MAFLD patients with T2DM are lacking in the study.
5. Although the majority of the metabolic risk factors have been discussed in the study, further comprehensive assessment is required.

## INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease and is defined as the presence of  $\geq 5\%$  hepatic steatosis (HS) (1, 2). Recently, it was recommended to rename NAFLD as metabolic associated fatty liver disease (MAFLD), which might increase the awareness of the disease and decrease its stigma (3, 4). NAFLD is associated with chronic diseases, such as insulin resistance and/or type 2 diabetes mellitus (T2DM), dyslipidemia, hypertriglyceridemia, and hypertension (5-8). The prevalence of NAFLD was reported to be 24-45%, with an estimated prevalence of 76% in patients with T2DM (9). For non-obese patients, NAFLD is associated with the elevated triglyceride (TG) level, enlarged waist circumference, and insulin resistance (10).

Chinese individuals are at substantially higher risks of NAFLD, even those with noticeably lower body mass index (BMI,  $\text{kg}/\text{m}^2$ ) values, compared with the US population (11). Factors, such as waist circumference, T2DM, increased TG level, low high-density lipoprotein (HDL)-cholesterol level, and metabolic syndrome are known as predictive factors for NAFLD in adults, of which the metabolic syndrome is considered as a strong predictive factor (12, 13). NAFLD is also associated with dyslipidemia characterized by high TG, high low-density lipoprotein (LDL), and low HDL-cholesterol levels (14). Determining the risk factors associated with a worse prognosis is essential to develop further effective therapeutic strategies.

Since the 21st century, the prevalence of NAFLD in China has significantly

1  
2  
3  
4  
5 increased to reach about one in three mainland Chinese residents (12). A recent  
6  
7 meta-analysis showed that the incidence of NAFLD is higher in the northern China  
8  
9 (35.78%) and lower in the northwestern China (21.52%) (15). Among provinces in  
10  
11 the northern China, Heilongjiang has the highest incidence, with up to 50.48% (15).  
12  
13 Nevertheless, the results might be biased due to the small number of studies, and the  
14  
15 incidence of NAFLD in the northern China is still significantly higher than that in the  
16  
17 southern provinces. In addition, the risk of NAFLD-related mortality has also  
18  
19 increased significantly, mainly due to liver fibrosis-associated diseases (16). NAFLD  
20  
21 has become an important public health concern, negatively influencing the Chinese  
22  
23 population, as well as increasing the socioeconomic burden (11, 12, 15). Therefore,  
24  
25 Chinese medical professionals and stakeholders urgently need to develop further  
26  
27 accurate early diagnostic methods for NAFLD. Multiple studies have reported that  
28  
29 NAFLD is a heterogeneous entity, and its development is related to sex, age, race,  
30  
31 mild-to-moderate alcohol consumption, dietary intake, lifestyle, obesity, metabolism,  
32  
33 genetic variations, and educational level (11, 12, 15, 16). With uneven economic  
34  
35 development and diverse lifestyles among the different provinces in China, the  
36  
37 epidemiology of NAFLD has shown remarkable regional differences. With  
38  
39 understanding the epidemiology of NAFLD in Liaoning province (China), we can  
40  
41 conduct targeted education and clinical research for precise prevention and control of  
42  
43 NAFLD. Moreover, after NAFLD was renamed MAFLD, few studies investigated the  
44  
45 prevalence of MAFLD.  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5 There have been no data from large-scale epidemiological investigations of  
6  
7 MAFLD in Liaoning province over the past 10 years. Therefore, the present  
8  
9 retrospective study aimed to investigate the incidence and disease characteristics of  
10  
11 MAFLD in Liaoning province. The physical examination data of residents of three  
12  
13 cities (Shenyang, Dandong, and Dalian) in Liaoning province were collected from  
14  
15  
16  
17  
18 2014 to 2018 with different economic levels.  
19  
20  
21  
22

## 23 **METHODS**

### 24 **Study subjects**

25  
26 This is a retrospective study of adults who underwent routine health examination  
27  
28 at Xikang Medical Center in Liaoning province (including clinics in Shenyang,  
29  
30 Dandong, and Dalian) between January 2014 and December 2018. The study was  
31  
32 conducted in accordance with the Declaration Helsinki, and the study protocol was  
33  
34 conducted in accordance with the Declaration Helsinki, and the study protocol was  
35  
36 approved by the Ethics Committee of the First Hospital of China Medical University  
37  
38 ([2020]2020-257-2). The Ethics Committee waived the requirement for informed  
39  
40 consent because of the retrospective nature of the study.  
41  
42  
43  
44  
45

46 The three cities are from different parts of the Liaoning province (North, South,  
47  
48 and East (Figure 1)), and they have different economic levels. Shenyang, located in  
49  
50 the north of Liaoning province, is a highly developed inland city, while Dalian in the  
51  
52 south of Liaoning province is a developed coastal city. Dandong, in the east of  
53  
54 Liaoning province, is a poorly developed city bordering North Korea.  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5 The inclusion criteria were as follows: 1) patients who aged >18 years old; 2)  
6  
7 patients who lived in Shenyang, Dalian, or Dandong for at least 5 years; 3)  
8  
9 participation in the annual physical examination; and 4) no missing data (as listed in  
10  
11 Table 1). The exclusion criteria were as follows: 1) liver cirrhosis; 2) liver cancer; 3)  
12  
13 any liver lesions; or 4) no ultrasound examination. For participants undergoing more  
14  
15 than one examination during the study period, only the first examination was involved  
16  
17 in this study. According to the guidelines, the diagnosis of MAFLD is no longer than  
18  
19 an exclusive diagnosis. Therefore, the diagnosed patients did not rule out conditions,  
20  
21 such as alcohol consumption and other liver diseases.  
22  
23  
24  
25  
26  
27

28 The selected patients were divided into MAFLD group and non-MAFLD group  
29  
30 based on the ultrasound evidence of hepatic steatosis, in addition to one of the  
31  
32 following two criteria, namely overweight/obesity ( $\text{BMI} \geq 23 \text{ kg/m}^2$ , according to the  
33  
34 standards recommended by the World Health Organization for Asians (17) or  $\text{BMI}$   
35  
36  $< 23 \text{ kg/m}^2$  with at least two evidences of metabolic dysregulation, such as blood  
37  
38 pressure  $\geq 130/85 \text{ mmHg}$ ,  $\text{TG} \geq 1.70 \text{ mmol/L}$ , and  $\text{HDL-cholesterol} < 1.0 \text{ mmol/L}$   
39  
40 for men and  $< 1.3 \text{ mmol/L}$  for women) (18). Regrettably, 3156 patients with T2DM  
41  
42 who received medical intervention were not included in this study, due to serious  
43  
44 incomplete medical records.  
45  
46  
47  
48  
49

### 50 51 **Patient and Public Involvement**

52  
53  
54 No patient was involved.  
55

### 56 57 **Physical examination**



1  
2  
3  
4  
5 All physical examinations involved in this study are part of the routine  
6  
7 examination. Blood pressure measurements, including systolic blood pressure (SBP)  
8  
9 and diastolic blood pressure (DBP), were performed twice after participants have  
10  
11 sited, in a calm state for at least 5 min, using an electronic sphygmomanometer  
12  
13 (HEM-7200; OMRON Healthcare, Kyoto, Japan). Height and weight were measured  
14  
15 in the morning on an empty stomach.  
16  
17  
18  
19  
20  
21  
22

### 23 **Laboratory examination**

24  
25 All physical blood tests included in this study are part of the routine examination.  
26  
27 Anterior cubital vein blood was drawn in the fasting state (at least 8 h). A midcourse  
28  
29 morning urine specimen was taken as well. Routine blood panel, liver function,  
30  
31 kidney function, serum uric acid (SUA) level, fasting blood glucose (FBG) level,  
32  
33 blood lipids, and routine urine analysis were assessed using a 7600 autoanalyzer  
34  
35 (Hitachi, Tokyo, Japan).  
36  
37  
38  
39  
40  
41  
42  
43

### 44 **Color Doppler ultrasound of the liver and gallbladder**

45  
46 A liver ultrasound is part of the routine examination. It was performed by two  
47  
48 experienced ultrasound radiologists with at least 5 years of experience using an IU 22  
49  
50 system (Philips Healthcare, Best, The Netherlands). A participant was diagnosed with  
51  
52 hepatic steatosis when the ultrasound examination showed that the liver had fatty liver  
53  
54 changes (hyperechogenicity due to the increased acoustic interface caused by the  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5 intracellular accumulation of lipid vesicles, blurring of vascular margins, enlarged  
6  
7 liver size, and increased acoustic attenuation (10, 19) .  
8  
9

### 10 11 12 **Statistical analysis**

13  
14  
15 R 3.5.3 and R Commander 2.5-3 were used for statistical analysis. The  
16  
17 categorical data were expressed as n (%) and were analyzed using the Chi-square test.  
18  
19 The continuous variables conforming to the normal distribution (according to the  
20  
21 Kolmogorov-Smirnov test) were expressed as mean  $\pm$  standard deviation and were  
22  
23 analyzed using the Student's t-test. Abnormally distributed continuous variables were  
24  
25 presented as median (interquartile range (IQR)) and were analyzed using the  
26  
27 Mann-Whitney U test. Factors associated with MAFLD were identified using  
28  
29 univariate analysis. Variables with P-value  $<0.05$  were included in a multivariate  
30  
31 logistic regression model. P-value  $<0.05$  was considered statistically significant.  
32  
33  
34  
35  
36  
37  
38  
39  
40

## 41 **RESULTS**

### 42 43 **Characteristics of the subjects**

44  
45 A total of 284,129 subjects were examined during the study period, and 204,394  
46  
47 subjects met the eligibility criteria. Table 1 presents the characteristics of the subjects.  
48  
49 The subjects' mean age was  $39.6 \pm 13.6$  years old. The number of male and female  
50  
51 subjects was 111,782 and 92,612, respectively. The male subjects' mean age was  
52  
53  $38.8 \pm 13.7$  years old, and that of female subjects was  $40.5 \pm 13.3$  years old. Shenyang  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5 included 78,329 subjects, who aged  $39.3 \pm 12.7$  years old. No routine health  
6  
7 examination was performed in Dandong in 2014. Dandong included 42,039 subjects,  
8  
9 who aged  $47.8 \pm 14.1$  years old. Finally, 84,026 subjects were from Dalian, who aged  
10  
11  
12  
13  $36.3 \pm 12.7$  years old.

### 14 15 16 17 18 **The prevalence of MAFLD among the healthy population**

19  
20 Among the 204,394 included subjects, 71,756 were diagnosed with MAFLD,  
21  
22 accounting for 35.28% (Table 1). The prevalence of MAFLD increased with age  
23  
24 (P<0.001), which was higher in men than in women (P<0.001), higher in  
25  
26 overweight/obese subjects than in lean ones (P<0.001), and was higher in Dandong,  
27  
28 followed by Shenyang and Dalian (P<0.001) (Table 1). The prevalence of MAFLD in  
29  
30 Shenyang, Dandong, and Dalian over the past 5 years was 36.83%, 40.42%, and  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
31.78%, respectively.

### 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 **The prevalence of MAFLD over time**

41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
The total prevalence of MAFLD from 2014 to 2018 was 30.01%, 30.11%,  
33.22%, 34.58%, and 32.19%, respectively. The prevalence of MALFD over the 5  
years mainly increased in the age-based group of 30-39 years old (P=0.006), in men  
(P=0.029) and in women (P=0.035) (Table 2). The prevalence of MAFLD in  
Shenyang over the past 5 years was basically consistent with the general trend in  
Liaoning. The prevalence of MAFLD in Dandong significantly increased annually

1  
2  
3  
4  
5 over the past 4 years. The prevalence of MAFLD in Dalian substantially increased in  
6  
7 2016, while it declined in 2017 and 2018 (Figure 2). The prevalence rate in men and  
8  
9 women over the past 5 years was basically consistent with the general trend of  
10  
11 MAFLD in Liaoning (Figure 3). With the increase of age, the prevalence of MAFLD  
12  
13 was elevated in Liaoning.  
14  
15  
16  
17  
18  
19

### 20 **Biomarkers for MAFLD**

21  
22 Table 3 presents the biomarkers in all subjects and according to  
23  
24 lean/overweight-obese. The number of subjects with overweight/obese MAFLD was  
25  
26 66,609, of whom the number of patients with T2DM was 3,550 (5.33%). The number  
27  
28 of cases with lean MAFLD was 5147, of whom the number of patients with T2DM  
29  
30 was 143 (2.78%). The number of cases who were diagnosed (for the first time) with  
31  
32 fasting blood glucose level over 7 was 289. Compared with the non-MAFLD group,  
33  
34 subjects in the MAFLD group had higher SBP, DBP, FBG, TG, total cholesterol  
35  
36 (TC), LDL-C, alanine transaminase (ALT), aspartate transaminase (AST), alkaline  
37  
38 phosphatase (ALP),  $\gamma$ -glutamyl transferase (GGT), blood urea nitrogen (BUN), serum  
39  
40 creatinine (sCr), and serum uric acid (SUA), higher frequencies of urine protein  
41  
42 (UPRO) and GBp, lower HDL-C, hematocrit (HCT), and mean corpuscular volume  
43  
44 (MCV), and lower frequency of UOB (all  $P < 0.001$ ). The same tendencies were  
45  
46 observed in lean subjects, while there was no significant difference in UPRO  
47  
48 (P=0.86).  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

### MAFLD-associated factors

Table 4 presents the results of the univariate and multivariate logistic regression analyses of the factors associated with MAFLD. In all subjects, BMI, SBP, DBP, FBG, TG, TC, LDL-C, HDL-C, ALT, AST, ALP, GGT, BUN, Scr, SUA, HCT, MCV, and UPRO were independently associated with MAFLD (all  $P < 0.001$ ), while UOB ( $P = 0.47$ ) and GBp ( $P = 0.21$ ) were not. In lean subjects, DBP, FBG, TG, TC, LDL-C, HDL-C, AST, ALP, GGT, Scr, SUA, HCT, and MCV were independently associated with MAFLD (all  $P < 0.001$ ), while SBP ( $P = 0.51$ ), ALT ( $P = 0.27$ ), BUN ( $P = 0.16$ ), UPRO ( $P = 0.57$ ), UOB ( $P = 0.06$ ), and GBp ( $P = 0.06$ ) were not.

### DISCUSSION

The present study showed that the prevalence of MAFLD in Shenyang, Dandong, and Dalian cities varied, and higher BMI value and age played significant roles in the development of the disease. In addition, biomarkers, such as DBP, FBG, TG, LDL-C, ALT, GGT, BUN, SUA, HCT, UPRO, GBs, and GBp were independently and positively correlated with the prevalence of MAFLD, whereas HDL-C and MCV were negatively correlated. Therefore, the prevalence of MAFLD in Liaoning was related to sex, cities with different economic statuses, BMI, and multiple metabolic indicators.

The increasing trend in the prevalence of NAFLD follows the level of

1  
2  
3  
4  
5 industrialization and urbanization. At present, China is the fastest-growing major  
6  
7 economy in the world, and there are problems associated with a westernized diet,  
8  
9 sedentary lifestyle, and metabolism, which are correlated with MAFLD. Thus, there is  
10  
11 a closer relationship between MAFLD and economy than NAFLD. Studies have  
12  
13 shown that the increase in the total annual NAFLD prevalence in China is consistent  
14  
15 with the improvement in the gross domestic product (GDP) per capita (20). An  
16  
17 increase in morbidity in various regions of the mainland China could be related to the  
18  
19 increase in GDP per capita, while areas with the highest GDP per capita ( $\geq$ \$13,000)  
20  
21 did not exhibit an increased incidence of NAFLD (21). According to the National  
22  
23 Bureau of Statistics of China, the GDP per capita of Liaoning province has ranked  
24  
25 first in the Northeast China over the past 5 years, whereas it is still in the  
26  
27 lower-middle level nationally. The present study revealed that the prevalence of  
28  
29 MAFLD in Liaoning (35.1%) was slightly higher than the overall prevalence in China  
30  
31 (29.2%) (12). The current study selected two economically developed cities (Dalian  
32  
33 and Shenyang) and one city with a moderate development (Dandong). The prevalence  
34  
35 of MAFLD in these three cities was inversely proportional to the level of urban  
36  
37 economic development. The prevalence of MAFLD in Dalian was lower than that in  
38  
39 Shenyang. This could be related to the fact that Dalian is a coastal city, with dietary  
40  
41 habits different from those of inland cities.  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52

53  
54 Differences in age were also confirmed. The prevalence of MAFLD in the  
55  
56 age-based group of 20-29 years old was 17.9%, while it was 45.6% in the age-based  
57  
58  
59  
60

1  
2  
3  
4  
5 group of >60 years old, which is in agreement with previous studies, which  
6  
7 demonstrated that age could play a crucial factor in the prevalence of NAFLD (11, 12,  
8  
9  
10 15).

11  
12 The present study indicated that the overall prevalence of MAFLD in men was  
13  
14 higher than that in women, which is basically consistent with the previously reported  
15  
16 findings in other regions of China (22). The prevalence of MAFLD in middle-aged  
17  
18 men was the highest and reached the peak at 40-49 years old (50.27%). This high  
19  
20 prevalence might be related to high stress, irregular work and rest, and decreased  
21  
22 metabolism among middle-aged men. The prevalence of MAFLD in women aging  
23  
24 over 50 years old was significantly higher, which could be related to the age range of  
25  
26 menopause.  
27  
28  
29  
30  
31

32  
33 Obesity is closely associated with metabolic diseases, such as MAFLD. The  
34  
35 current study confirmed that BMI  $\geq 23$  kg/m<sup>2</sup> is an independent risk factor for  
36  
37 MAFLD in Liaoning. Therefore, for overweight and obese individuals, it is necessary  
38  
39 to improve diet and exercise management, even using drugs or surgery, if required. It  
40  
41 has been reported that the global NAFLD prevalence in lean population was 5%-26%  
42  
43 (23). In the present study, the prevalence of NAFLD in lean population was 10.75%,  
44  
45  
46 which is similar to previously reported results (24).  
47  
48  
49

50  
51 In this study, both lean-MAFLD and non-lean-MAFLD were closely related to  
52  
53 metabolic indicators. Those metabolic indicators were also associated with T2DM,  
54  
55  
56 metabolic syndrome, obesity, and liver diseases, as supported by previous studies (11,  
57  
58  
59  
60

1  
2  
3  
4  
5 12, 15, 22-24). In addition to obesity, variations in the prevalence of MAFLD follow  
6  
7 the epidemic trends of T2DM and MetS. The prevalence of MAFLD in  
8  
9 hyperlipidemia and T2DM patients is higher, reaching 27%-92% and 28%-70%,  
10  
11 respectively. Patients with MAFLD mainly have hyperlipidemia, hypertension,  
12  
13 T2DM, and metabolic syndrome (25). In the current study, multivariate logistic  
14  
15 regression analysis found that DBP, TG, LDL-C, FBG, and SUA were independent  
16  
17 risk factors for MAFLD, while HDL-C was independently associated with MAFLD.  
18  
19 Therefore, additional attention should be paid to hyperlipidemia, hypertension, and  
20  
21 T2DM to assess their influences on the prevention and treatment of MAFLD.  
22  
23 Regarding the correlation between SUA and MAFLD, SUA elevation was reported as  
24  
25 one of the risk factors for MAFLD (26).  
26  
27

28  
29  
30  
31  
32  
33 Although genetic susceptibility was not examined in the current study, it is  
34  
35 involved in NAFLD. Polymorphisms in PNPLA3 (27), SREBF-2 (28), CETP (28,  
36  
37 29), and APOC3 (30) have been found to be associated with lean-NAFLD. In addition  
38  
39 to genetic polymorphisms, lean-NAFLD cases have increased bile acid and FXR  
40  
41 activity due to metabolic abnormalities and changes in intestinal microbial  
42  
43 composition (31, 32). These factors should be assessed in the future studies.  
44  
45  
46  
47  
48

49  
50 Regarding the diabetes, because 3156 patients had previously received systemic  
51  
52 treatment for diabetes, the current blood glucose levels and metabolic indicators were  
53  
54 in the normal range, thus, in order to reduce the error in the analysis of risk factors,  
55  
56 we excluded these patients. In addition, diabetic patients analyzed in the present study  
57  
58  
59  
60



1  
2  
3  
4  
5 were previously diagnosed, of whom 289 patients were found to have elevated fasting  
6  
7 blood glucose levels for the first time. As physical examinations did not involve  
8  
9 OGTT and repeated tests, we did not classify such patients as diabetic.

10  
11  
12 This study has some limitations. Although the examinations were performed at  
13  
14 the same clinic, they were conducted at three different physical locations over the past  
15  
16 5 years. Biases due to the different locations and changes in practice over time could  
17  
18 not be excluded. Due to the large number of physical examinations and no  
19  
20 measurement of waist circumference and high-sensitivity C-reactive protein  
21  
22 (hs-CRP), the diagnosis of MAFLD in some patients with normal BMI might be  
23  
24 ignored. In addition, ultrasound is operator-dependent, and a bias in the diagnosis of  
25  
26 MAFLD could not be excluded. Finally, this was a cross-sectional study that could  
27  
28 not provide any causal relationship between MAFLD and the associated factors.  
29  
30  
31  
32  
33  
34  
35

36 In conclusion, the prevalence of MAFLD in Liaoning was found to be associated  
37  
38 with sex, cities with different economic statuses, BMI, and multiple metabolic  
39  
40 indicators. Longitudinal studies are necessary to further determine factors associated  
41  
42 with the development of MAFLD.  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55

## 56 REFERENCES

57  
58  
59  
60

- 1  
2  
3  
4  
5 1. Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of  
6  
7 nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence,  
8  
9 and outcomes. *Hepatology*. 2016;64:73-84.  
10  
11
- 12 2. Stal P. Liver fibrosis in non-alcoholic fatty liver disease - diagnostic challenge  
13  
14 with prognostic significance. *World J Gastroenterol*. 2015;21:11077-87.  
15  
16
- 17 3. Eslam M, Sanyal AJ, George J, et al. MAFLD: A Consensus-Driven Proposed  
18  
19 Nomenclature for Metabolic Associated Fatty Liver Disease. *Gastroenterology*.  
20  
21 2020;158:1999-2014 e1.  
22  
23
- 24 4. Fouad Y, Waked I, Bollipo S, et al. What's in a name? Renaming 'NAFLD' to  
25  
26 'MAFLD'. *Liver Int*. 2020;40:1254-61.  
27  
28
- 29 5. Pai RK. NAFLD Histology: a Critical Review and Comparison of Scoring  
30  
31 Systems. *Curr Hepatol Rep*. 2019;18:473-81.  
32  
33
- 34 6. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and  
35  
36 natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in  
37  
38 adults. *Aliment Pharmacol Ther*. 2011;34:274-85.  
39  
40
- 41 7. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of  
42  
43 non-alcoholic fatty liver disease: practice guideline by the American  
44  
45 Gastroenterological Association, American Association for the Study of Liver  
46  
47 Diseases, and American College of Gastroenterology. *Gastroenterology*.  
48  
49 2012;142:1592-609.  
50  
51
- 52 8. Non-Alcoholic Fatty Liver Disease: Assessment and Management. National  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5 Institute for Health and Care Excellence: Guidance. London 2016.

6  
7 9. Rinella ME. Nonalcoholic fatty liver disease: a systematic review. JAMA.  
8  
9  
10 2015;313:2263-73.

11  
12 10. Shen FF, Lu LG. Advances in noninvasive methods for diagnosing nonalcoholic  
13  
14  
15 fatty liver disease. J Dig Dis. 2016;17:565-71.

16  
17 11. Zhou J, Zhou F, Wang W, et al. Epidemiological Features of NAFLD From 1999  
18  
19  
20 to 2018 in China. Hepatology. 2020;71:1851-64.

21  
22 12. Zhou F, Zhou J, Wang W, et al. Unexpected Rapid Increase in the Burden of  
23  
24  
25 NAFLD in China From 2008 to 2018: A Systematic Review and Meta-Analysis.  
26  
27  
28 Hepatology. 2019;70:1119-33.

29  
30 13. Caballeria L, Auladell MA, Toran P, et al. Risk factors associated with  
31  
32  
33 non-alcoholic fatty liver disease in subjects from primary care units. A case-control  
34  
35  
36 study. BMC Gastroenterol. 2008;8:44.

37  
38 14. Hartmann P, Schnabl B. Risk factors for progression of and treatment options for  
39  
40  
41 NAFLD in children. Clin Liver Dis (Hoboken). 2018;11:11-5.

42  
43 15. Wu Y, Zheng Q, Zou B, et al. The epidemiology of NAFLD in Mainland China  
44  
45  
46 with analysis by adjusted gross regional domestic product: a meta-analysis. Hepatol  
47  
48  
49 Int. 2020;14:259-69.

50  
51 16. Dulai PS, Singh S, Patel J, et al. Increased risk of mortality by fibrosis stage in  
52  
53  
54 nonalcoholic fatty liver disease: Systematic review and meta-analysis. Hepatology.  
55  
56  
57 2017;65:1557-65.

17. Consultation WHOE. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet*. 2004;363:157-63.
18. Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic associated fatty liver disease: an international expert consensus statement. *Journal of Hepatology*. 2020;73(1):202-209.
19. Mahale AR, Prabhu SD, Nachiappan M, et al. Clinical relevance of reporting fatty liver on ultrasound in asymptomatic patients during routine health checkups. *J Int Med Res*. 2018;46:4447-54.
20. Cai J, Zhang XJ, Li H. Progress and challenges in the prevention and control of nonalcoholic fatty liver disease. *Med Res Rev*. 2019;39:328-48.
21. Fan JG, Kim SU, Wong VW. New trends on obesity and NAFLD in Asia. *J Hepatol*. 2017;67:862-73.
22. Zhu JZ, Zhou QY, Wang YM, et al. Prevalence of fatty liver disease and the economy in China: A systematic review. *World J Gastroenterol*. 2015;21:5695-706.
23. Wang AY, Dhaliwal J, Mouzaki M. Lean non-alcoholic fatty liver disease. *Clin Nutr*. 2019;38:975-81.
24. Shi Y, Wang Q, Sun Y, et al. The Prevalence of Lean/Nonobese Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis. *J Clin Gastroenterol*. 2020;54:378-87.
25. Fan JG, Wei L, Zhuang H, et al. Guidelines of prevention and treatment of nonalcoholic fatty liver disease (2018, China). *J Dig Dis*. 2019;20:163-73.

- 1  
2  
3  
4  
5 26. Ma Z, Xu C, Kang X, et al. Changing trajectories of serum uric acid and risk of  
6  
7 non-alcoholic fatty liver disease: a prospective cohort study. *J Transl Med.*  
8  
9 2020;18:133.  
10  
11  
12 27. Musso G, Cassader M, Bo S, et al. Sterol regulatory element-binding factor 2  
13  
14 (SREBF-2) predicts 7-year NAFLD incidence and severity of liver disease and  
15  
16 lipoprotein and glucose dysmetabolism. *Diabetes.* 2013;62:1109-20.  
17  
18  
19 28. Adams LA, Marsh JA, Ayonrinde OT, et al. Cholesteryl ester transfer protein  
20  
21 gene polymorphisms increase the risk of fatty liver in females independent of  
22  
23 adiposity. *J Gastroenterol Hepatol.* 2012;27:1520-7.  
24  
25  
26 29. Petersen KF, Dufour S, Hariri A, et al. Apolipoprotein C3 gene variants in  
27  
28 nonalcoholic fatty liver disease. *N Engl J Med.* 2010;362:1082-9.  
29  
30  
31 30. Li C, Guo P, Okekunle AP, et al. Lean non-alcoholic fatty liver disease patients  
32  
33 had comparable total caloric, carbohydrate, protein, fat, iron, sleep duration and  
34  
35 overtime work as obese non-alcoholic fatty liver disease patients. *J Gastroenterol*  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
31. Safari Z, Gerard P. The links between the gut microbiome and non-alcoholic fatty  
liver disease (NAFLD). *Cell Mol Life Sci.* 2019;76:1541-58.
32. Suk KT, Kim DJ. Gut microbiota: novel therapeutic target for nonalcoholic fatty  
liver disease. *Expert Rev Gastroenterol Hepatol.* 2019;13:193-204.

**Table 1.** Characteristics of the patients with non-MAFLD and MAFLD

Subgroups	Age (years), Mean±SD	All N=204,3 94	Non-MAFLD n=132,638	MAFLD n=71,7 56	Prevalence (%)	P
Age						<0.001
20-29		22,822	18,728	4094	17.94	
30-39		80,227	54,671	25,556	31.85	
40-49		44,464	27,913	16,551	37.22	
50-59		30,861	17,173	13,688	44.35	
≥60		26,020	14,153	11,867		
Sex						<0.001
Male	38.8±13.7	111,782	60,222	51,560	46.13	
Female	40.5±13.3	92,612	72,416	20,196	21.81	
BMI (kg/m <sup>2</sup> )						<0.001
<23		79,271	74,124	5147	6.49	
≥23		125,123	58,514	66,609	53.23	
City						<0.001

---

						01
	Shenya	39.3±12.7	78,329	50,265	28,064	36.83
	ng					
	Dando	47.8±14.1	42,039	25,048	16,991	40.42
	ng					
	Dalian	36.3±12.7	84,026	57,325	26,701	31.78
	Overall	39.6±13.6	204,394	132,638	71,756	35.11

---

MAFLD: metabolic-associated fatty liver disease; BMI: body mass index.

**Table 2.** Changes in the prevalence of MAFLD over time (2014-2018)

Subgroups	Year, %					P
	2014	2015	2016	2017	2018	
<b>Age (years)</b>						
20-29	16.43	17.20	17.30	18.82	18.18	0.081
30-39	29.24	28.60	31.05	33.37	34.33	0.006
40-49	35.65	34.50	35.40	39.04	38.69	0.200
50-59	46.32	39.40	41.67	46.96	45.44	0.636
≥60	44.83	40.65	45.34	48.39	46.50	0.234
<b>Sex</b>						
Male	42.60	42.63	44.36	48.12	48.45	0.029
Female	14.85	19.33	21.49	24.63	22.67	0.035
<b>BMI (kg/m<sup>2</sup>)</b>						
<23	5.08	5.35	6.68	7.36	6.80	0.058
≥23	54.93	50.37	52.15	55.08	53.76	0.510
<b>City</b>						
Shenyang	34.89	34.80	34.27	37.36	36.92	0.182
Dandong	-	30.06	34.29	42.66	44.17	0.039
Dalian	26.36	29.00	33.20	32.36	32.98	0.048
Overall	30.01	30.11	33.22	34.58	32.19	<0.001

BMI: body mass index.



**Table 3.** Comparison of the metabolic tests between non-MAFLD and MAFLD

Variables	Overall			Lean (BMI<23)			Overweight (BMI >=23)		
	Non-MAFLD	MAFLD	P	Non-MAFLD	MAFLD	P	Non-MAFLD	MAFLD	P
SBP, mmHg	118±18	129±19	<0.001	114±16	122±19	<0.001	123±18	129±19	<0.001
DBP, mmHg	70±11	77±13	<0.001	67±10	73±12	<0.001	72±12	77±13	<0.001
FBG, mmol/L	5.15±1.30	5.82±1.63	<0.001	5.04±1.22	5.63±1.65	<0.001	5.3±1.18	5.83±1.63	<0.001
TG, mmol/L	1.07±0.85	2.12±1.73	<0.001	0.91±0.64	1.79±1.46	<0.001	1.28±1.01	2.14±1.75	<0.001
TC, mmol/L	4.41±1.43	4.96±1.34	<0.001	4.29±1.41	4.94±1.36	<0.001	4.55±1.43	4.97±1.34	<0.001
LDL-C, mmol/L	1.99±1.34	2.42±1.43	<0.001	1.9±1.28	2.46±1.38	<0.001	2.09±1.40	2.42±1.43	<0.001
HDL-C, mmol/L	1.01±0.71	0.9±0.60	<0.001	1.06±0.73	0.99±0.64	<0.001	0.93±0.67	0.9±0.60	<0.001
ALT, U/L	19.37±17.28	36.58±27.98	<0.001	17.09±14.34	27.89±21.40	<0.001	22.19±19.98	37.2±28.29	<0.001
AST, U/L	19.59±11.18	25.85±13.56	<0.001	18.76±10.03	23.55±13.08	<0.001	20.62±12.38	26.02±13.57	<0.001
ALP, U/L	7.01±22.44	9.62±25.91	<0.001	5.51±20.85	8.48±24.35	<0.001	8.98±24.13	9.7±26.02	<0.001

GGT, U/L	18.42±24.10	39.36±42.82	<0.001	15.54±20.76	31.41±48.78	<0.001	21.99±27.27	37.71±42.34	<0.001
BUN, mmol/L	4.32±1.97	4.8±1.80	<0.001	4.17±1.90	4.65±1.77	<0.001	4.51±2.04	4.81±1.80	<0.001
Scr, µmol/L	58.57±26.43	66.63±24.76	<0.001	56.12±25.14	62.05±22.61	<0.001	61.62±27.66	66.96±24.88	<0.001
SUA, µmol/L	283.17±125.06	369.05±135.06	<0.001	263.87±116.14	330.07±123.40	<0.001	307.09±131.43	371.84±135.42	<0.001
HCT, %	21.57±21.35	20.32±22.42	<0.001	21.95±20.97	20.36±21.90	<0.001	21.1±21.80	20.32±22.46	<0.001
MCV, fl	47.2±44.74	41.66±44.42	<0.001	48.78±44.68	42.74±44.70	<0.001	45.23±44.74	41.58±44.40	<0.001
UPRO, n (%)	6.70%	9.20%	<0.001	6.30%	6.20%	0.86	7.30%	9.40%	<0.001
UOB, n (%)	11.10%	8.80%	<0.001	11.20%	9.40%	0.00	10.80%	8.80%	<0.001
GBp, n (%)	7.40%	8.90%	<0.001	6.20%	8.60%	<0.001	8.90%	9.70%	<0.001

SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting plasma glucose; TG: triglycerides; TC: total cholesterol;

LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; ALT: alanine aminotransferase; AST:

aspartate aminotransferase; ALP: alkaline phosphatase; GGT:  $\gamma$ -glutamyl transpeptidase; BUN: blood urea nitrogen; Scr: serum

creatinine; SUA: serum uric acid; HCT: hematocrit; MCV: mean corpuscular volume; UPRO: urine protein; UOB: urine occult blood;

1  
2  
3  
4  
5 GBp: gallbladder polyps.  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

For peer review only

**Table 4.** Multivariable analyses of the factors associated with MAFLD

Variables	Univariable logistical regression			Multivariable logistical regression				
	OR	OR (95% CI)	P	OR	OR (95% CI)	P		
<b>MAFLD</b>								
BMI (kg/m <sup>2</sup> )								
<23	0.057	0.056	0.060	<0.001	0.125	0.119	0.130	<0.001
≥23								
SBP, mmHg	1.033	1.033	1.034	<0.001	1.003	1.003	1.005	<0.001
DBP, mmHg	1.053	1.052	1.054	<0.001	1.014	1.012	1.016	<0.001
FBG, mmol/L	1.541	1.520	1.559	<0.001	1.122	1.104	1.131	<0.001
TG, mmol/L	2.899	2.854	2.953	<0.001	1.651	1.627	1.691	<0.001
TC, mmol/L	1.378	1.365	1.392	<0.001	0.879	0.866	0.893	<0.001
LDL-C, mmol/L	1.267	1.255	1.277	<0.001	1.231	1.216	1.259	<0.001

1									
2									
3									
4									
5	HDL-C, mmol/L	0.799	0.785	0.813	<0.001	0.717	0.690	0.740	<0.001
6									
7	ALT, U/L	1.040	1.038	1.040	<0.001	1.036	1.035	1.038	<0.001
8									
9									
10	AST, U/L	1.055	1.054	1.057	<0.001	0.979	0.977	0.981	<0.001
11									
12									
13	ALP, U/L	1.004	1.004	1.005	<0.001	0.998	0.998	1.000	<0.001
14									
15	GGT, U/L	1.025	1.025	1.026	<0.001	1.002	1.002	1.002	<0.001
16									
17									
18	BUN, mmol/L	1.145	1.139	1.154	<0.001	1.019	1.007	1.032	<0.001
19									
20									
21	Scr, µmol/L	1.014	1.013	1.014	<0.001	0.995	0.994	0.996	<0.001
22									
23									
24	SUA, µmol/L	1.005	1.005	1.006	<0.001	1.003	1.002	1.003	<0.001
25									
26	HCT, %	0.998	0.997	0.998	<0.001	1.006	1.003	1.008	<0.001
27									
28									
29	MCV, fl	0.997	0.997	0.997	<0.001	0.994	0.993	0.995	<0.001
30									
31									
32	UPRO, n (%)	1.407	1.342	1.462	<0.001	1.112	1.069	1.198	<0.001
33									
34	UOB, n (%)	0.762	0.749	0.811	<0.001	1.000	0.933	1.033	0.47
35									
36									
37	GBp, n (%)	1.233	1.176	1.280	<0.001	1.026	0.981	1.090	0.21
38									
39									
40									
41									
42									
43									
44									
45									
46									

**Lean (BMI<23), MAFLD**

SBP, mmHg	1.027	1.025	1.029	<0.001	1.999	0.995	1.002	0.51
DBP, mmHg	1.046	1.042	1.048	<0.001	1.018	1.012	1.024	<0.001
FBG, mmol/L	1.393	1.346	1.424	<0.001	1.098	1.064	1.133	<0.001
TG, mmol/L	2.771	2.642	2.891	<0.001	1.878	1.781	1.968	<0.001
TC, mmol/L	1.498	1.465	1.565	<0.001	0.891	0.860	0.941	<0.001
LDL-C, mmol/L	1.455	1.393	1.485	<0.001	1.372	1.301	1.430	<0.001
HDL-C, mmol/L	1.890	0.831	0.920	<0.001	0.695	0.631	0.741	<0.001
ALT, U/L	1.028	1.026	1.030	<0.001	1.025	1.024	1.030	0.27
AST, U/L	1.028	1.026	1.030	<0.001	0.971	0.969	0.980	<0.001
ALP, U/L	1.006	1.004	1.007	<0.001	1.000	0.998	1.001	<0.001
GGT, U/L	1.016	1.016	1.018	<0.001	1.001	1.001	1.004	<0.001
BUN, mmol/L	1.150	1.133	1.182	<0.001	1.022	0.990	1.059	0.16

Scr, $\mu\text{mol/L}$	1.010	1.008	1.012	<0.001	0.898	0.987	0.993	<0.001
SUA, $\mu\text{mol/L}$	1.005	1.005	1.006	<0.001	1.004	1.004	1.004	<0.001
HCT, %	0.996	0.995	0.998	<0.001	1.016	1.005	1.023	<0.001
MCV, fl	0.997	0.996	0.998	<0.001	0.993	0.986	0.995	<0.001
UPRO, n (%)	1.000	0.841	1.149	<0.001	0.995	0.795	1.130	0.57
UOB, n (%)	0.802	0.716	0.926	<0.001	0.947	0.757	1.004	0.06
GBp, n (%)	1.444	1.242	1.629	<0.001	1.221	0.992	1.337	0.06

MAFLD: metabolic associated fatty liver disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting plasma glucose; TG: triglyceride; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT:  $\gamma$ -glutamyl transpeptidase; BUN: blood urea nitrogen; Scr: serum creatinine; SUA: serum uric acid; HCT: hematocrit; MCV: mean corpuscular volume; UPRO: urine protein; UOB: urine occult blood; GBp: gallbladder polyps.

## FIGURE LEHENDS

**Figure 1.** The location of the three study cities in Liaoning Province.

**Figure 2.** The prevalence of MAFLD in different cities from 2014 to 2018. The data for Dandong City in 2014 are lacking.

**Figure 3.** The prevalence of MAFLD in males is significantly higher than that in females (2014-2018). \*\*\* $P < 0.001$ .





Figure 1. The location of the three study cities in Liaoning Province.

80x71mm (600 x 600 DPI)

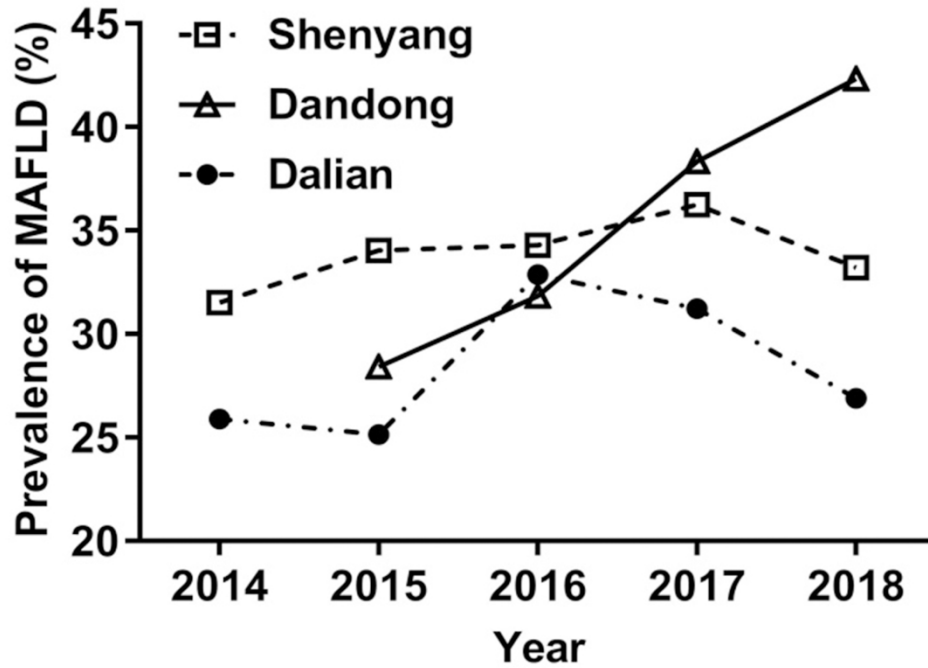


Figure 2. The prevalence of MAFLD in different cities from 2014 to 2018. The data for Dandong City in 2014 are lacking.

80x61mm (600 x 600 DPI)

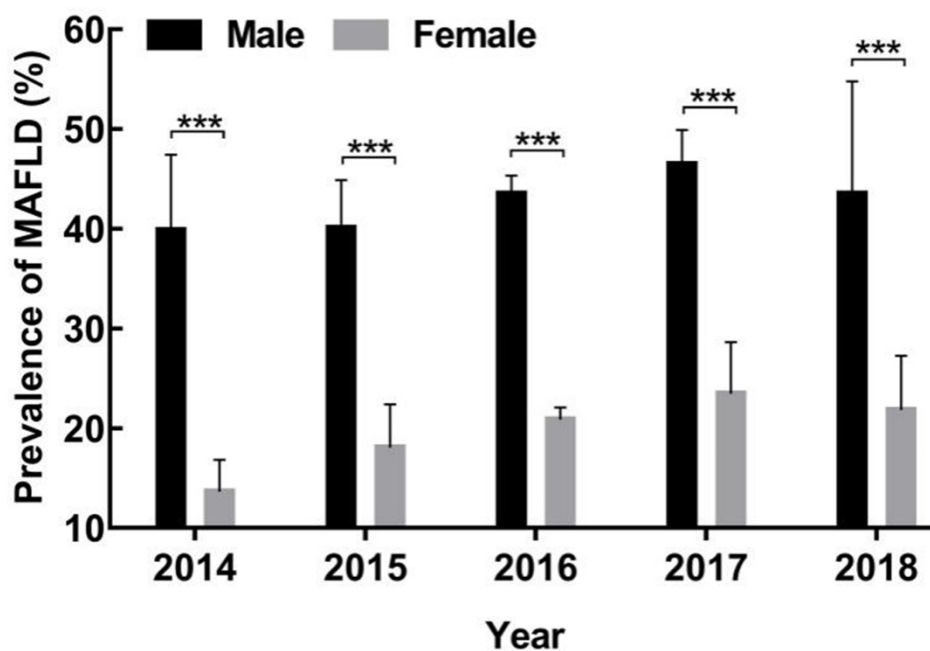


Figure 3. The prevalence of MAFLD in males is significantly higher than that in females (2014-2018).  
\*\*\*P<0.001.

80x55mm (600 x 600 DPI)

**STROBE Statement—checklist of items that should be included in reports of observational studies**

Section/item	Item No	Recommendation	Reported on Page Number/Line Number	Reported on Section/Paragraph
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract		
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found		
<b>Introduction</b>				
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported		
Objectives	3	State specific objectives, including any prespecified hypotheses		
<b>Methods</b>				
Study design	4	Present key elements of study design early in the paper		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection		
Participants	6	(a) <b>Cohort study</b> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <b>Case-control study</b> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <b>Cross-sectional study</b> —Give the eligibility criteria, and the sources and methods of selection of participants		
		(b) <b>Cohort study</b> —For matched studies, give matching criteria and number of exposed and unexposed <b>Case-control study</b> —For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable		
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		
Bias	9	Describe any efforts to address potential sources of bias		
Study size	10	Explain how the study size was arrived at		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why		

Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	
		(b) Describe any methods used to examine subgroups and interactions	
		(c) Explain how missing data were addressed	
		(d) <b>Cohort study</b> —If applicable, explain how loss to follow-up was addressed <b>Case-control study</b> —If applicable, explain how matching of cases and controls was addressed <b>Cross-sectional study</b> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) <b>Cohort study</b> —Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	<b>Cohort study</b> —Report numbers of outcome events or summary measures over time	
		<b>Case-control study</b> —Report numbers in each exposure category, or summary measures of exposure	
		<b>Cross-sectional study</b> —Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence		
Generalisability	21	Discuss the generalisability (external validity) of the study results		
<b>Other information</b>				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based		

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

For peer review only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46