Heliyon 10 (2024) e24905

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Association between the traditional Chinese medicine constitution and metabolic dysfunction-associated fatty liver disease in older people: A cross-sectional study

Tianran Shen [a,b,1], Shupei Wang [a,1], Zhihao Wang [a], Hanlu Jia [a], Yuan Wei [a], Yu Li [a], Qiutong Zheng [a], Yuting Li [a], Luanzhao Pan [c,**], Qingsong Chen [a,b,*]

[a] School of Public Health, Guangdong Pharmaceutical University, Guangzhou, Guangdong, 510310, China
[b] Guangdong Provincial Engineering Research Center of Public Health Detection and Assessment, Guangdong Pharmaceutical University, Guangzhou, Guangdong, 510310, China
[c] Zhongshan Torch Development Zone People's Hospital, Zhongshan, Guangdong, 528400, China

ARTICLE INFO

Keywords:
Metabolic dysfunction-associated fatty liver disease (MAFLD)
Traditional Chinese medicine constitution (TCMC)
Phlegm-dampness constitution (PDC)
Older

ABSTRACT

Background: Few studies have focused on the relationship between the traditional Chinese medicine constitution (TCMC) and metabolic dysfunction-associated fatty liver disease (MAFLD) in older populations. We sought to investigate the distribution of MAFLD and the TCMC in older people, and provide a theoretical basis for TCMC-based management of MAFLD in this population.

Methods: A cross-sectional study was conducted among older (≥65 years) individuals in Zhongshan, China. Information on common sociodemographic characteristics, medical history, anthropometric measurements, and the TCMC was collected. The chi-square test, multivariable logistic regression analysis, subgroup analysis, and inverse probability weighting of the propensity score were used to explore the relationship between MAFLD and the TCMC.

Results: Of 7085 participants, 1408 (19.9 %) had MAFLD. The three most common TCMC types in MAFLD patients were "phlegm-dampness", "gentleness", and "yin-deficiency". After adjustment for gender, age, tobacco smoking, alcohol consumption, body mass index, abnormal waist-to-hip ratio, hypertension, diabetes mellitus, and dyslipidemia, MAFLD was positively associated with the phlegm-dampness constitution (PDC) ($OR_{adjusted}$ (95 % CI) = 1.776 (1.496–2.108), $P < 0.001$), and negatively correlated with the qi-depression constitution (0.643 (0.481–0.860), 0.003). A stronger correlation between the PDC and MAFLD was observed in men compared with women ($OR_{adjusted}$ = 2.04 (95%CI = 1.47–2.84) *vs.* 1.70 (95%CI = 1.39–2.08), $P_{interaction}$ = 0.003) as well as between people who smoked tobacco and non-tobacco-smoking individuals (2.11 (1.39–3.21) *vs.* 1.75 (1.45–2.12), 0.006).

Abbreviations: TCMC, traditional Chinese Medicine Constitution; PDC, phlegm-dampness constitution; MAFLD, metabolic dysfunction-associated fatty liver disease; T2DM, type-2 diabetes mellitus; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglycerides; BMI, body mass index; WHR, waist-to-hip ratio; WC, waist circumference; HC, hip circumference; IQR, interquartile range; IPTW, inverse probability of treatment weighting; SMD, standardized mean difference; SD, standard deviation; OR, odds ratio; CI, confidence interval.

* Corresponding author. School of Public Health, Guangdong Pharmaceutical University, 283 Jianghai Road, Haizhu District, Guangzhou, 510310, China.
** Corresponding author.
E-mail addresses: 494205718@qq.com (L. Pan), qingsongchen@aliyun.com (Q. Chen).
[1] Tianran Shen and Shupei Wang contributed equally to this work.

https://doi.org/10.1016/j.heliyon.2024.e24905
Received 28 May 2023; Received in revised form 12 December 2023; Accepted 17 January 2024
Available online 18 January 2024

Conclusions: A positive relationship was observed between MAFLD and the PDC in older people living in Zhongshan. Early detection and treatment of the PDC (especially in men and smokers) could prevent the occurrence and development of MAFLD.

1. Introduction

Metabolic dysfunction-associated fatty liver disease (MAFLD) is the most common chronic liver disease worldwide, with an estimated overall prevalence of 37 % [1]. A meta-analysis of observational data in patients with non-alcoholic fatty liver disease (NAFLD) revealed an increased chance of being diagnosed with MAFLD [2]. This redefinition challenges understanding of this disease [3], seriously endangers human health, and imposes a huge economic burden upon society. Drugs to treat MAFLD in the USA and European Union are not available. The heterogeneity of the clinical presentation and course of MAFLD may be influenced by age, gender, ethnicity, diet, tobacco smoking, alcohol consumption, genetic predisposition, microbiota, and metabolic status [4,5].

The "traditional Chinese medicine constitution" (TCMC; *Ti Zhi* in Chinese) is a concept used to distinguish individual differences in human physiological characteristics through the lens of TCM. The TCMC is an integrated state of life and health comprising several elements of morphological structure, physiological function, and psychological state [6]. In 2009, through a series of large-scale, multicenter, nationwide epidemiological surveys and studies, the Chinese Academy of Traditional Chinese Medicine promulgated the *TCM Constitution of the Classification and Determination* [6], turning it into a uniform and standardized method to determine TCMC type. Due to the influence of congenital or acquired factors, the variability of an individual's TCMC leads to susceptibility to certain pathogenic factors, or susceptibility/tendency to develop certain diseases, which forms the background for certain types of diseases [7,8]. The TCMC has unique advantages in preventing and controlling chronic diseases. This feature enables the TCMC to provide more options for the prevention and treatment of chronic diseases.

There are large differences in a person's innate endowment of the TCMC, and similarly in the distribution of the TCMC among different groups of people [9]. The older population has reduced metabolic function. They can have multiple diseases, which may have complex causes and a long course, and a history of polypharmacy use. Hence, an older population will have disorders in glucolipid metabolism. Also, older people often tend to have a biased TCMC [10] and there is a correlation between their frail condition and the TCMC [11].

Research has shown a strong correlation between the occurrence of metabolic disorders and the TCMC [12–14]. In fact, studies have been conducted on the distribution of TCMC types in NAFLD [15,16], but relevant, rigorous, large-sample investigations on the physical characteristics are lacking. Moreover, there is a significant difference between the new nomenclature (MAFLD) and the traditional nomenclature (NAFLD) in terms of disease connotation. The latter highlights hepatic steatosis, whereas the former emphasizes the necessary presence of metabolic disorders. Moreover, MAFLD criteria incorporate some patients with NAFLD not identified by NAFLD criteria. The MAFLD population has more comorbidities and a worse prognosis than patients suffering from NAFLD only [17]. Furthermore, a systematic review and meta-analysis found that geographic regions were significantly associated with NAFLD prevalence, accounting for 35.27 % of the heterogeneity [18]. Due to different climatic environments and regional environments, coupled with differences in lifestyle habits, the TCMC of a population also has regional differences. Current research around MAFLD and TCM is limited by regional and population factors. Multicenter, large-scale, standardized clinical epidemiological studies of MAFLD and the TCMC are scarce. Therefore, investigating the distribution of the TCMC of MAFLD is a rational approach.

We set out to explore the relationship between MAFLD and the TCMC in people aged ≥65 years in Zhongshan (a city in South China that is a part of the Lingnan region). Our aim was to clarify the distribution of the TCMC of MAFLD, and to identify the types of TCMC susceptible to MAFLD. We hoped that our data could aid development of strategies for the prevention and control of MAFLD from the perspective of adjusting TCMC bias. Ultimately, we hope to provide a scientific basis for the development of "individualized" prevention and control of MAFLD for older people based on TCM theory.

2. Patients and methods

2.1. Study participants

The study protocol was approved (Medical Ethics [2019] number 109) by the Ethics Committee of Guangdong Pharmaceutical University (Guangdong, China). All study participants provided written informed consent.

A cross-sectional study was conducted from August to October 2020. Based on the National Basic Public Health Service Program of China, the survey population was older people (≥65 years) who underwent medical examinations provided by Torch Development Zone Hospital and Minzhong Hospital in Zhongshan City. This survey population had good compliance with the medical-examination survey of these hospitals, which was conducive to (and improved the quality of) our on-site data collection. Simultaneously, trained technicians collected information from the study population from completed structured questionnaires, anthropometric measurements, TCMC, blood analyses, electrocardiography, b-ultrasound, and other clinical examinations.

The inclusion criteria were: (1) age ≥65 years; (2) good verbal communication and clear expression; (3) completion of the TCMC questionnaire; (4) able to provide samples of venous blood after a fast; (5) availability of imaging examinations (b-ultrasound).

The exclusion criteria were patients: (i) aged <65 years; (ii) with major chronic diseases (e.g., cancer, mental illness, stroke); (iii) who could not complete the questionnaire independently; (iv) who did not complete the questionnaire; (v) for whom information from physical examinations was not available.

After screening for inclusion and exclusion criteria, the final number of individuals assessed was 7085 (flowchart of the study population is shown as Fig. 1).

The formula for estimation of sample size for cross-sectional surveys was [Formula (1)]:

$$N = \frac{Z^2_{(1-\alpha)/2} p(1-p)}{\delta^2} \quad (1)$$

where N represents the sample size, ($Z_{(1-\alpha)/2}$) is the percentile corresponding to an area of $1-\alpha$ under a standard normal distribution, p denotes the expected incidence, and δ is the allowable error of p. The current prevalence of MAFLD in Asia is 29.62 % [19]. Thus, the sample size was calculated using $\alpha = 0.05$, ($Z_{(1-\alpha)/2}$) $= 1.96$, $p = 0.2962$, $\delta = 0.1$, $p = 0.03$, and the final sample size was calculated as 890 cases. Considering a dropout rate of 20 %, at least 1113 cases would need to be included in our study. The number of respondents was 7085 cases.

2.2. Measurement of main variables

2.2.1. Diagnosis of MAFLD

According to a new definition of MAFLD proposed by an international panel of experts [19,20], the diagnosis of MAFLD is based on an ultrasound diagnosis of hepatic steatosis and the presence of at least one of three criteria: clinical evidence of overweight or obesity (body mass index (BMI) of an Asian population ≥23 kg/m^2); type-2 diabetes mellitus (T2DM); metabolic dysfunction. The latter was defined as the presence of at least two metabolic-risk abnormalities from the following: (1) waist circumference (WC) ≥90 cm in men and ≥80 cm in women; (2) blood pressure ≥130/85 mmHg or specific drug therapy; (3) triglycerides (TG) level in plasma ≥1.70 mmol/L or specific drug therapy; (4) high-density lipoprotein-cholesterol (HDL-C) level in plasma <1.0 mmol/L in men and <1.3 mmol/L in women, or specific drug therapy; (5) pre-DM (fasting glucose level of 5.6–6.9 mmol/L, 2-h post-load glucose level of 7.8–11.0 mmol/L, or glycated-hemoglobin level of 5.7 %–6.4 %); (6) Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) score ≥2.5; (7) high-sensitivity C-reactive protein (HS-CRP) level in plasma >2 mg/L. The medical examination did not include screening for the glucose level at 2 h post-load, insulin, or HS-CRP, so these three items were not available for assessment of abnormal metabolic disorders, and these criteria were not implemented in the present study.

2.2.2. Determination of the TCMC

We used the *TCM Constitution on the Old Age Scale of the Classification and Determination* (see Supplementary Materials for further detail) [21]. This is a national standard issued by the Chinese Association of Traditional Chinese Medicine. It is used to classify the nine types of the TCMC: gentleness, qi-deficiency, yang-deficiency, yin-deficiency, phlegm-dampness, dampness-heat, blood-stasis, qi-depression, and special diathesis [22,23].

2.3. Measurement of covariates

Information on sociodemographic characteristics (e.g.,gender, age, tobacco smoking, alcohol consumption), disease history, family

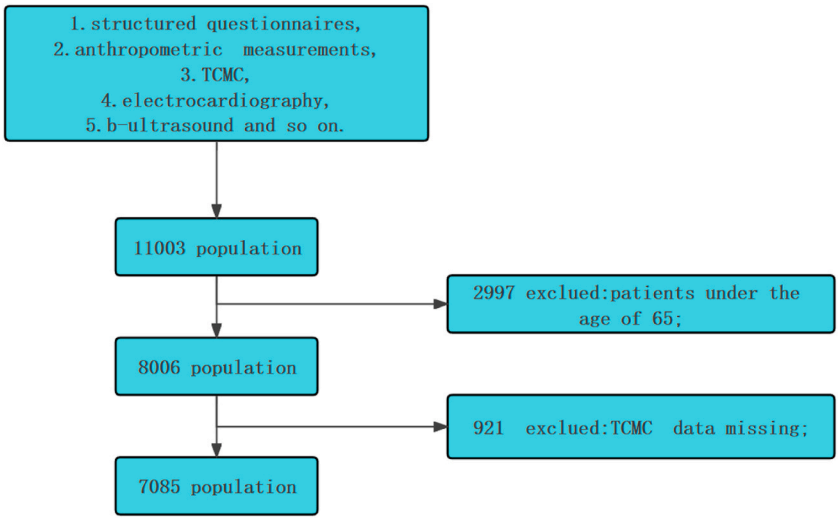

Fig. 1. Flowchart of the study population.

Table 1
Characteristics of participants with MAFLD at baseline.

Characteristic	MAFLD			*P*
	Total	No	Yes	
Total	7085 (100.0)	5677 (80.1)	1408 (19.9)	
Age, years, (mean ± SD)	71.35 ± 5.58	71.57 ± 5.69	70.47 ± 4.99	<0.001*
Gender (n, %)				<0.001*
male	2961 (41.8)	2545 (44.8)	416 (29.5)	
female	4124 (58.2)	3132 (55.2)	992 (70.5)	
Tobacco smoking (n, %)				<0.001*
no	5332 (75.3)	4167 (73.4)	1165 (82.7)	
yes	1753 (24.7)	1510 (26.6)	243 (17.3)	
Alcohol consumption (n, %)				<0.001*
no	5692 (80.3)	4464 (78.6)	1228 (87.2)	
yes	1393 (19.7)	1213 (21.4)	180 (12.8)	
Abnormal WHR (n, %)				<0.001*
no	1310 (18.5)	1232 (21.7)	78 (5.5)	
yes	5775 (81.5)	4445 (78.3)	1330 (94.5)	
BMI, kg/m^2 (n, %)				<0.001*
<23	2928 (41.3)	2768 (48.8)	160 (11.4)	
≥23	4157 (58.7)	2909 (51.2)	1248 (88.6)	
Hypertension (n, %)				<0.001*
no	3725 (52.6)	3156 (55.6)	569 (40.4)	
yes	3360 (47.4)	2521 (44.4)	839 (59.6)	
Diabetes mellitus (n, %)				<0.001*
no	6033 (85.2)	4983 (87.8)	1050 (74.6)	
yes	1052 (14.8)	694 (12.2)	358 (25.4)	
Dyslipidemia (n, %)				<0.001*
no	4280 (60.4)	3722 (65.6)	558 (39.6)	
yes	2805 (39.6)	1955 (34.4)	850 (60.4)	
TC (mmol/L)	5.21 ± 1.10	5.16 ± 1.08	5.41 ± 1.15	<0.001*
TG (mmol/L)	1.77 ± 1.22	1.60 ± 0.98	2.47 ± 1.72	<0.001*
LDL-C (mmol/L)	3.13 ± 0.90	3.11 ± 0.90	3.22 ± 0.92	<0.001*
HDL-C (mmol/L)	1.42 ± 0.37	1.46 ± 0.38	1.24 ± 0.32	<0.001*
GLU (mmol/L)	5.67 ± 2.00	5.64 ± 1.98	5.77 ± 2.10	0.033*
TCMC (n, %)				
Gentleness				<0.001*
no	3609 (50.9)	2704 (47.6)	905 (64.3)	
yes	3476 (49.1)	2973 (52.4)	503 (35.7)	
Qi-deficiency				0.028*
no	6326 (89.3)	5046 (88.9)	1280 (90.9)	
yes	759 (10.7)	631 (11.1)	128 (9.1)	
Yang-deficiency				0.011*
no	6372 (89.9)	5080 (89.5)	1292 (91.8)	
yes	713 (10.1)	597 (10.5)	116 (8.2)	
Yin-deficiency				0.151
no	5711 (80.6)	4557 (80.3)	1154 (82.0)	
yes	1374 (19.4)	1120 (19.7)	254 (18.0)	
Phlegm-dampness				<0.001*
no	4427 (62.5)	3893 (68.6)	534 (37.9)	
yes	2658 (37.5)	1784 (31.4)	874 (62.1)	
Dampness-heat				0.717
no	6622 (93.5)	5303 (93.4)	1319 (93.7)	
yes	463 (6.5)	374 (6.6)	89 (6.3)	
Blood-stasis				0.054
no	6070 (85.7)	4841 (85.3)	1229 (87.3)	
yes	1015 (14.3)	836 (14.7)	179 (12.7)	
Qi-depression				0.004*
no	6578 (92.8)	5246 (92.4)	1332 (94.6)	
yes	507 (7.2)	431 (7.6)	76 (5.4)	
Special diathesis				0.602
no	6801 (96.0)	5446 (95.9)	1355 (96.2)	
yes	284 (4.0)	231 (4.1)	53 (3.8)	

MAFLD: Metabolic dysfunction-associated fatty liver disease; BMI: body mass index; WHR: waist-to-hip ratio; TC: total cholesterol; TG: triglycerides; LDL-C: low-density lipoprotein-cholesterol; HDL-C: high-density lipoprotein-cholesterol; GLU: fasting glucose; TCMC: traditional Chinese medicine constitution.
*$P < 0.05$.

history, and lifestyle were collected using a validated structured questionnaire. Study participants were asked questions, item-by-item, and our trained and qualified researchers completed the questionnaire based on their responses. Tobacco smoking was divided into "never smoking" and "smoking". "Smokers" were defined as those who reported cumulative smoking of >100 cigarettes/five packs over their lifetime. "Alcohol consumption" was defined as regular consumption of alcohol in the past year (at least once a week for 6 months) or abstinence. The height, weight, BMI, WC, and hip circumference (HC) of participants were measured by trained physical examiners. The waist-to-hip ratio (WHR) was calculated as WC divided by HC. A WHR abnormality was defined as ≥0.9/0.85 in men/women, respectively.

Venous blood was collected and tested ≥8 h after fasting. DM was diagnosed if the patient had been diagnosed with DM at the township (community) level, at hospital, or if he/she was taking any anti-DM medication currently [24,25]. Hypertension was diagnosed if the patient had been diagnosed with hypertension at the township level, at hospital, or if he/she was taking any anti-hypertensive medication currently [26]. According to *Guidelines for the prevention and treatment of dyslipidemia in Chinese adults* (2016 revised edition), plasma levels of total cholesterol (TC) ≥6.2 mmol/L, TG ≥ 2.3 mmol/L, HDL-C <1.0 mmol/L, and low-density lipoprotein-cholesterol (LDL-C) ≥4.1 mmol/L were defined as exceeding the normal range, respectively. Dyslipidemia was diagnosed if one of the parameters stated above was exceeded [27,28].

2.4. Statistical methods

Data were double-entered, checked by EpiData 3.0 (www.epidata.dk), and organized into an Excel™ (Microsoft, Redwood, WA, USA) database. Categorical variables are described using frequencies or percentages. The mean ± standard deviation (SD) is used to describe continuous variables. The chi-square test and Student's *t*-test were employed for comparison between groups. Multivariable logistic regression analysis was undertaken to explore the relationship between the TCMC and MAFLD. Subgroup and interaction analyses were also undertaken to examine if this association differed due to confounding factors such as sex, age, BMI, or WHR.

We carried out sensitivity analysis. To verify the stability of the results, participants were grouped according to whether they had the phlegm-dampness constitution (PDC). Then, a "synthetic sample" was created using weights based on the propensity score, followed by inverse probability of treatment weighting (IPTW) of the propensity score. This analysis controlled for covariates with stable IPTW calculated from the propensity score [29]. The odds ratio (OR) and 95 % confidence interval (95%CI) for the PDC and MAFLD were calculated by a weighted logistic regression model. Confounding treatment-weighted inverse probabilities were controlled by correctly constructed propensity scores that eliminated the imbalance of measured covariates between study groups. Common tests used to assess if covariates are balanced after matching include the standardized mean difference (SMD) and variance ratio [30]. A universally accepted threshold is lacking. However, a SMD <0.1 is, in general, considered negligible [29–31] and SMD <0.25 is an acceptable threshold [32]. Usually, a variance ratio close to 1 or <2 is considered to denote a matched equilibrium [30].

Statistical analyses were carried out using SPSS 25.0 (IBM, Armonk, NY, USA) and SAS 9.4 (SAS Institute, Cary, NC, USA). $P < 0.05$ (two-sided) was considered significant.

3. Results

3.1. Patient characteristics at baseline

Table 1 demonstrates the characteristics of 7085 survey respondents at baseline. There were 2961 men (41.8 %) and 4124 women (58.2 %). The mean age was (71.35 ± 5.58) years. A total of 1408 (19.9 %) patients had MAFLD. The MAFLD group had a higher proportion of women, hypertension, dyslipidemia, and abnormal WHR. Differences ingender, age, as well as the prevalence of tobacco smoking, alcohol consumption, abnormal WHR, hypertension, DM, and dyslipidemia were significant between the MAFLD population

Table 2
Multivariable logistic regression analysis of MAFLD and TCM constitution.

TCMC	Crude model		Minimally adjusted model		Fully adjusted model	
	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
Gentleness	0.773 (0.655–0.914)	0.003*	0.780 (0.659–0.920)	0.004*	0.873 (0.728–1.047)	0.142
Qi-deficiency	0.833 (0.639–1.038)	0.103	0.883 (0.706–1.105)	0.278	0.830 (0.654–1.052)	0.123
Yang-deficiency	0.826 (0.660–1.034)	0.096	0.774 (0.616–0.972)	0.027	0.920 (0.721–1.174)	0.501
Yin-deficiency	0.873 (0.734–1.037)	0.121	0.880 (0.739–1.047)	0.151	0.887 (0.737–1.067)	0.202
Phlegm-dampness	3.153 (2.715–3.662)	<0.001*	3.351 (2.878–3.903)	<0.001*	1.776 (1.496–2.108)	<0.001*
Dampness-heat	1.032 (0.793–1.344)	0.813	1.053 (0.805–1.377)	0.707	1.028 (0.774–1.366)	0.846
Blood-stasis	0.784 (0.650–0.946)	0.011*	0.818 (0.676–0.989)	0.038*	0.888 (0.726–1.086)	0.247
Qi-depression	0.732 (0.559–0.960)	0.024*	0.639 (0.486–0.841)	0.001*	0.643 (0.481–0.860)	0.003*
Special diathesis	0.921 (0.669–1.269)	0.616	0.945 (0.683–1.308)	0.734	1.002 (0.712–1.412)	0.989

TCMC: Traditional Chinese medicine constitution; OR: odds ratio; CI: confidence interval.
Crude model: adjusted for nine types of the TCMC. Minimally adjusted model: adjusted for the nine types of the TCMC, as well as gender, and age. Fully adjusted model: adjusted for the nine types of the TCMC, as well as gender, age, tobacco smoking, alcohol consumption, BMI, abnormal WHR, hypertension, diabetes mellitus, and dyslipidemia.
*$P < 0.05$.

and non-MAFLD population ($P < 0.05$ or $P < 0.001$). Table S1 demonstrates the characteristics of patients with NAFLD at baseline.

3.2. Distribution of the TCMC of patients with MAFLD

The distribution of the TCMC of patients with MAFLD is shown in Table 1. With respect to the TCMC of 1408 individuals with MAFLD: 874 cases (62.1 %) had the PDC; 503 patients (35.7 %) had a gentleness constitution; 254 individuals (18.0 %) had the yin-deficiency constitution; 179 patients (12.7 %) had the blood-stasis constitution; 128 cases (9.1 %) had the qi-deficiency constitution; 116 individuals (8.2 %) had the yang-deficiency constitution; 89 cases (6.3 %) had the dampness-heat constitution; 76 individuals (5.4 %) had the qi-depression constitution; 53 cases (3.8 %) had the special diathesis constitution. There were significant differences in the prevalence of the gentleness constitution, qi-deficiency constitution, yang-deficiency constitution, PDC, and qi-depression constitution between the MAFLD population and non-MAFLD population ($P < 0.05$ or $P < 0.001$).

3.3. Multivariable logistic analysis of the TCMC and MAFLD

Multivariable logistic regression was employed to analyze the relationship between the TCMC and MAFLD (Table 2). The latter was used as the dependent variable. Nine types of the TCMC were used as independent variables. A crude model adjusted for the nine types of the TCMC. PDC and MAFLD had a significant positive association (OR (95%CI) = 3.153 (2.715–3.662), $P < 0.001$). When the fully adjusted model adjusted for the nine types of the TCMC as well as gender, age, tobacco smoking, alcohol consumption, BMI, abnormal WHR, hypertension, DM, and dyslipidemia, a significant association remained between the PDC and MAFLD ($OR_{corrected}$ (95%CI) = 1.776 (1.496–2.108), $P < 0.001$). In addition, there was a significant negative association between the qi-depression constitution and MAFLD ($OR_{corrected}$ (95%CI) = 0.643 (0.481–0.860), $P = 0.003$). There was no significant relationship between other types of the TCMC and MAFLD in the fully adjusted model.

3.4. Subgroup analysis of PDC and MAFLD

Subgroup analysis (Fig. 2) showed a strong positive association between the PDC and MAFLD at different levels of different factors (except alcohol consumption and normal WHR). A stronger association between the PDC and MAFLD was observed in men compared with women ($OR_{adjusted}$ = 2.04 (95%CI = 1.47–2.84) *vs*. 1.70 (95%CI = 1.39–2.08), $P_{interaction} = 0.003$). A stronger correlation between the PDC and MAFLD was observed for individuals who smoked tobacco compared with non-tobacco-smoking individuals ($OR_{adjusted}$ =

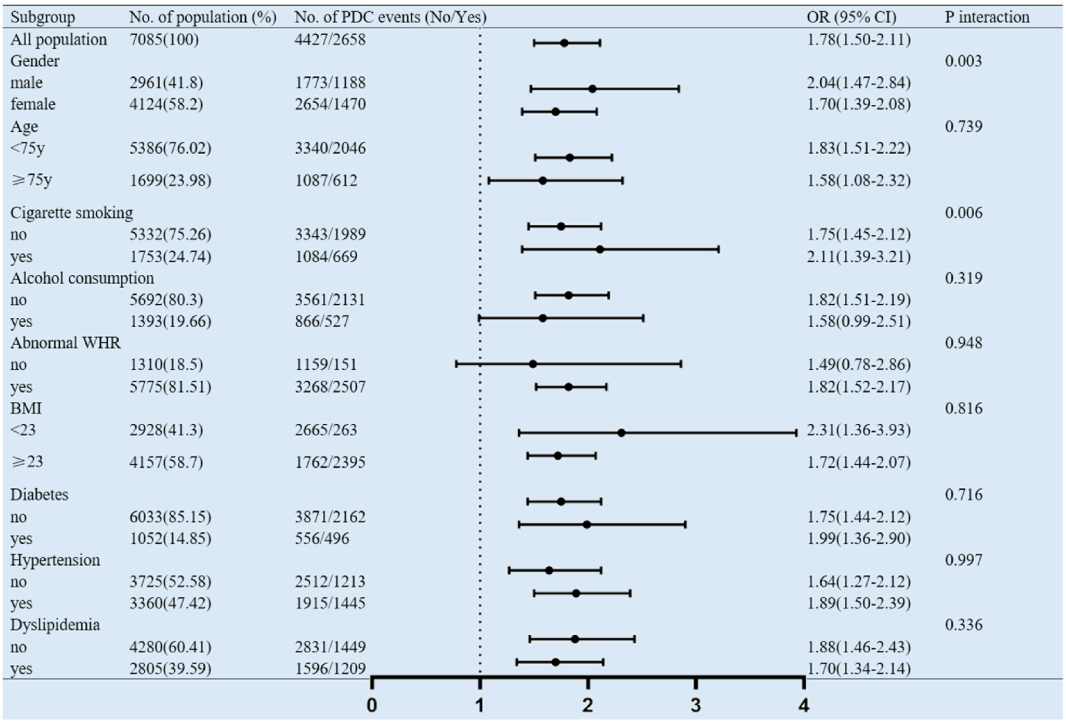

Fig. 2. Subgroup analysis MAFLD: Metabolic dysfunction-associated fatty liver disease; PDC: phlegm-dampness constitution; BMI: body mass index; WHR: waist-to-hip ratio; OR: odds ratio; CI: confidence interval; $P_{interaction}$: interaction test within subgroup analysis to investigate the relationship between the PDC and MAFLD separately in a population with different levels of confounding factors (e.g., gender, age, tobacco smoking). The interaction between the phlegm-dampness constitution with each confounding factor was examined.

2.11 (95%CI = 1.39–3.21) *vs.* 1.75 (95%CI = 1.45–2.12), $P_{interaction} = 0.006$).

3.5. Sensitivity analysis

In addition, participants were grouped according to whether they had the PDC. The covariates with stable IPTW calculated based on the propensity score were then controlled for, including confounding factors such as age, gender, tobacco smoking, alcohol consumption, BMI, WHR, hypertension, DM, dyslipidemia, and the other eight types of TCMC. The SMD of matched confounding factors was <0.1 or <0.2 between the PDC group and non-PDC group, thereby indicating that the covariates were balanced after matching (Table S2). Fig. S1 represents the distribution of the logit of propensity scores after matching: the covariates were smooth if the distribution was similar between the PDC group and non-PDC group. After adjustment for confounding variables, the weighted logistic regression model calculated an OR (95%CI) of 1.78 (1.42–2.24) for the PDC and MAFLD (Table 3). These data were consistent with the results of the fully adjusted model in the multivariable logistic regression analysis.

4. Discussion

Different types of the TCMC have been found to be closely related to several specific diseases [7,9]. Therefore, the TCMC has unique advantages and application value in the early identification and prevention of diseases.

We demonstrated an association between the PDC and MAFLD. First, more participants with the PDC had MAFLD compared with participants who did not have the PDC. After controlling for confounding variables such as age, sex, tobacco smoking, alcohol consumption, BMI, WHR, hypertension, DM, dyslipidemia, as well as the eight other types of the TCMC by multivariable logistic regression analysis, the PDC continued to have a positive association with MAFLD, data which are consistent with results from studies by Liang and colleagues and Zhu and coworkers [16,33]. First, the hot climate in the Lingnan region, frequent rain, and high air humidity can lead to the development of phlegm and dampness. The topography in Lingnan is complex and diverse, and the south is adjacent to the sea. Therefore, the PDC was one of the common types of TCMC in the Lingnan area. The PDC has been shown to be a high-risk factor for several chronic metabolic diseases, such as hyperlipidemia, DM, and NAFLD [14,34,35], and is considered to be a “common soil” for endocrine, nutritional, and metabolic diseases [35]. Based on TCM theory, MAFLD is caused mainly by the interaction of the PDC and abnormal function of the liver and spleen. PDC formation has some influence on the normal physiological functions of the liver and spleen [36]. Therefore, the PDC is one of the most important intrinsic bases for NAFLD development. A study of whole-gene DNA--methylation profiles was done in people with the PDC. Results showed that the differentially expressed genes associated with methylation in people with the PDC were abundant in multiple metabolic pathways compared with those in people with the gentleness constitution. This finding indicates a potential risk of metabolic disorders in individuals with the PDC [37]. In recent years, studies on molecular mechanisms (e.g., DNA methylation, RNA, intestinal flora) have demonstrated, in several aspects, that PDC formation is associated with insulin resistance, oxidative stress, increase in free fatty acids, energy metabolism, endocrine disorders, genetics, and disorders in the metabolism of glucose and lipids [38–40]. In conclusion, the PDC is closely related to the occurrence and development of MAFLD.

Subgroup analysis with interaction-effect analysis revealed that male participants with the PDC or participants with the PDC who smoked tobacco were more likely to develop MAFLD. A meta-analysis using observational data showed that MAFLD was associated significantly with a high BMI, hypertension, DM, lipid level, high fibrosis score, and being male [3,5]. Multiple studies have shown that tobacco smoking is positively associated with NAFLD, but the underlying mechanisms of this association are unclear [41–43]. Other studies have shown that individuals who smoked tobacco were 1.8-times more likely to develop the PDC than non-tobacco-smokers [44]. This phenomenon may be because the male population is more likely to smoke tobacco and consume alcohol, and to preferentially choose a greasy and salty diet, which may induce the accumulation of phlegm and dampness in the body [45]. The potential mechanisms of the interaction between gender or tobacco smoking and the PDC on MAFLD are not clear. However, a biased constitution can be modified and the lifestyle changed, thereby alleviating disease development. Some experimental studies have found that expectorant and phlegmatic prescriptions can alleviate liver injury in NAFLD and non-alcoholic steatohepatitis [46,47].

A cure for MAFLD is lacking due to uncertainty regarding the mechanism of action [48]. A healthy lifestyle is essential to counteract the early stages of MAFLD [49]. The TCMC is also an important basis for predicting the progression, regression, and prognosis of a disease [38]. Also, study of the PDC is a good entry point to explore metabolic disorders [42,50]. The disease spectrum of the PDC is dominated by metabolic disorders, as well as cardiovascular and cerebrovascular diseases [51]. Regardless of the disease, people with the PDC carry a higher risk of metabolic disorders [38]. Therefore, combining the TCMC with disease susceptibility, identifying

Table 3
Association of the phlegm-dampness constitution with MAFLD after IPTW matching.

After IPTW	Phlegm-dampness constitution			
	No	Yes	OR (95%CI)	*P*
MAFLD (n, %)	618 (14.8)	641 (20.1)	1.78 (1.42–2.24)	0.002*

MAFLD: Metabolic dysfunction-associated fatty liver disease; IPTW: inverse probability of treatment weighting; OR: odds ratio; CI: confidence interval.
*$P < 0.05$.

susceptible people, and improving the TCMC can prevent diseases before they occur, prevent them from spreading, and aid interventions. In conclusion, people with the PDC (especially men or tobacco smokers) should be the focus of MAFLD surveillance. With regard to adjustment of a biased TCMC, alterations in lifestyle and daily dietary habits by regulating the PDC are important for the prevention and treatment of chronic diseases and reducing the risk of MAFLD.

The stability of our results was verified further by sensitivity analysis of the IPTW of the propensity score. Our results were deemed stable and reliable according to this method.

Our study had three main limitations. First, this was a cross-sectional study, so we could demonstrate only a correlation between the PDC and MAFLD. Second, there may have been some degree of recall bias in self-reported data from questionnaires (e.g., alcohol consumption, tobacco smoking). Third, the status of fatty liver is not based on liver biopsy, but on abdominal ultrasonography, so we could not determine the severity of fatty liver. Further studies are needed to provide data to confirm the histology of the liver. Therefore, multicenter, large-scale, and standardized clinical epidemiological investigations of MAFLD and TCMC should be carried out. The causal relationship between the PDC and MAFLD (or the molecular mechanisms of PDC and MAFLD) should be determined in cohort studies or basic-science studies (as should the role of sex and tobacco smoking in the PDC and MAFLD).

5. Conclusions

We demonstrated a positive correlation between the PDC and MAFLD. The association between the PDC and MAFLD was stronger in men or those who smoked tobacco. Contrary to the experience of some practitioners of TCM, we found a negative association between the qi-depression constitution and MAFLD. Therefore, in the obligatory annual study in China (Traditional Chinese Medicine Management Plan for the Elderly), active intervention should be carried out for older people judged to have phlegm-dampness (especially the male population and those who smoke tobacco). The development of MAFLD could be prevented through correcting the PDC and quitting tobacco smoking.

Ethics approval

Written informed consent was obtained from all respondents before the questionnaire survey. The study protocol was approved (Medical Ethics [2019] number 109) by the Ethics Committee of Guangdong Pharmaceutical University (Guangdong, China).

Data availability statement

Data will not be required for this article.

Funding

This work was supported financially by the Medical Science and Technology Foundation of Guangdong Province (No. 2019GCZX012), Zhongshan Third Batch of Social Public Welfare and Basic Research Special Project (Health Care Key Project; No. 2020B3017), General Project of Guangzhou Basic and Applied Basic Research Project (No. 202201010545), and Medical Science and Technology Foundation of Guangdong Province (No. A2020112).

CRediT authorship contribution statement

Tianran Shen: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Shupei Wang:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Zhihao Wang:** Writing – original draft, Visualization, Formal analysis. **Hanlu Jia:** Resources, Data curation. **Yuan Wei:** Resources, Data curation. **Yu Li:** Resources, Investigation. **Qiutong Zheng:** Resources, Investigation. **Yuting Li:** Supervision. **Luanzhao Pan:** Project administration, Funding acquisition, Conceptualization. **Qingsong Chen:** Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no competing interests.

Acknowledgments

We acknowledge with gratitude the contributions of the residents of Zhongshan City, all medical staff and volunteers from the Torch Development Zone Hospital and Minzhong Hospital of Zhongshan City who participated in medical examinations, as well as all researchers from Guangdong Pharmaceutical University.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e24905.

References

[1] E. Kaya, Y. Yilmaz, Epidemiology, natural history, and diagnosis of metabolic dysfunction-associated fatty liver disease: a comparative review with nonalcoholic fatty liver disease, Adv. Endocrinol. Metabol. 13 (2022 Dec 10) 20420188221139650.
[2] G.E.H. Lim, A. Tang, C.H. Ng, Y.H. Chin, W.H. Lim, D.J.H. Tan, et al., An observational data meta-analysis on the differences in prevalence and risk factors between MAFLD vs NAFLD, Clin. Gastroenterol. Hepatol. 21 (3) (2023 Mar) 619–629.e7.
[3] K.E. Chan, T.J.L. Koh, A.S.P. Tang, J. Quek, J.N. Yong, P. Tay, et al., Global prevalence and clinical characteristics of metabolic-associated fatty liver disease: a meta-analysis and systematic review of 10 739 607 individuals, J. Clin. Endocrinol. Metab. 107 (9) (2022 Aug 18) 2691–2700.
[4] M.T. Julián, S. Ballesta, G. Pera, A. Pérez-Montes de Oca, B. Soldevila, L. Caballería, et al., Abdominal obesity and dsyglycemia are risk factors for liver fibrosis progression in NAFLD subjects: a population-based study, Front. Endocrinol. 13 (2023 Jan 13) 1051958.
[5] S.Y. Tang, J.S. Tan, X.Z. Pang, G.H. Lee, Metabolic dysfunction associated fatty liver disease: the new nomenclature and its impact, World J. Gastroenterol. 29 (3) (2023 Jan 21) 549–560.
[6] Q. Wang, TCM Body Consititution[M], Beijing, People's Medical Publishing House, 2009.
[7] Q. Wang, On 3 key issues in the study of the constitution of traditional Chinese medicine (Part One), J. Tradit. Chin. Med. 47 (2006) 250–252.
[8] Q. Wang, On 3 key issues in the study of the constitution of traditional Chinese medicine (Part Two), J. Tradit. Chin. Med. 47 (2006) 329–332.
[9] J. Di, Y.B. Zhu, Q. Wang, Y.Y. Wang, [Correspondence analysis of Chinese medical constitution features in different ages population], Zhongguo Zhong Xi Yi Jie He Za Zhi 34 (5) (2014 May) 627–630 (Chinese).
[10] H. Zhang, S.S. Wang, Investigation of Chinese medicine constitution of the elderly residents and the correlative factor research of the biased constitution, World Journal of Integrated Traditional and Western Medicine 7 (11) (2012) 972–974+997.
[11] X. Ma, H. Tang, J. Zeng, X. Pan, X. Luo, J. Liao, et al., Traditional Chinese medicine constitution is associated with the frailty status of older adults: a cross-sectional study in the community, Evid Based Complement Alternat Med 2022 (2022 May 25) 8345563.
[12] Y.B. Zhu, Q. Wang, C.Y. Wu, G.M. Pang, J.X. Zhao, S.L. Shen, et al., [Logistic regression analysis on relationships between traditional Chinese medicine constitutional types and overweight or obesity], Zhong Xi Yi Jie He Xue Bao 8 (11) (2010 Nov) 1023–1028 (Chinese).
[13] Y. Zhu, H. Shi, Q. Wang, Y. Wang, X. Yu, J. Di, et al., Association between Nine Types of TCM Constitution and Five Chronic Diseases: A Correspondence Analysis Based on a Sample of 2,660 Participants, vol. 2017, Evid Based Complement Alternat Med, 2017 9439682.
[14] Q. Huang, X.S. Zhao, S.N. Sun, L.Q. He, J. Yang, J.Y. Chen, et al., [Correlation analyses between obesity/overweight and constitutions of Chinese medicine/Cardio- vascular risk factors in elderly residents of a community in Guangzhou], Zhongguo Zhong Xi Yi Jie He Za Zhi 36 (10) (2016 Oct) 1208–1212 (Chinese).
[15] K. Zhu, Y. Guo, C. Zhao, S. Kang, J. Li, J. Wang, et al., Etiology exploration of non-alcoholic fatty liver disease from traditional Chinese medicine constitution perspective: a cross-sectional study, Front. Public Health 9 (2021 May 12) 635818.
[16] Y. He, G. Wang, H. Peng, Analysis of TCM constitution distribution in 393 patients with nonalcoholic fatty liver disease, Jiangxi J Tradit Chin Med 50 (2019) 45–47 (in Chinese).
[17] V.H. Nguyen, M.H. Le, R.C. Cheung, M.H. Nguyen, Differential clinical characteristics and mortality outcomes in persons with NAFLD and/or MAFLD, Clin. Gastroenterol. Hepatol. 19 (10) (2021 Oct) 2172–2181.e6.
[18] Z.M. Younossi, P. Golabi, L. de Avila, J.M. Paik, M. Srishord, N. Fukui, et al., The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: a systematic review and meta-analysis, J. Hepatol. 71 (4) (2019 Oct) 793–801.
[19] M. Eslam, P.N. Newsome, S.K. Sarin, Q.M. Anstee, G. Targher, M. Romero-Gomez, et al., A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement, J. Hepatol. 73 (1) (2020 Jul) 202–209.
[20] M. Eslam, S.K. Sarin, V.W. Wong, J.G. Fan, T. Kawaguchi, S.H. Ahn, et al., The Asian Pacific Association for the Study of the Liver clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease, Hepatol Int 14 (6) (2020 Dec) 889–919.
[21] X. Liu, The development and preliminary application analysis of the scale for the classification and judgment of the constitution of older Chinese medicine. Dissertation for Doctoral Degree, Beijing University of Chinese Medicine, Beijing, 2013.
[22] China Association of Chinese Medicine, Classification and determination of the constitution of TCM and TCM constitution scale (Version: ZYYXH/T157-2009), World J Integr Trad West Med 4 (2009) 303–304.
[23] Q. Wang, The Foundation of the Classification Diagnosis Standards for the Constitutions of TCM, 2009, pp. 16–26. China Standardization.
[24] Diabetes Branch of Chinese Medical Association, Chinese guidelines for the prevention and treatment of type 2 diabetes mellitus (2020 edition), Int. J. Endocrinol. Metabol. 41 (5) (2021) 482–548.
[25] W. Jia, J. Weng, D. Zhu, et al., Chinese Diabetes Society. Standards of medical care for type 2 diabetes in China 2019, Diabetes Metab Res Rev 35 (6) (2019 Sep) e3158.
[26] Joint Committee for Guideline Revision, Chinese guidelines for prevention and treatment of hypertension-A report of the revision committee of Chinese guidelines for prevention and treatment of hypertension, J Geriatr Cardiol 16 (3) (2018) 182–241.
[27] Chinese Joint Committee Chinese guidelines for prevention and treatment of dyslipidemia in adults (2016 Revision), Chin. J. Cardiol. 31 (2016) 937–952 (in Chinese).
[28] C. Yu, M. Wang, S. Zheng, et al., Comparing the diagnostic criteria of MAFLD and NAFLD in the Chinese population: a population-based prospective cohort study, J Clin Transl Hepatol 10 (1) (2022 Feb 28) 6–16.
[29] W.A. Ray, C.P. Chung, C.M. Stein, W. Smalley, E. Zimmerman, W.D. Dupont, et al., Association of rivaroxaban vs apixaban with major ischemic or hemorrhagic events in patients with atrial fibrillation, JAMA 326 (23) (2021 Dec 21) 2395–2404.
[30] Z. Zhang, H.J. Kim, G. Lonjon, Y. Zhu, Written on behalf of AME Big-Data Clinical Trial Collaborative Group. Balance diagnostics after propensity score matching, Ann. Transl. Med. 7 (1) (2019 Jan) 16.
[31] J.S. Haukoos, R.J. Lewis, The propensity score, JAMA 314 (15) (2015 Oct 20) 1637–1638.
[32] E.A. Stuart, B.K. Lee, F.P. Leacy, Prognostic score-based balance measures can be a useful diagnostic for propensity score methods in comparative effectiveness research, J. Clin. Epidemiol. 66 (8 Suppl) (2013 Aug) S84–S90.e1.
[33] S.H. Han, K.Z. Li, J.M. Zheng, Z.X. Zheng, M.C. Lin, M.Y. Xu, et al., [Study on the distribution of Chinese medical constitutions of hypertension complicated diabetes patients], Zhongguo Zhong Xi Yi Jie He Za Zhi 33 (2) (2013 Feb) 199–204 (Chinese).
[34] F. Bai, H. Luo, L. Wang, L. Zhu, Y. Guan, Y. Zheng, et al., A meta-analysis of the association between diabetes mellitus and traditional Chinese medicine constitution, Evid Based Complement Alternat Med 2021 (2021 Aug 4) 6390530.
[35] J. Shin, T. Li, L. Zhu, et al., Obese individuals with and without phlegm-dampness constitution show different gut microbial composition associated with risk of metabolic disorders, Front. Cell. Infect. Microbiol. 12 (2022 Jun 1) 859708.
[36] Z. Wang, W. Lian, Experimental discussion on the pathogenesis and treatment ideas of phlegm-damp fatty liver [C]//Chinese society of traditional Chinese medicine, body composition branch, Beijing university of traditional Chinese medicine, in: Proceedings of the Seventh Symposium on Body Composition in Traditional Chinese Medicine of the Chinese Academy of Traditional Chinese Medicine, 2009, p. 5 [publisher unknown].
[37] H. Yao, S. Mo, J. Wang, Y. Li, C.Z. Wang, J.Y. Wan, et al., Genome-wide DNA methylation profiles of phlegm-dampness constitution, Cell. Physiol. Biochem. 45 (5) (2018) 1999–2008.
[38] L. Dong, Y. Zheng, D. Liu, et al., Analyses of long noncoding RNA and mRNA profiles in subjects with the phlegm-dampness constitution, BioMed Res. Int. 2021 (2021 Dec 10) 4896282.
[39] J. Shin, T. Li, L. Zhu, Q. Wang, X. Liang, Y. Li, et al., Obese individuals with and without phlegm-dampness constitution show different gut microbial composition associated with risk of metabolic disorders, Front. Cell. Infect. Microbiol. 12 (2022 Jun 1) 859708.
[40] Lingru Li, Study on the Correlation between Phlegm-Damp Body Type and Obesity Subtypes and the Mechanism of Oxidative Stress that Predisposes to Metabolic Syndrome [D], Beijing University of Traditional Chinese Medicine, 2012.

[41] M. Okamoto, T. Miyake, K. Kitai, S. Furukawa, S. Yamamoto, H. Senba, et al., Cigarette smoking is a risk factor for the onset of fatty liver disease in nondrinkers: a longitudinal cohort study, PLoS One 13 (4) (2018 Apr 17) e0195147.
[42] H.S. Jung, Y. Chang, M.J. Kwon, E. Sung, K.E. Yun, Y.K. Cho, et al., Smoking and the risk of non-alcoholic fatty liver disease: a cohort study, Am. J. Gastroenterol. 114 (3) (2019 Mar) 453–463.
[43] S.W. Lai, Smoking and nonalcoholic fatty liver disease, Am. J. Gastroenterol. 114 (6) (2019 Jun) 998.
[44] H. You, T. Zhang, W. Feng, Y. Gai, Association of TCM body constitution with insulin resistance and risk of diabetes in impaired glucose regulation patients, BMC Compl. Alternative Med. 17 (1) (2017 Sep 11) 459.
[45] Q. Wang, Y.B. Zhu, Epidemiological investigation of constitutional types of Chinese medicine in general population: based on 21, 948 epidemiological investigation data of nine provinces in China, China Journal of Traditional Chinese Medicine and Pharmacy 24 (1) (2009) 7–12.
[46] Q. Feng, W. Liu, S.S. Baker, H. Li, C. Chen, Q. Liu, et al., Multi-targeting therapeutic mechanisms of the Chinese herbal medicine QHD in the treatment of non-alcoholic fatty liver disease, Oncotarget 8 (17) (2017 Apr 25) 27820–27838.
[47] J. Leng, F. Huang, Y. Hai, H. Tian, W. Liu, Y. Fang, et al., Amelioration of non-alcoholic steatohepatitis by Qushi Huayu decoction is associated with inhibition of the intestinal mitogen-activated protein kinase pathway, Phytomedicine 66 (2020 Jan) 153135.
[48] K. Pafili, M. Roden, Nonalcoholic fatty liver disease (NAFLD) from pathogenesis to treatment concepts in humans, Mol. Metabol. 50 (2021 Aug) 101122.
[49] P. Hamurcu Varol, E. Kaya, E. Alphan, Y. Yilmaz, Role of intensive dietary and lifestyle interventions in the treatment of lean nonalcoholic fatty liver disease patients, Eur. J. Gastroenterol. Hepatol. 32 (10) (2020 Oct) 1352–1357.
[50] Q. Wang, Individualized medicine, health medicine, and constitutional theory in Chinese medicine, Front. Med. 6 (1) (2012 Mar) 1–7.
[51] Q. Wang, Response and advantages of TCM somatology in big health issues, Journal of Beijing University of Traditional Chinese Medicine 44 (3) (2021) 197–202.