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Lifestyle Interventions for Non-Obese Patients Both with, and at Risk, of Non-Alcoholic Fatty Liver Disease

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Non-alcoholic fatty liver disease occurring in non-obese subjects (the so-called non-obese NAFLD) is a highly prevalent but neglected liver condition, which is closely associated with metabolic disorders and suboptimal lifestyles. Landmark studies have shown that lifestyle interventions are potentially beneficial in decreasing the risk of developing non-obese NAFLD and in ameliorating NAFLD in non-obese individuals with pre-existing NAFLD. Lifestyle interventions usually refer to changes in eating habits and physical activity, both of which have a powerful effect on non-obese NAFLD and on risk factors for non-obese NAFLD. However, to date, patients and health-care professionals have a poor awareness and understanding of non-obese NAFLD and the beneficial effects of lifestyle interventions in this patient population. The aim of this narrative review is to briefly discuss the evidence for the effects of lifestyle changes and what changes are needed amongst medical personnel and other stakeholders in order to raise awareness of non-obese NAFLD.

Keywords: Exercise; Feeding behaviors; Fructose; Life style; Non-alcoholic fatty liver disease; Social planning

INTRODUCTION

Non-obese non-alcoholic fatty liver disease (non-obese NAFLD), first discovered in Asia, has been increasingly recognized worldwide [1]. Currently, the number of individuals with non-obese NAFLD has reached epidemic proportions, with approximately 5% to 30% of the general population in different regions having this condition [2]. It has been reported that non-obese NAFLD prevalence is highest in Hispanic and Asian (35.1% and 35.6%, respectively) ethnic groups, followed by White (30.0%) and Black (11.6%; $P<0.001$) ethnic groups [3]. Non-obese NAFLD is influenced by an unhealthy diet and a sedentary lifestyle and these factors are also affected by host genetics, metabolism, endocrinology, and other factors such as gut microbiota [4-10]. The medical burden of non-obese NAFLD is aggravated by the fact that individuals with non-obese NAFLD may develop long-term liver-related complications and multiple extra-hepatic comorbidities, such as cardiovascular disease and chronic kidney disease [11-14]. For example, recent data has demonstrated that around 40% of the global NAFLD population are classified as non-obese, among which 39.0% (95% confidence interval [CI], 24.1 to 56.3) had non-alcoholic steatohepatitis (NASH), 29.2% (95% CI, 21.9 to 37.9) had significant fibrosis (stage ≥2), and 3.2% (95% CI, 1.5 to 5.7) had cirrhosis [11]. It has been estimated that the annual health care burden related to each patient with non-obese

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NAFLD is $1,613 in the USA and €1,163 in the Europe, respectively [15]. Consequently, it is now apposite that we should attach great importance to this long-term ignored and detrimental disease.

The importance of lifestyle factors in the development of non-obese NAFLD creates an opportunity to utilize healthy lifestyle modifications as the first-line treatment to slow the increasing prevalence of non-obese NAFLD worldwide [16,17]. First, evidence from an Asian randomized controlled trial involving 154 NAFLD individuals showed that a 12-month lifestyle intervention aimed at improving physical activity and a healthy diet successfully induced remission of NAFLD (as assessed by proton-magnetic resonance spectroscopy) in 67% of non-obese subjects compared with 18% in the control group [18]. This trial also showed that non-obese subjects achieved remission of NAFLD with 3% to 5% weight reduction; the same could only be achieved in obese subjects with 7% to 10% weight reduction [18]. Second, the severity of metabolic abnormalities is found to be milder in patients with non-obese NAFLD compared to their obese counterparts with NAFLD (Tables 1 and 2) [3,11,18-24]. Finally, most of the drugs for non-obese NAFLD, targeting different molecules such as peroxisome proliferator-activated receptor (PPAR)-α/γ agonists, pan-PPAR agonists, sodium-glucose cotransporter 2 inhibitors, or glucagon-like peptide-1 receptor agonists, are still in clinical development or being tested in large randomized clinical trials [25]. Nonetheless, except for lifestyle interventions, strategies that promote population-level improvements in health are also needed to complement intensive-intervention approaches in high-risk populations [26].

Table 1. Differences in NAFLD-related metabolic abnormalities between non-obese and obese individuals with NAFLD in original studies

Study	Study type	Population	Non-obese vs. obese NAFLD
Wong et al. (2018) [18]	Randomized controlled trial	*n*=154, ^{1}H-MRS-proven NAFLD	Lower WC/FPG
Feldman et al. (2017) [19]	Cross-sectional study	*n*=187, ultrasound-proven NAFLD	Lower WC/TG/FPG/HOMA-IR
Chen et al. (2020) [20]	Cross-sectional study	*n*=538, biopsy-proven NAFLD	Lower WHR/TG/FBG/HOMA-IR Lower incidence of type 2 diabetes mellitus
Younes et al. (2022) [21]	Prospective longitudinal study	*n*=1,339, biopsy-proven NAFLD	Lower WC/TG/FPG Lower incidence of type 2 diabetes mellitus
Tan et al. (2022) [22]	Cross-sectional study	*n*=1,812, biopsy-proven NAFLD	Lower WC Lower prevalence of central obesity/prediabetes or diabetes/hypertension
Zou et al. (2020) [3]	Cross-sectional study	*n*=14,365, US-FLI-defined NAFLD	Lower WC/BP/FPG/HOMA-IR

NAFLD, non-alcoholic fatty liver disease; ^{1}H-MRS, proton-magnetic resonance spectroscopy; WC, waist circumference; FPG, fasting plasma glucose; TG, triglyceride; HOMA-IR, homeostasis model assessment of insulin resistance; WHR, waist-to-hip ratio; US-FLI, US fatty liver index; BP, blood pressure.

Table 2. Differences in NAFLD-related metabolic abnormalities between non-obese and obese individuals with NAFLD in meta-analytic studies

Study	Study composition	Non-obese vs. obese NAFLD
Ye et al. (2020) [11]	*n*=10,576,383, from 93 studies (84 cross-sectional and 5 prospective)	Lower BP/HOMA-IR
Lu et al. (2020) [23]	*n*=205,307, from 33 studies (26 cross-sectional, 4 prospective, and 3 retrospective)	Lower WC/BP/HbA1c Lower incidence of central obesity/dyslipidemia/diabetes/hypertension
Ito et al. (2021) [24]	*n*=258,531, from 73 studies (55 cross-sectional, 6 prospective, 9 outcome analyses, and 6 NAFLD characteristics data only)	Lower WC/FPG/HbA1c/HOMA-IR Lower incidence of central obesity/dyslipidemia/diabetes/hypertension

NAFLD, non-alcoholic fatty liver disease; BP, blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance; WC, waist circumference; HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose.

INTERVENTIONS AND TREATMENTS FOR NON-OBESE NAFLD

The American Association for the Study of Liver Diseases (AASLD) has stated that lifestyle modifications, consisting of hypocaloric diet and exercise, should be advocated to treat most patients with NAFLD, regardless of the patient's body weight [27]. Therefore, it is also clinically important for non-obese patients with NAFLD that they are encouraged to make lifestyle changes when appropriate.

Healthy eating in the treatment of non-obese NAFLD

It is difficult for individuals in society to maintain a healthy diet and healthy eating patterns with the advent of a "fast food" era. Not only has the consumption of refined sugar and fructose increased in recent times, but also unhealthy dietary habits, including frequent and irregular patterns of eating (≥6 times daily), have increased rapidly [4,28]. Preliminary studies have suggested that these behaviors are associated with a spectrum of liver injury in non-obese patients, including non-alcoholic fatty liver (NAFL), NASH, cirrhosis, and hepatocellular carcinoma [4]. The possible underlying mechanisms contributing to the development and progression of NAFLD in non-obese individuals include increased hepatic *de novo* lipogenesis (DNL), inhibition of fat oxidation, greater insulin resistance (IR), circadian rhythm disorders, and intestinal dysbiosis. Consequently, it is widely acknowledged that lifestyle changes targeting each of these processes should be advocated in non-obese patients both at risk of, and with, pre-existing NAFLD.

Diet: first started with quitting fructose

Hypercaloric, high fat, low insoluble dietary fiber and high glycemic index diets may be involved in the pathophysiology of non-obese NAFLD, among which high dietary sucrose and fructose consumption seems to be the major contributor [16,28]. In recent years, added sugar in soft drinks, which is a common source of fructose, has increased rapidly with the introduction of sweeteners by the drinks industry [28]. For example, soft drinks intake has increased markedly over the last century and by the year 2000 accounted for approximately 10% of overall energy intake in the average American [29,30]. Furthermore, preliminary studies have also confirmed that the higher intake of sugar-sweetened beverages happens among younger people (adolescents and adults in their twenties) and among ethnic minorities (African Americans, Hispanics, and Native Americans) [31,32].

Until now, some evidence shows that fructose when consumed at levels typical of Western diets can lead to an increase in visceral adipose tissue, liver fat accumulation (NAFL) and other ectopic fat depots in non-obese individuals [33]. A minority of non-obese patients with NAFL may then develop the more advanced forms of NAFLD, and the evidence also suggests that increased fructose intake may promote progression to more advanced forms of NAFLD in both non-obese children and adults [34,35]. In non-obese NAFLD individuals who consume a substantial amount of fructose; both carbohydrate responsive-element binding protein and sterol regulatory element binding protein 1c are indirectly activated by the high circulating levels of insulin and glucose associated with hepatic and whole-body IR, as well as the fructose-derived metabolites [33,36]. Activation of these two proteins upregulates the full complement of enzymes required for DNL, thereby contributing to the hepatic storage of free fatty acids [37-39]. Furthermore, hepatic metabolism of fructose also inhibits mitochondrial β-oxidation of long-chain fatty acids and impairs triglyceride export in individuals with non-obese NAFLD [40]. Due to the molecular instability of its five-membered furanose ring, fructose promotes protein fructosylation and formation of reactive oxygen species, which eventually results in hepatic inflammation and fibrosis in non-obese individuals with NAFLD [40].

It is therefore important to consider how best to manage individuals who are non-obese and who are diagnosed with NAFLD [1]. Reduction of fructose consumption may decrease liver fat, visceral adipose tissue and DNL, and improve IR [41]. It is also important for subjects to pay more attention to the mode of fructose intake, because this may also affect its biological impact. For example, in animal studies, fructose provided in liquid form is more deleterious than that incorporated into solid food [42,43]. Additionally, sugar ingested as a single large daily bolus is more detrimental than frequent ingestion of smaller amounts of fructose [43]. Thus, it is advisable to ingest fructose in food and avoid large quantities of fructose in drinks.

Clock: follow the "time restricted feeding"

A 21st century lifestyle (for example, involving travelling, commuting, jet lag, night, or rotating shift work) creates "circadian misalignment" and has emerged as a major contributor to metabolic liver diseases, including NAFLD and NASH, regard-

less of the presence or absence of obesity [44]. Changes in circadian gene expression in hepatocytes, endothelial cells, and Kupffer cells, which in turn influence metabolism in the liver [45,46], may adversely affect the development and progression of non-obese NAFLD.

In most cases, circadian rhythms in humans are mediated by the supra-chiasmatic nuclei (SCN), which is a master clock in the brain setting the time for all other peripheral body clocks in the liver and intestine [47]. Studies have shown that temporal signals such as the timing of food intake may reset peripheral tissue clocks without affecting the SCN central clock rhythms [48], and this may affect subsequent changes in non-obese NAFLD (Fig. 1). Except for abnormalities of systemic metabolism (including glucose, lipid, cholesterol, and bile acid metabolism), it has been suggested that disturbances of the circadian clock machinery may lead to autophagy, endoplasmic reticulum stress and increased oxidative stress in hepatocytes, all of which may promote the development of non-obese NAFLD and its progression to NASH [49]. Additionally, changes in feeding time may reshape the rhythmicity and composition of gut microbiota, which produces bacterial metabolites, such as secondary bile acids and short-chain fatty acids [50]. These gut microbiota-derived metabolites can affect liver metabolism, mainly through a variety of pathways, including contact-dependent mechanisms like pattern recognition receptors and contact-independent mechanisms, as well as changes in intestinal barrier integrity [50].

Recently, a dietary therapy called time restricted feeding (TRF) has attracted a lot of scientific interest and aims at aligning peripheral and central circadian rhythms, by restricting dietary intake to certain times of the day on every day. This style and pattern of eating has the potential for use as a treatment

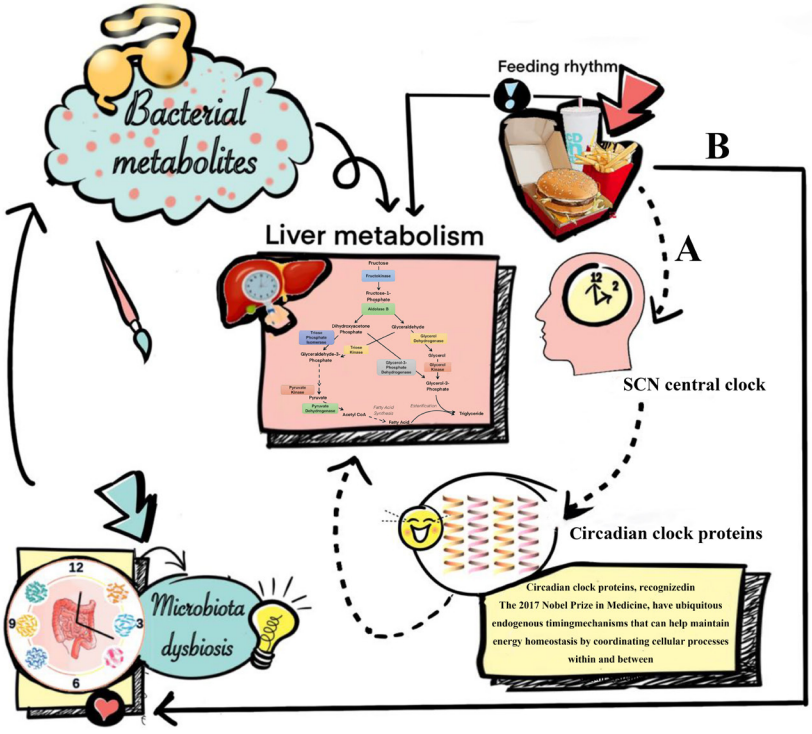

Fig. 1. Feeding rhythms and non-obese non-alcoholic fatty liver disease (NAFLD). Feeding rhythms can reset peripheral tissue clocks and subsequently leads to non-obese NAFLD without influencing the supra-chiasmatic nuclei (SCN) central clock rhythms. (A with dotted line) Directly cause non-obese NAFLD, possibly via resetting the liver clock; resetting liver clock can not only change the systemic metabolism like glucose, lipid, cholesterol and bile acid metabolism, but also lead to autophagy, endoplasmic reticulum stress and increased oxidative stress in hepatocytes. All these factors have been confirmed to be associated with the occurrence of non-obese NAFLD. (B with solid line) Indirectly cause non-obese NAFLD, possibly via changing the gut microbiome; gut microbiome may be another key factor involved in the development of non-obese NAFLD. When the gut microbiome changes (dysbiosis), secondary metabolites are produced, e.g., short-chain fatty acids and bile acids, which may contribute to development of non-obese NAFLD.

for NAFLD or NASH in non-obese individuals [49]. TRF does not necessarily reduce calorie intake and it has been shown that TRF increases hepatic fatty acid β-oxidation, decreases hepatic glucose production, as well as reduces macrophage infiltration and hepatic inflammation, all of which are potentially beneficial for the remission of NAFLD or NASH in non-obese individuals [51]. TRF may significantly change the gut microbiome diversity with a decrease of *Escherichia* and enrichment of *Prevotellaceae* and *Bacteroideaceae* [52]. Recently, it has been confirmed that *Escherichia fergusonii* may promote non-obese NAFLD by interfering with host hepatic lipid metabolism through its own msRNA 23487 [53]. Consequently, it may be important to advocate TRF especially restricting food intake to the middle of the day, as food intake at this time is associated with an abnormal metabolic and inflammatory response in the liver [54-58].

Physical activity in the treatment of non-obese NAFLD

Physical inactivity, driven by the high prevalence of sedentary behaviors within the population, is becoming increasingly common worldwide. For example, the most recent global estimates show that one in four (27%) adults [59] and more than three-quarters (81%) of adolescents [60] do not meet the recommendations for aerobic exercise, as outlined in the 2010 Global Recommendations on Physical Activity for Health [61]. In fact, sedentary behaviors, typically characterized by reduced muscle activity, are closely associated with sarcopenia, systemic IR and low-grade inflammation, all of which can contribute to the progression of non-obese NAFLD.

The spectrum of evidence underpinning the link between physical activity and health is particularly compelling in relation to the development of non-obese NAFLD. Prospective observational research has reported that moderate to vigorous physical activity levels are consistent with current recommendations associated with a reduced risk of incident non-obese NAFLD and resolution of already present non-obese NAFLD [62]. Some mechanistic studies have described several pathways linking increased physical activity to improvement of non-obese NAFLD. First and foremost, there is a complex interaction between three major organs: adipose tissue, liver, and skeletal muscles in non-obese NAFLD, and physical exercise may improve IR in these three organs [63]. An improvement of IR in peripheral tissues may also reduce glucose transport to the liver from muscle tissue and decrease free fatty acid flux to the liver, thus reducing DNL and potentially decreasing liver fat content [63]. Second, exercise reduces the risk of sarcopenia, which is an important risk factor for non-obese NAFLD [64,65]. Furthermore, improved muscle function may further reduce systemic IR and improve hepatic inflammation [66]. Finally, exercise also increases cardiorespiratory fitness, which is particularly useful in decreasing cardiovascular risk in patients with non-obese NAFLD [64].

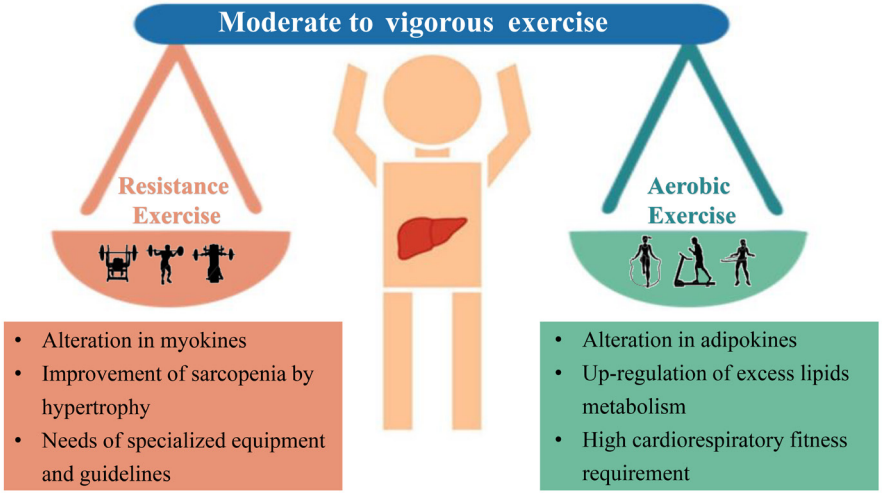

Fig. 2. Characteristics of two different types of physical activities. Moderate to vigorous physical activity levels are recommended to decrease the risk of new non-obese non-alcoholic fatty liver disease (NAFLD) and resolve the already present non-obese NAFLD. Two different types of exercise for preventing or treating non-obese NAFLD, i.e., aerobic or resistance exercise, can produce comparable hepato-protective effects with similar frequency, duration, and periods of exercise.

There are two different groups of exercise for preventing or treating non-obese NAFLD, i.e., aerobic or resistance exercise (Fig. 2). Current evidence shows that both forms of exercise produce comparable therapeutic effects with similar frequency, duration, and periods of exercise (40–45 minute/session three times/week for 12 weeks) [67]. Aerobic exercise, such as running and cycling, is a low-cost, convenient, and extremely high energy-consuming intervention. Not only does aerobic exercise require good cardiorespiratory fitness because of its high oxygen consumption, but also it is sometimes not feasible in older patients due to arthritis, discomfort, and fatigue [68]. Therefore, resistance exercise, utilizing muscle strength mass and bone density, may be preferable for many patients with NAFLD and seems to produce metabolic benefits with less energy consumption [67]. Thus, subgroups such as the elderly who have sarcopenia, arthritis, or poor cardiorespiratory fitness, may prefer exercise with a low intensity exercise volume [4]. Until now, a beneficial exercise program has not been elucidated for patients with non-obese NAFLD. We propose that exercise targets should be similar for non-obese or obese patients, namely 4.5 metabolic equivalents (METs), 45 minutes/session, and three times/week for aerobic exercise or 3.5 METs, 45 minutes/session, and three times/week for resistance exercise [4].

SOCIAL PLANNING TOWARDS NON-OBESE NAFLD MANAGEMENT

Several compelling and practical guidelines suggest that treatment schemes for patients with NAFLD should be accompanied by population-level efforts to raise awareness. Such efforts should include "sustained government initiatives comprising advocacy, community support, private sector engagement, and continuous media communication" (Fig. 3).

National government level strategies

Despite the significant challenges that non-obese NAFLD present, guidelines and a strategy for non-obese NAFLD are largely absent from the current global health discourse, so they should be addressed in the future sustainable development goals [69]. Also, there are no unified methods for differentiating patients, which may be partially due to the outdated no-

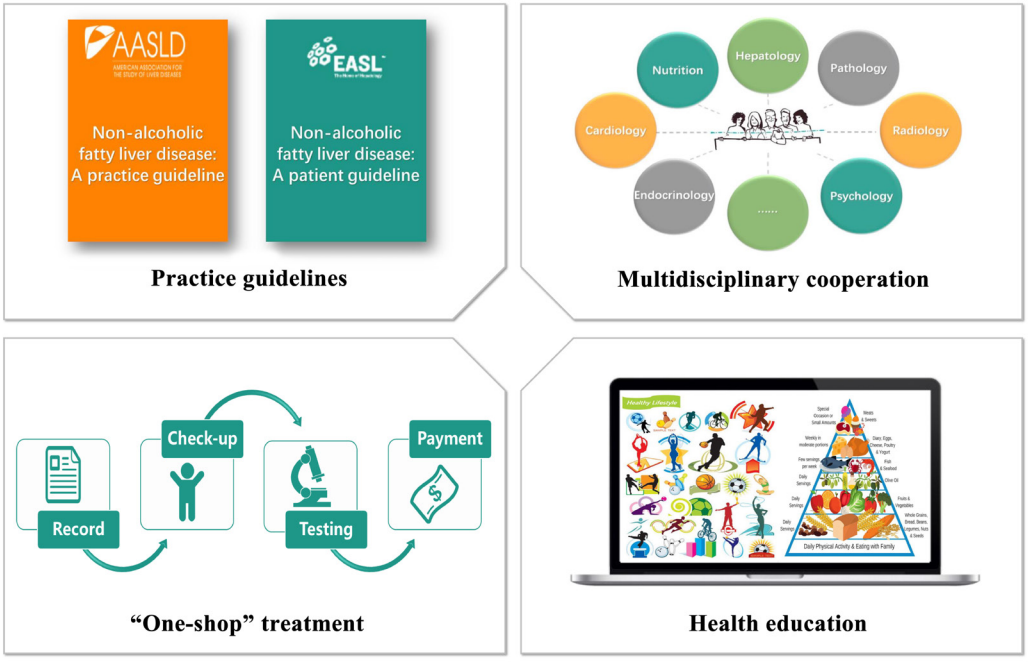

Fig. 3. Developing a strategy for non-obese non-alcoholic fatty liver disease (NAFLD). Organizations and governments should develop guidelines and policies for non-obese patients with NAFLD. We propose that developing a strategy for non-obese NAFLD needs to involve the development of guidelines, multidisciplinary cooperation between different types of health-care professionals, establishing a unified 'one stop shop' for the completion of care, and improved education of patients, health-care professionals and managers.

menclature and definition [70,71]. Consequently, it is crucial for organizations and governments to establish a framework which targets policy development and individual-level treatment making. The first step is to establish guidelines for non-obese NAFLD at the regional level, including health system structures and funding, as well as reimbursement systems in each country or region [26,72]. The emergence of guidelines can contribute to the unified management of non-obese NAFLD worldwide as well as being beneficial and educational for health-care professionals involved in the diagnosis and management of non-obese NAFLD [70]. In addition, based on the complexity of non-obese NAFLD and its close relationship with metabolic-dysfunction associated fatty liver disease, it is important to establish multidisciplinary care for this patient group [70,71,73-75]. Multidisciplinary clinics, which are emerging models of health care delivery, usually provide individuals with coordinated care services from different medical specialists to diagnose problems, evaluate disease severity, and develop treatment plans [74]. This approach may facilitate the cooperation of diverse services delivered at different levels of the health-care system (primary, secondary, and tertiary) [70], and also improve patient experience and quality of life in NAFLD care, while reducing health care costs [74]. Last, but not least, putting NAFLD on the global public health and development agendas, and promoting NAFLD as a global public health issue is central [76], because there is a significant knowledge gap between liver specialists and non-liver specialists [77].

Regional government level strategies

The next level of public-health action refers to the community service, which also has a marked impact on disease management [78]. A primary public-health strategy should enable a "one-stop shop" approach, indicating that all check-ups, recordings and follow-up visits are completed on one site [79-81]. This approach ensures that care is well cooperated and integrated and enables patients' demands to be assessed and resolved [70]. Additionally, education of managers is a pre-requisite for successful intervention programs, which include low glycemic index diet, TRF, and appropriate physical activity. Offering healthy lifestyle education in school can also be effective for disease prevention because it is useful for students to learn how to eat healthily and exercise [82]. Another effective public-health instrument is to construct community infrastructure including cycle pathways, leisure centers, public footpaths, and parks so that this may facilitate and encourage patients to engage in physical activity [83].

Personal level strategies

Non-obese NAFLD is often referred to as a self-inflicted disease, implying that personal behavioral choices are primary determinants of our chances of developing these conditions [73]. Thus, it is significant for individuals, especially those subjects who carry the patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) rs738409 GG genotype, to develop an improved understanding of non-obese NAFLD, learn how to monitor their own condition, and assess the effectiveness of various therapeutic strategies [84-86]. First and foremost, individuals should be encouraged to participate in, and be offered health lectures, to facilitate them taking an active role in their own health-care (thereby learning directly from their doctors the importance of healthy diet and exercise as well as the direct impact that making these changes may have on their medical conditions). Second, individuals should be encouraged to monitor (where relevant) body weight, waist circumference, blood pressure, plasma glucose, and triglyceride concentrations, all of which are risk factors for non-obese NAFLD, as well as make a detailed diet and exercise plan.

CONCLUSIONS

Non-obese NAFLD is now established as a major public-health challenge in both developing and developed countries. The potential to treat NAFLD in non-obese individuals by lifestyle interventions is now firmly established. A healthy diet, regular eating habits and increased physical activity are central to lifestyle modifications, and their promotion should form a key component of any therapeutic initiative for NAFLD, regardless of the patient's body weight.

CONFLICTS OF INTEREST

Ming-Hua Zheng has been international editorial board members of the *Diabetes & Metabolism Journal* since 2022. He was not involved in the review process of this review. Otherwise, there was no conflict of interest.

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