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REVIEW

Therapies for patients with coexisting heart failure with reduced ejection fraction and non-alcoholic fatty liver disease

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Abstract

Heart failure with reduced ejection fraction (HFrEF) and nonalcoholic fatty liver disease (NAFLD) are two common comorbidities that share similar pathophysiological mechanisms. There is a growing interest in the potential of targeted therapies to improve outcomes in patients with coexisting HFrEF and NAFLD. This manuscript reviews current and potential therapies for patients with coexisting HFrEF and NAFLD. Pharmacological therapies, including angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, mineralocorticoids receptor antagonist, and sodium-glucose cotransporter-2 inhibitors, have been shown to reduce fibrosis and fat deposits in the liver. However, there are currently no data showing the beneficial effects of sacubitril/valsartan, ivabradine, hydralazine, isosorbide nitrates, digoxin, or beta blockers on NAFLD in patients with HFrEF. This study highlights the importance of considering HFrEF and NAFLD when developing treatment plans for patients with these comorbidities.

Further research is needed in patients with coexisting HFrEF and NAFLD, with an emphasis on novel therapies and the importance of a multidisciplinary approach for managing these complex comorbidities.

Key Words: Non-alcoholic fatty liver disease; Heart Failure; Heart failure reduced ejection fraction; Novel therapies; Cardiovascular disease

Core Tip: This manuscript provides an overview of potential therapies for patients with coexisting heart failure with reduced ejection fraction and nonalcoholic fatty liver disease (NAFLD). The authors discuss the current research of pathogenesis in heart failure and NAFLD, as well as pharmacological therapies that have been shown benefits. We also discuss the potential role of diet, physical activity and novel therapies in managing these conditions.

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INTRODUCTION

Heart failure (HF) is a major clinical, economic, and public health concern worldwide. The prevalence of HF in the United States and Europe is estimated to be 1.5% to 1.9% of the population, reaching a considerable number among people aged > 65 years[1]. The predominant etiologies of HF include coronary artery disease (CAD), hypertension, tachyarrhythmia, and valvular disease, and as an additional emerging risk factor, non-alcoholic fatty liver disease (NAFLD)[2].

NAFLD represents evidence of hepatic steatosis (*via* imaging or histology) with a lack of secondary causes of hepatic fat accumulation and can be categorized as non-alcoholic fatty liver (Without evidence of hepatocellular injury) or Non-alcoholic Steatohepatitis (NASH: Hepatocellular injury with or without fibrosis)[3]. Most patients with NAFLD have associated conditions, such as obesity, diabetes mellitus, hypertension, and dyslipidemia. Recently, NAFLD has been associated with other conditions such as chronic kidney disease, osteoporosis, obstructive sleep apnea, psoriasis, colorectal cancer, and HF.

Some authors have mentioned that the association between NAFLD and cardiovascular disease (CVD) is inconsistent. They hypothesized that this connection might disappear after controlling for modifiable CVD risk factors[4]. However, there are strong arguments connecting NAFLD to CVD. Chiang *et al*[5] demonstrated that non-obese and relatively healthy subjects with NAFLD have an increased risk of developing cardiovascular events[5]. In addition to Chiang *et al* [5], other studies have shown that NAFLD patients have an increased risk of CVD after adjusting for major demographic, clinical, and metabolic confounders[6].

Furthermore, emerging epidemiological studies support a strong and independent association between NAFLD and HF. These studies estimated that the prevalence of HF in patients diagnosed with NAFLD is 6.4%, with a higher risk for HF preserved ejection fraction (HFpEF) than HF reduced ejection fraction (HFrEF)[7].

The association between HF and NAFLD involves similar processes in both HFpEF and HFrEF, which are mediated by inflammatory and fibrotic processes. The pathophysiological relationship between NAFLD and HFpEF is attributable, at least in part, to the secretion of adipokines and proinflammatory cytokines, such as leptin, which, at the level of the liver tissue, has profibrotic activity, and in the heart, it produces cardiac hypertrophy and endothelial dysfunction. Other important factors are tumor necrosis factor-α (TNF-α) and interleukin (IL) -6, which contribute to hepatocyte injury and NAFLD, whereas damaged hepatocytes release IL-33, which promotes a profibrotic effect. In the heart, IL-33 is released in response to myocardial fiber stretching[8].

PATHOPHYSIOLOGY LINKING NAFLD WITH CARDIOVASCULAR DISEASE AND HFrEF

Several pathophysiological mechanisms have been proposed to explain this relationship. One potential mechanism by which fatty liver may increase the risk of HF is an increased prothrombotic state and systemic inflammation[8]. The hypercoagulable state of NAFLD is multifactorial and complex. Some studies have suggested that oxidative injury to lipids and lipoproteins may underlie thrombophilia[9]. Plasminogen activator inhibitor type 1 (PAI-1), the most thrombophilic factor reported, significantly increases with exposure to non-oxidized low-density lipoprotein (LDL) and is directly related to hepatic steatosis[10]. Another important process in this proinflammatory stress is the apoptotic pathway, which is activated in NASH as a result of fatty acid-mediated changes in the permeability of lysosomes and mitochondria with the release of cathepsins and cytochrome C, respectively. This activates the proapoptotic caspase cascade (fatty acid

lipotoxicity), thereby resulting in a procoagulant state and contributing to atherosclerotic injury[11]. This process may explain why patients with NAFLD have a higher rate of major cardiovascular (CV) events (30% *vs* 8%)[12]. Additionally, NAFLD is associated with increased production of proinflammatory cytokines, such as IL-6 and high-sensitivity C-reactive protein (Hs-CRP), mitochondrial dysfunction eliciting reactive oxygen species (ROS) production, and stress biomarkers, such as fibroblast growth factors (FGFs), which increase the risk of CV and liver-related mortality[13,14] (Figure 1).

NAFLD is associated with high serum levels of total cholesterol, triglyceride, and LDL-cholesterol levels[15]. This dyslipidemia profile plays an important role in the pathogenesis of atherosclerosis. Nevertheless, existing data suggest that NAFLD *per se* might be an independent risk factor for CAD, even after adjusting for age, sex, traditional coronary risk factors, and visceral adipose tissue[16].

Cardiac structural and functional alterations are pivotal processes in HF in NAFLD patients. Most studies showed echocardiographic changes suggestive of left ventricular (LV) diastolic dysfunction, such as LV hypertrophy, increased left atrial volume, impaired LV relaxation, and higher left-sided filling pressures[17,18]. Furthermore, another study showed that hepatic steatosis and fibrosis are associated with diastolic dysfunction and are correlated with altered myocardial glucose uptake[19]. In addition, patients with NAFLD experience epicardial fat thickness, and both are at increased risk of coronary artery calcification[20].

Patients with NAFLD are also at an increased risk for cardiac arrhythmias, which can further increase the risk of LV dysfunction and HF. Cai *et al*[21] showed that NAFLD is associated with an increased risk of atrial fibrillation, and the strength of the association increases partially with the coexistence of cardiometabolic risk factors. In addition, Hung *et al*[22] found that mild, moderate, and severe NAFLD was associated with a high risk of heart rate-corrected QT (QTc) interval prolongation in both diabetic and nondiabetic subgroups. This mechanism is supported by the systemic inflammation and oxidative stress associated with NAFLD, which may trigger cardiac electrical and autonomic remodeling of the heart[23].

WHAT IS THE RELATIONSHIP BETWEEN NAFLD AND CARDIOVASCULAR DISEASE?

NAFLD and clinical CVD share similar risk factors (*i.e.*, sedentary lifestyle, smoking, physiological stress, and sleep deprivation/disorders). Accumulation of visceral and ectopic fat leads to the release of toxic metabolites and the activation of inflammatory pathways, ultimately leading to both entities[24]. With progressive NAFLD, factors such as insulin resistance, activated renin-angiotensin-aldosterone system (RAAS), and oxidative stress markers have the potential to increase the risk of cardiac disease and HF[25]. Specifically, the RAAS system is activated as a compensatory mechanism in early HF owing to hypoperfusion and sympathetic activation, leading to a cascade of angiotensin II and aldosterone, which are responsible for increased preload and afterload at the expense of salt and water retention, cardiac remodeling, and vasoconstriction[26,27].

It has been found that liver disease, renal failure, and diabetes contribute to greater mortality in patients with HFrEF compared to patients with HFpEF[28]. However, a recent cohort study and meta-analysis demonstrated that patients with NAFLD are at an increased risk of incident HFpEF rather than HFrEF[7,29].

Simon *et al*[30] showed that patients with biopsy-proven NAFLD had a significantly higher incidence of HF across all stages of NAFLD. Likewise, in a recent meta-analysis, NAFLD patients had a lower ejection fraction than non-NAFLD patients and increased left ventricular mass and epicardial adipose thickness[31].

These findings support the notion that NAFLD is a "multisystem" disease with multiple potential pathophysiological mechanisms that may increase the risk of HF. Herein, we discuss the possible mechanism of ventricular dysfunction and its impact on the patient's lifestyle. Therefore, our review provides an overview of novel therapies for patients with coexisting HFrEF and NAFLD with the aim of developing future interventions to prevent and treat both diseases.

NON-PHARMACOLOGICAL THERAPIES FOR PATIENTS WITH NAFLD AND HFrEF

Lifestyle modifications

Lifestyle modifications, such as dietary changes, physical activity, and weight loss, are first-line treatments for NAFLD. These modifications affect body fat adipose deposits, which also influences the development of CV comorbidities[18]. It has been studied that HF is associated with splanchnic circulation congestion, which leads to bowel wall edema and impaired intestinal barrier function, which concomitantly promotes bacterial translocation and inflammation[32]. For example, trimethylamine N-oxide, an organic compound from gut bacteria, is an independent predictor of poor prognosis in patients with HF and is strongly linked to the pathogenesis of CVD[33].

Dietary change is one of the most important factors for the treatment of NAFLD and HF. Montemayor *et al*[34] concluded that customized hypocaloric dietary and enhanced physical activity interventions may be useful in ameliorate NAFLD[34]. The Mediterranean Diet, rich in vegetables, fruits, legumes, potatoes, non-refined cereals, fish, white meat, and red wine, seems to have a favorable association with NAFLD in Iranian adults, especially in women and patients with or without abdominal obesity[35]. The DASH diet, which is rich in antioxidants, micronutrients, fiber, and nitrates and has low saturated and trans fats, has been shown to decrease proinflammatory cytokines and ROS, restore micronutrient status, and promote endothelial function[36]. Belanger *et al*[37] demonstrated that a DASH diet progressively reduced high-sensitivity cardiac troponin I and Hs-CRP over 12 wk[37].

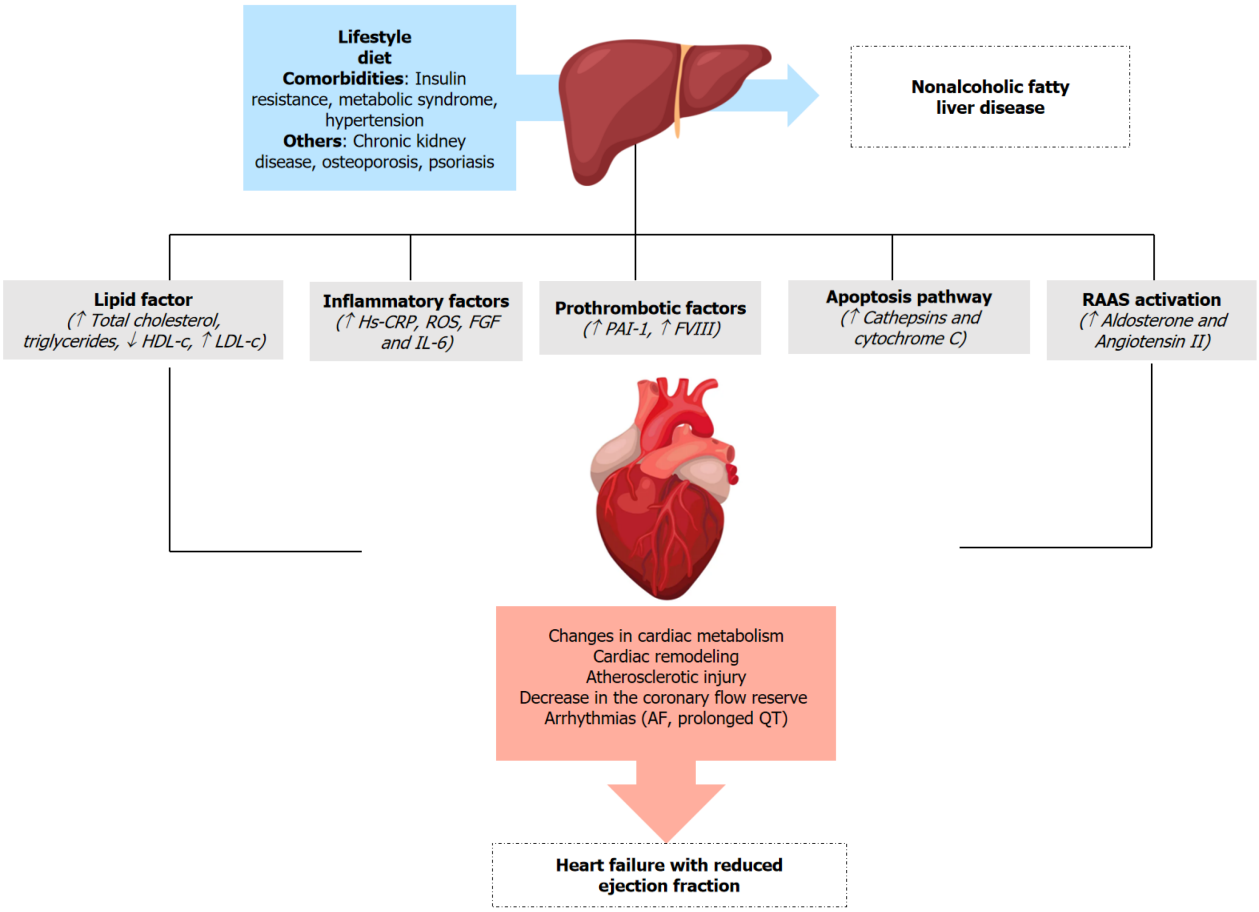

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Figure 1 Pathophysiology of non-alcoholic fatty liver disease and heart failure with reduced ejection fraction. LDL-c: Low-density lipoprotein-cholesterol; HDL-c: High-density lipoprotein-cholesterol; Hs-CRP: High-sensitivity C-reactive protein; ROS: Reactive oxygen species; FGF: Fibroblast growth factor; IL: Interleukin; PAI-1: Plasminogen activator inhibitor type 1; AF: Atrial fibrillation; RAAS: Renin angiotensin aldosterone system.

Bariatric Surgery

Bariatric surgery (BS) is one of the most effective treatments for obesity and its comorbidities[38]. The literature suggests that BS has also been associated with long-term improvements or even resolution of NAFLD in both clinical and histological features and has been shown to reduce CVD risk in patients with obesity by improving glucose tolerance and lipid panels[39-41]. Additionally, a recent meta-analysis showed that BS was associated with lower incidences of HF and myocardial infarction (MI)[42]. Another study showed that 96 months after BS, the cumulative incidence of HF was 4.2% and 11.5% in the surgical and non-surgical groups, respectively[43]. All these effects of BS seem to be related to changes triggered by gastrointestinal hormones such as Glucagon-like peptide 1 (GLP-1), gastric inhibitory polypeptide, leptin, gut hormone peptide YY, and ghrelin after anatomical intervention.

Additionally, changes in the gut microbiota are crucial for NAFLD[38]. Studies have shown a relationship between the gut microbiome and HF development[44]. This interplay involves gut microbial metabolites (which serve as mediators in HF pathophysiology), immune responses, and a vicious cycle caused by gut hypoperfusion in HF and subsequent additional microbiome alterations[33,44].

PHARMACOLOGICAL THERAPIES IN HFREF WITH EFFECT ON NAFLD

Currently, several therapies with strong evidence of benefit for HFrEF have also been reported to have an effect on NAFLD. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have been shown to reduce fibrosis and fat deposition in the liver. Mineralocorticoids receptor antagonist (MRA), such as spironolactone, have been reported to have a clear effect on the combination of this diuretic with vitamin E. Sodium-glucose cotransporter 2 inhibitors (SGLT-2i) have been reported to reduce liver stiffness and improve steatosis. Unfortunately, there are currently no data showing the beneficial effects of sacubitril/valsartan, ivabradine, hydralazine, isosorbide nitrates, digoxin, or beta-blockers (BB) on NAFLD (Table 1).

ACEIs and ARBs

ACEIs and ARBs block the effects of angiotensin II. These drugs are commonly prescribed to treat high blood pressure

Table 1 Effects on non-alcoholic fatty liver disease of drugs that have strong evidence of benefit on heart failure

Drug	HF phenotype with evidence of benefit	Effect on NAFLD Population	Comparator	Study
ACEI	HFrEF	Reduced liver-related events, liver cancer, and cirrhosis complications[47]	Placebo	Cohort
ARB	HFrEF	Trial failed to evidence that losartan 50 mg has antifibrotic effects on NASH due to widespread use[102]	Placebo	Trial
		Patients with CKD-NAFLD taking ACEI or ARB had significantly lower liver stiffness degrees in comparison to those without those drugs[103]	Placebo	Cohort
		Losartan 100 mg in children reduced alkaline phosphatase, but not ALT at 24 wk[104]	Placebo	Trial
		Losartan 50 mg in children reduced ALT more frequently than those patients with placebo[105]	Placebo	Trial
		Telmisartan 40 mg reduced free fatty acid level and increased liver-to-spleen ratio in diabetic patients with NAFLD[106]	Losartan	Trial
		Telmisartan had similar effects to vitamin E in NAFLD histology[107]	Vitamin E	Trial
		Telmisartan 40/80 mg improved NAFLD activity score and fibrosis in NASH[108]	Lifestyle modification	Trial
		Telmisartan and olmesartan improved HOMA-IR and ALT levels[48]	Before-after comparison	Quasiexperimental
		Losartan significantly decreased steatosis degree and visceral adipose tissue, addition of simvastatin further decreased those parameters[109]	Amlodipine and simvastatin	Trial
		Amlodipine, lisinopril and rosuvastatin decreased ALT and alkaline phosphatase[110]	Therapy without rosuvastatin	Trial
Diuretics	HFrEF and congested HFpEF	In patients with NAFLD and diabetes lisinopril and hydrochlorothiazide were associated with less likelihood of advanced fibrosis, while furosemide and spirono-lactone had higher likelihood of it[111]	Other therapies	Cohort
		Spironolactone and vitamin E reduced NAFLD liver fat score, insulin, and HOMA-IR[55,112]	Vitamin E alone	Trial
		Five subjects received eplerenone. The study stopped early due to an unexpected increase in hepatic fat at 24 wk[113]		Open-label proof-of-concept study
SGLT2 inhibitors	HFrEF and HFpEF	Empagliflozin reduced liver stiffness measurement and steatosis (in patients with significant steatosis at baseline), liver fat level, AST, ALT and insulin in patients with NAFLD without diabetes[114]	Placebo	Trial
		Tofogliflozin significantly improved the fibrosis scores, steatosis, hepatocellular ballooning, and lobular inflam-mation[115]	Glimepiride	Trial
		Empagliflozin plus diabetes therapy better-improved liver fat in NAFLD patients with diabetes[116]	Diabetes therapy without empagliflozin	Trial
		Dapagliflozin and omega-3 carboxylic acids reduced liver fat[117]	Placebo	Trial
		Ipragliflozin as add-on diabetes therapy reduced liver steatosis in NAFLD patients with diabetes[118]	Metformin and pioglitazone	Trial
		Empagliflozin was associated with reduction of ALT, liver stiffness and controlled attenuation parameter in patients with NAFLD and diabetes[119]	Before-after comparison	Cohort
		Luseogliflozin improved liver-to-spleen ratio and liver fat in NAFLD patients with diabetes[120]	Metformin	Trial
		Dapagliflozin and pioglitazone significantly increased liver-to-spleen ratio. Only dapagliflozin decreased visceral fat area in patients with NAFLD and diabetes [121]	Pioglitazone and glimepiride	Trial

	Ipragliflozin reduced visceral fat area, but not AST or ALT, in patients with NAFLD and diabetes[122]	Pioglitazone	Trial

ACEI: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blockers; HFrEF: Heart failure with reduced ejection fraction; HFpEF: Heart failure preserved ejection fraction; NASH: Non-alcoholic Steatohepatitis; CKD: Chronic kidney disease; NAFLD: Nonalcoholic fatty liver disease; ALT: Alanine aminotransferases; AST: Aspartate aminotransferases; SGLT2: Sodium-glucose cotransporter 2; HOMA-IR: Homeostatic model assessment for insulin resistance.

and HF. However, recent studies have suggested that ACEIs and ARBs may have beneficial effects on NAFLD[45]. Angiotensin II is a key contributor to abnormal lipid metabolism in NAFLD. Angiotensin II can worsen insulin sensitivity, generate ROS, and trigger the production of inflammatory cytokines such as TNF-α, IL-6, and PAI-1, all of which contribute to NAFLD progression[46]. For this reason, Zhang *et al*[47], in their retrospective cohort study of over 12000 patients with NAFLD, found that treatment with ACEIs for at least six months was associated with a lower risk of liver cancer and cirrhosis. Nevertheless, this effect was not seen with ARBs[42]. These data are surprising for Enjoji *et al* [48], who showed that ARBs can restore intracellular insulin signaling and facilitate the movement of excess fat from non-adipose tissues to adipocytes, which may improve markers of liver function such as transaminases, hepatic steatosis, and inflammation[48,49]. Furthermore, several clinical trials and meta-analyses have suggested that ACEIs and ARBs are effective in reducing mortality and hospitalization in patients with HFrEF and Advanced Kidney Disease[50]. Gilstrap *et al*[51] conducted a study to investigate the impact of BB and renin-angiotensin system inhibitors (RASi) on the outcomes of patients aged over 65 years with HFrEF. The study found that the use of BB and/or RASi at hospital discharge was associated with lower 30-d and 1-year mortality rates, even among patients aged > 85 years[51]. Similarly, the CHARM-Alternative trial investigated the use of candesartan *vs* placebo in patients with HF who were intolerant of ACE inhibitors. The study found that during a median follow-up of 3 years, hospitalization or cardiovascular-related death was reported in 33% of candesartan patients *vs* 40% of placebo patients[52].

Spironolactone

Patients with NAFLD and HFrEF may experience beneficial outcomes with the use of aldosterone antagonists such as spironolactone and eplerenone. Wada *et al*[53] investigated the effects of eplerenone on nonalcoholic steatohepatitis and metabolic syndrome in a mouse model. The results showed that Eplerenone effectively ameliorated insulin resistance, blood pressure, and hepatic steatosis with fibrotic changes by inhibiting the inflammatory response in Kupffer cells and macrophages[53]. Similarly, spironolactone effectively improves the accumulation of triglycerides in the liver, reduces inflammation, and downregulates gluconeogenic and lipogenic gene expression[54]. Furthermore, combination therapy with spironolactone and vitamin E appears to have a positive effect on serum insulin levels in individuals with NAFLD [55].

Patients with HF and reduced ejection fraction may benefit from the use of MRA such as spironolactone, as they have been shown to reduce mortality when administered at low doses of 25 mg to prevent hyperkalemia[56]. However, the ATHENA-HF Trial found that a high dose of spironolactone or eplerenone may be a safe and effective treatment option for patients with HFrEF because it is associated with a reduction in NT-pro brain natriuretic peptide (BNP) levels, reduction in body weight, and improved symptoms of HF, such as dyspnea and fatigue, by reducing myocardial fibrosis and improving ventricular function[57,58]. Thus, evidence suggests that RAAS inhibitors, regardless of dose, may be particularly beneficial in patients with HFrEF.

SLGT-2i

SGLT-2i suppress glucose reabsorption in the proximal tubule of the kidney, resulting in excretion of glucose in the urine and improvement of insulin resistance. Initially developed as a diabetes mellitus therapy strategy independent of insulin [59]. The improvement in hyperglycemia and insulin resistance may be related to the control of lipogenesis through transcriptional regulation of lipogenic genes, including acetyl-CoA carboxylase and fatty acid synthase, and the development of hepatic steatosis[60].

Several studies have reported that SGLT-2i can inhibit the development of NAFLD and improve histological hepatic steatosis or steatohepatitis in experimental animal models[61]. Another possible mechanism of action of SGLT-2i in NAFLD is the weight-and visceral fat-dependent effects and inhibition of de novo lipogenesis in the liver[62].

SGLT-2i have been shown to reduce the risk of cardiovascular death or hospitalization in patients with HFrEF with or without type 2 diabetes mellitus (T2DM). There are several randomized controlled trials such as DAPA-HF, EMPEROR-Reduced, EMPULSE[63], EMPIRE-HF, SOLOIST-WHF[64], and CANVAS trials[65]. In addition to the most updated American College of Cardiology (ACC) guidelines for the management of HF, SGLT-2i has become a mainstay in the treatment of HFrEF and HFpEF.

A recent meta-analysis, including 1950 patients, evaluated liver structure and function in patients taking SGLT-2i with placebo or other oral antidiabetic drugs. It revealed a decrease in liver function tests (LFT), such as serum alanine and aspartate aminotransferases and gamma-glutamyl transferase, and a decrease in liver steatosis[66]. Another meta-analysis showed that SGLT-2i also reduced liver fat content and improved LFT in patients with NAFLD, as estimated by cardiac magnetic resonance proton density fat fraction[67].

These findings imply that SGLT-2i may be an effective treatment for patients with both NAFLD and HFrEF.

POTENTIAL PHARMACOLOGICAL THERAPIES

GLP-1 receptor agonists

GLP-1 is an incretin hormone secreted in the gut in response to meal ingestion, which increases insulin secretion and inhibits glucagon production, targeting pancreatic β-cells. Consequently, GLP-1 receptor agonists improve hyperglycemia and delay gastric emptying, thereby promoting weight loss[68]. They can be an attractive therapeutic option for treating patients with NAFLD, particularly those with associated diabetes mellitus and obesity.

A multicenter, randomized, double-blind, placebo-controlled trial showed that liraglutide was associated with the resolution of NASH with no worsening of fibrosis score, improvement in steatosis, and hepatocyte ballooning score[69]. Liraglutide and exenatide have been attributed to decreases in trunk fat content, especially in the android region, which is associated with NAFLD and is closely associated with CVD risk[70,71].

In preclinical studies, some of the well-described effects of GLP-1 may reflect indirect mechanisms in the heart, such as augmentation of ventricular function in animals with HF or ischemia-induced ventricular dysfunction, attenuation of the development or progression of atherosclerosis or plaque formation, augmented myocardial or coronary artery blood flow rate control, reduced blood pressure, increased secretion of atrial natriuretic factor, and inhibition of platelet aggregation [72].

According to current guidelines, GLP-1 receptor agonists have no effect on the risk of HF hospitalization, which suggests that they are safe to use but are not beneficial in preventing HF in at-risk patients. Therefore, it should be used cautiously during acute decompensation[73].

Three small randomized controlled trials of GLP-1 receptor agonists were conducted in patients with HFrEF. The LIVE and FIGHT trials studied liraglutide *vs* placebo and showed no changes in left ventricular ejection fraction (LVEF), quality of life, or functional class at 24 wk. Albiglutide has also been studied and showed no significant differences in LVEF, BNP, 6-min walk test, myocardial glucose, or oxygen use[74]. GLP-1 RAs have a positive chronotropic effect, causing an increase in heart rate and induced increases in cAMP levels, which may worsen HF and increase the risk of death[75].

Although observations from treatment with GLP-1RAs and NAFLD suggest beneficial data, observations from randomized trials suggest no clear benefit in HF-related outcomes and even uncertainty regarding safety in patients with HFrEF. Larger studies of patients with HFrEF are recommended.

Tirzepatide

A novel medication for the treatment of T2DM, tirzepatide, a dual glucose-dependent insulinotropic polypeptide and a GLP-1 receptor agonist, has shown promising results in ongoing clinical trials, not only for T2DM but also for improving body weight and steatosis[76]. They compared its effects with those of dulaglutide on NAFLD biomarkers and fibrosis in patients with diabetes mellitus and found that a higher tirzepatide dose significantly decreased NAFLD biomarkers and increased adiponectin levels[77]. Additionally, SURPASS-3, using magnetic resonance imaging, demonstrated that tirzepatide significantly reduced liver fat content, visceral adipose tissue volume, and abdominal subcutaneous adipose tissue[78].

Currently, the efficacy and safety of tirzepatide in patients with HFpEF and obesity are being assessed[79]. No current data supports the use of tirzepatide in patients with HFrEF. Studies on patients with HFrEF are recommended.

Metformin

Metformin is a biguanide that can improve insulin sensitivity and regulate glucose utilization by the liver[80]. Metformin treatment has been shown to be effective in alleviating hepatic lipogenesis in animal models of NAFLD through various mechanisms. However, in clinical studies, metformin modestly reduced body mass index, liver fat content, and liver enzyme levels in patients with NAFLD and diabetes. Despite these reports on the benefits of metformin, some contradictory results still exist. Despite these reports on the benefits of metformin, conflicting results remain. Combination treatments with other antidiabetic drugs, especially thiazolidinedione, GLP-1 receptor agonists, and SGLT2 inhibitors, demonstrated greater efficacy. Further research with a larger sample size is required to confirm these findings[81].

Left ventricular hypertrophy is a common finding in patients with ischemic heart disease and is associated with mortality in those with CVD. Metformin has been shown to reduce oxidative stress and left ventricular mass index. These results suggest a favorable effect of metformin on the left ventricular mass index and LVEF in patients with or without preexisting CVD[82]. In a recent report of diabetic patients with advanced HFrEF, patients treated with metformin demonstrated better quality of life and improved outcomes than patients not receiving metformin. Metformin remains one of the frontline drugs for the treatment of patients with HFrEF and Diabetes Mellitus[83].

The long-term clinical impact of metformin on HFrEF requires additional research despite its potential therapeutic effects on NAFLD.

Thiazolidinediones

Thizolidenidiones act as peroxisome proliferator-activated receptor-g activators in adipose, muscle, and liver tissues, resulting in a decrease in glucose production and subsequent increase in glucose utilization[84].

A recent meta-analysis compared placebo and pioglitazone, a thiazolidinedione, and found that it significantly improved steatosis grade, inflammation grade, and ballooning grade, whereas in the fibrosis stage, there was no significant improvement in pioglitazone compared with placebo. In addition, pioglitazone significantly reduced fasting blood glucose, glycosylated hemoglobin, serum alanine, and aspartate aminotransferase levels. Owing to the lack of relevant randomized controlled trials and short intervention times, long-term studies are needed to verify its efficacy and

safety[85]. Another systematic review showed that pioglitazone consistently improved histological parameters and normalized liver transaminases, although the evidence supporting the benefits of other drugs in this class is minimal. Thiazolidinediones, particularly pioglitazone, have proven efficacious in patients with NAFLD/NASH[86].

Rosiglitazone has been shown to increase the risk of MI and HF, whereas pioglitazone decreased the risk of major adverse cardiovascular events, such as MI and stroke, but increased the risk of HF[87]. Pioglitazone was associated with higher rates of HF hospitalization in a smaller randomized controlled trial of participants with more severe symptomatic HFrEF than placebo[88]. Patients with T2DM with New York Heart Association functional class I-II CHF and reduced LVEF were randomized to 52 wk of treatment with rosiglitazone, and there were significantly more confirmed events of new or worsening edema and increased HF medication in the rosiglitazone group[89]. According to current guidelines for the treatment of HF from the ACC, given the existing evidence, thiazolidinediones should be avoided in patients with reduced LVEF[90].

In conclusion, although thiazolidinediones have demonstrated efficacy in patients with NAFLD, they are not recommended for diabetic patients at a high risk of HF, as they have been proven to increase the risk of HF in this group of patients.

Statins

Statins are safe for patients with NAFLD across the disease spectrum, including those with advanced liver disease, and lead to a demonstrable reduction in cardiovascular morbidity and mortality. The management of dyslipidemia in NAFLD should include the use of moderate- to high-intensity statins as first-line therapy, based on lipid risk levels and atherosclerotic ASCVD risk scores[91].

These medications can impair insulin sensitivity and secretion by pancreatic β-cells and increase insulin resistance in the peripheral tissues. Statins may also contribute to statin-induced T2DM[92]. Moreover, statin use is associated with a significant reduction in cardiovascular mortality and morbidity in both primary and secondary prevention strategies. A reduction in the risk of new-onset HF in patients with a high cardiovascular risk and hospitalization for HF has also been reported[25]. Rosuvastatin did not reduce the primary outcome or the number of deaths from any cause in older patients with systolic HF, although it did reduce the number of cardiovascular hospitalizations[93].

Statins may have a beneficial effect on CV outcomes irrespective of HF etiology and LVEF. Lipophilic statins (*e.g.*, atorvastatin) and non-hydrophilic statins (*e.g.*, rosuvastatin or pravastatin) showed significant reductions in clinical outcomes; however, lipophilic statins seem to be much more favorable for patients with HF[94].

Statins appear to have beneficial effects in NAFLD. Although there is the possibility of triggering T2DM, statins have more benefits than inconveniences in the treatment of NAFLD and reduce the risk of HFrEF.

NOVEL THERAPIES OR *IN VITRO* STUDIES INVESTIGATING NEW DRUGS

Similarly, potential beneficial molecules for NAFLD are currently being investigated. Niacin, a vitamin derived from tryptophan metabolism, is known for its effect on dyslipidemia; however, recent studies have indicated that niacin reduces hepatic fat accumulation and steatosis, inflammation, and fibrosis by inhibiting diacylglycerol acyltransferase 2, an enzyme responsible for the synthesis of triglycerides, blocking the activation of hepatic stellate cells, and decreasing the activity of matrix metalloproteinases 2 and 9[95].

Sesquiterpene glycoside, an extract of the dried root Codonopsis pilosula, is a common drug used in traditional Chinese medicine because of its affordable cost and anti-inflammatory effects[96]. Therefore, a recent study provided evidence that the use of sesquiterpene glycosides in mice could protect against NAFLD in patients with T2DM. These findings were related to the repair of insulin signaling and inhibition of cytochrome P450 2E1 (CYP2E1) and NOD-like receptor family 3 *in vivo* and *in vitro;* thus, reducing oxidative stress, inflammation, and inflammatory cytokines and preventing insulin resistance[97].

Flavonoids (*i.e.* Baicalein, silymarin, rutin, and quercetin) has also shown hepatic protection by modulating the function of CYP2E1. These molecules are usually found in fruits, vegetables, and plant-derived beverages, and are used as nutritional supplements. They can improve insulin resistance, endoplasmic reticulum stress, lipid peroxidation, and fibrosis[98].

FGF21 is a hormone that plays an important role in regulating metabolic pathways[99]. This hormone is mainly produced by the liver and its signaling is associated with NAFLD pathogenesis[100]. In addition, FGF21 regulates lipid and glucose metabolism, which is correlated with CVD and HF. In summary, FGF21 may be a potential biomarker for prognosis prediction and as a treatment target in the future. However, further studies are required to determine their precise roles[101].

CONCLUSION

HFrEF is a major public health problem worldwide. Additionally, due to the rising incidence of obesity and associated comorbid conditions, such as diabetes mellitus and metabolic syndrome, NAFLD has also become a common condition. Multiple recent studies have shown a strong association between HF, especially the HFrEF subtype, and NAFLD. Although there are multiple proposed pathophysiological mechanisms, most are common factors in the development of systemic inflammation. To date, several non-pharmacological, pharmacological, and surgical interventions have been

studied in patients with concomitant HFrEF and NAFLD. Evidence shows the potential benefits of dietary changes; certain medications, such as ACEI, ARB, MRA, and SGLT-2i; and BS. However, there is still a lack of robust data and well-designed clinical trials investigating several other drugs or novel therapies that could benefit from these conditions and improve outcomes.

FOOTNOTES

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Abstract

BACKGROUND

Effective management of major cardiovascular risk factors is of great importance to reduce mortality from cardiovascular disease (CVD). The Survey of Risk Factors in Coronary Heart Disease (SURF CHD) II study is a clinical audit of the recording and management of CHD risk factors. It was developed in collaboration with the European Association of Preventive Cardiology and the European

Society of Cardiology (ESC). Previous studies have shown that control of major cardiovascular risk factors in patients with established atherosclerotic CVD is generally inadequate. Azerbaijan is a country in the South Caucasus, a region at a very high risk for CVD.

AIM

To assess adherence to ESC recommendations for secondary prevention of CVD based on the measurement of both modifiable major risk factors and their therapeutic management in patients with confirmed CHD at different hospitals in Baku (Azerbaijan).

METHODS

Six tertiary health care centers participated in the SURF CHD II study between 2019 and 2021. Information on demographics, risk factors, physical and laboratory data, and medications was collected using a standard questionnaire in consecutive patients aged ≥ 18 years with established CHD during outpatient visits. Data from 687 patients (mean age 59.6 ± 9.58 years; 24.9% female) were included in the study.

RESULTS

Only 15.1% of participants were involved in cardiac rehabilitation programs. The rate of uncontrolled risk factors was high: Systolic blood pressure (BP) (SBP) (54.6%), low-density lipoprotein cholesterol (LDL-C) (86.8%), diabetes mellitus (DM) (60.6%), as well as overweight (66.6%) and obesity (25%). In addition, significant differences in the prevalence and control of some risk factors [smoking, body mass index (BMI), waist circumference, blood glucose (BG), and SBP] between female and male participants were found. The cardiovascular health index score (CHIS) was calculated from the six risk factors: Non- or ex-smoker, BMI < 25 kg/m^2, moderate/vigorous physical activity, controlled BP (< 140/90 mmHg; 140/80 mmHg for patients with DM), controlled LDL-C (< 70 mg/dL), and controlled BG (glycohemoglobin < 7% or BG < 126 mg/dL). Good, intermediate, and poor categories of CHIS were identified in 6%, 58.3%, and 35.7% of patients, respectively (without statistical differences between female and male patients).

CONCLUSION

Implementation of the current ESC recommendations for CHD secondary prevention and, in particular, the control rate of BP, are insufficient. Given the fact that patients with different comorbid pathologies are at a very high risk, this is of great importance in the management of such patients. This should be taken into account by healthcare organizers when planning secondary prevention activities and public health protection measures, especially in the regions at a high risk for CVD. A wide range of educational products based on the Clinical Practice Guidelines should be used to improve the adherence of healthcare professionals and patients to the management of CVD risk factors.

Key Words: Coronary heart disease; Cardiovascular risk factors; Secondary prevention; Clinical practice guidelines; Clinical audit; Survey of risk factors

Core Tip: The article stresses the value of audit studies in clinical practice. It confirms that the control rate of major cardiovascular risk factors is insufficient and stresses the importance of an individual approach to the secondary prevention of atherosclerotic coronary heart disease, considering patients' gender, comorbidities, cultural peculiarities, and the region of their residence.

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INTRODUCTION

Atherosclerotic cardiovascular disease (CVD) (ASCVD) remains the leading cause of morbidity and mortality worldwide. According to recent data, the incidence and mortality rates of CVDs have declined in high-income countries, and the majority of global deaths from CVD occur in low- and middle-income countries[1].

The World Health Organization's 'Global Plan of Action for Noncommunicable Diseases (NCDs) Prevention and Control 2013-2020' aims to reduce mortality from these causes by a quarter by 2025[2]. Two of the nine global targets

focus directly on CVD prevention and control. The recently published European Society of Cardiology (ESC) guidelines on CVD prevention are designed to help health professionals identify the best strategies for managing modifiable risk factors in patients with established ASCVD[3].

Effective control of CVD risk factors plays a critical role in reducing mortality from CVDs. International registry studies provide valuable information on the current status of the problem, identify deficits, and contribute to improving the quality of care and clinical outcomes in different countries.

The Survey of Risk Factors in Coronary Heart Disease (SURF CHD) II study is a clinical audit of the recording and management of CHD risk factors, developed in collaboration with the European Association of Preventive Cardiology and the ESC. It was conducted in countries representing Europe, Asia, and Middle East and more recently North Africa, and South America to assess the recording and monitoring of cardiovascular risk factors in patients with established CHD, and to evaluate the effectiveness of implementation of and adherence to clinical guidelines in daily practice[4,5]. Previous studies have shown that control of major cardiovascular risk factors in patients with established ASCVD varies from country to country, and is generally inadequate[4].

Azerbaijan is located in the South Caucasus region, at the crossroads of Asia and Europe, and is one of the regions at a very high risk for CVDs[6]. Our study aimed to assess adherence to ESC recommendations[7] for secondary prevention of a CVD based on the measurement of both modifiable risk factors and their therapeutic management in patients with confirmed CHD at different hospitals in Baku (Azerbaijan).

MATERIALS AND METHODS

Study design and data collection

Six tertiary public (3) and private (3) health care centres from Baku (Azerbaijan) participated in the cross-sectional SURF CHD II study between November 2019 and July 2021. A one-page standard questionnaire of the study was used to collect information electronically on demographics, diagnostic category, risk factors, physical and laboratory data, and prescribed medications from consecutive patients aged ≥ 18 years with established CHD during routine outpatient visits.

The study protocol was approved by the Ethics Committee of Azerbaijan Society of Cardiology (ASC). CHD was defined as any of the following events in the history: Coronary artery bypass grafting (CABG); elective or urgent percutaneous coronary intervention (PCI); acute coronary syndrome (ACS), defined as cardiac chest pain at rest with objective evidence of acute ischemia or infarction; or stable angina pectoris (SAP), defined as clinical angina with objective confirmation by a positive exercise electrocardiogram or positive myocardial perfusion imaging or presence of stenosis of 70% or more in at least one coronary artery on coronary angiogram.

The questionnaire included demographics, risk factor history, risk factor measurements, and most recent laboratory measurements taken during outpatient visits by cardiologists. Demographic information included age, sex, ethnic group, and educational level. For the risk factor history, information was collected on smoking history, physical activity, family history of CVD, and previous history of hypertension, dyslipidaemia, and diabetes mellitus (DM) type I or II. We also collected information on risk factor and laboratory measurements: Height, weight, calculated body mass index (BMI), waist circumference (WC), systolic blood pressure (BP) (SBP) and diastolic BP (DBP), fasting blood glucose (BG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), and glycated haemoglobin (HbA1c) for patients with DM.

Participation in cardiac rehabilitation (CR) and use of cardiac medications such as antiplatelet agents, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), Ca antagonists, other antihypertensive drugs, diuretics, statins, PCSK9 inhibitors, other lipid-lowering drugs, insulin, oral hypoglycaemic drugs, and nitrates were also reported in the questionnaire.

Variable definition

Smoking history was categorized into the current smoker (if participants were smokers at the time of the questionnaire or in the previous 6 mo), non-smoker, and ex-smoker (participants that had quit smoking more than 6 mo ago). The level of physical activity was divided into less, more, and equal to the recommended level: 30 min of moderately vigorous physical activity three to five times per week. It was considered that participants had a family history of premature CVD if they had a first-degree relative with a history of ASCVD before the age of 55 years for a male or 65 years for a female. The highest level of education, history of hypertension, dyslipidaemia, DM type 1 or type 2, and participation in CR were documented.

Depending on the BMI value, the following categories were identified[8]: Underweight < 18.5 kg/m^2, normal weight 18.5-24.9 kg/m^2, and overweight 25-29.9 kg/m^2; obesity I degree: 30-34.9 kg/m^2, obesity II degree: 35-39.9 kg/m^2, and obesity III degree: ≥ 40 kg/m^2. WC ≥ 88 cm in women and ≥ 102 cm in men was defined as abdominal obesity[7,8]. Arterial hypertension (AH) was established with the use of antihypertensives or BP > 140/90 mmHg[9]. Dyslipidaemia was defined as the use of statins or TC level of ≥ 200 mg/dL, LDL-C level of ≥ 130 mg/dL, TG level of ≥ 150 mg/dL, and HDL-C level of ≤ 40 mg/dL in men and ≤ 50 mg/dL in women[10]. DM was defined as the use of an antidiabetic drug or HbA1c level of ≥ 6.5%/or fasting BG level of ≥ 126 mg/dL[11].

Therapeutic targets were in accordance with ESC Guidelines and were identified as follows: Uncontrolled AH-SBP ≥ 140 mmHg or DBP ≥ 90 mmHg; uncontrolled DM-HbA1c ≥ 7%; uncontrolled LDL-C ≥ 70 mg/dL. Lifestyle targets were defined as reaching targets for smoking status (non-/ex-smoker), BMI < 25, and moderate/vigorous physical activity[7].

A cardiovascular health index score (CHIS) was calculated to summarize the burden of risk factors. The CHIS was calculated as the number of risk factors that each participant presented, from the following six risk factors: Non-/ex-smoker, BMI < 25 kg/m^2, moderate/vigorous physical activity, controlled BP (< 140/90 mmHg; 140/80 mmHg for patients with DM), controlled LDL-C (< 70 mg/dL), and controlled BG (HbA1c < 7% or BG < 126 mg/dL). The following categories were defined: Poor, CHIS ≤ 2; intermediate, CHIS = 3-4; good, CHIS = 5-6[4].

Statistical analysis

Cases with missing data were excluded from the analysis. Statistical processing of the results was carried out using the Microsoft Excel and IBN SPSS Statistica v.21 software packages. The parameters were tested for normality of distribution using the Kolmogorov-Smirnov test. For normally distributed variables, descriptive statistics were used: mean ± SD, minimum, median, and maximum. To determine the statistical significance of differences between the two groups, Student's *t*-test (for continuous variables that showed a normal distribution), non-parametric Mann-Whitney *U* test (for continuous variables that did not show a normal distribution), and χ^2 test were used. $P < 0.05$ was accepted as being statistically significant.

RESULTS

Study population

Data from 687 consecutive CHD outpatients (mean age 59.6 ± 9.6 years) were included in the study, and 171 (24.9%) of the participants were women.

Demographic characteristics and CHD category, hospital admission, and participation in CR according to the sex of patients are summarized in Table 1. All patients were Caucasian. The mean age of the female patients was significantly higher than that of the men ($P < 0.0001$). Of all patients, 39.4% were admitted to the hospital during the last year for a CHD-related reason, and only 15.1% participated in CR programs. Male participants in this study were found to have a higher prevalence in ACS and PCI ($P = 0.001$ and $P = 0.004$, respectively). More women than men had systolic AH (SAH) ($P = 0.0002$). No significant differences in the number of patients who underwent CABG, hospital admission in the last year, and participation in CR were observed between male and female patients.

Prevalence of cardiovascular risk factors

Table 2 represents the cardiovascular risk factors stratified by sex. A higher rate of smoking was found among males (32% *vs* 1.8% in female patients). The number of female patients with no smoking history was significantly higher compared to the male participants (96.5% and 29%, respectively). The sex differences were statistically significant for all categories of smoking history ($P < 0.00001$).

Of all participants, 48.3% reported a family history of premature CVD. There were no sex differences on this indicator.

A history of hypertension was reported by most patients (78.2%), while dyslipidemia and diabetes were reported by 37.1% and 45.1% of patients, respectively. Statistically significant sex differences between the groups were found in the prevalence of diabetes (55.6% *vs* 41.7% in females and males, respectively; $P = 0.002$).

It should be mentioned that body weight and height were not measured in all subjects, and consequently, BMI was calculated only in 31.4% of all participants. The risk factor and laboratory measurement results are displayed in Table 3. The mean BMI value in these patients was found to be 28.4 kg/m^2, with the mean value of 29.6 kg/m^2 in females and 28 kg/m^2 in males ($P = 0.002$).

Waist circumference was measured only in 30 participants (4.4%, 13 females and 17 males), and it was high in 63.3% of those patients. Among them, 83.6% of females and 47.1% of males had abdominal obesity ($P = 0.034$).

In relation to laboratory data, there were no significant differences between male and female participants in TC, LDL, HDL, TG, or HbA1c values. However, BG levels were found to be higher in female patients ($P = 0.04$).

Risk factor targets and CHIS categories

Lifestyle targets and CHIS categories in patients are represented in Figure 1. Non/ex-smokers were predominant among female participants ($P < 0.00001$). Approximately 60% of patients showed adequate physical activity, without significant differences between groups. However, in terms of BMI values, female patients had significantly higher values than male participants ($P = 0.0294$).

CHIS categories were calculated in 84 (12.2%) patients who had all the necessary clinical and laboratory measurements done. Good, intermediate, and poor categories were identified in 6%, 58.3%, and 35.7% of patients, respectively (without statistical differences between female and male patients).

Risk factor control

When analyzing uncontrolled BP rates across different categories of AH, the prevalence of uncontrolled SBP was higher than that of other BP categories (Table 4). There were no statistical differences between females and males within each category. Differences between the two groups were only observed in the category of isolated systolic hypertension with a higher prevalence in women ($P = 0.029$).

The rates of uncontrolled risk factors in patients with a previous history of hypertension ($n = 537$), dyslipidaemia ($n = 255$), and DM ($n = 310$) are represented in Figure 2. As shown in the figure, uncontrolled SBP was detected in 292 (54.6%), and uncontrolled DBP was found in 204 (39%) participants. Systolic-diastolic AH (SDH) was found in 169 (31.5%),

Table 1 Demographic characteristics and disease category of the patients (*n* = 687)

	Total, *n* = 687	Female, *n* = 171	Male, *n* = 516	*P* value
Age (years)	59.6 ± 9.58	62.4 ± 8.9	58.6 ± 9.6	< 0.0001
CHD category, *n* (%)				
CABG	153 (22.3)	41 (24)	112 (22)	> 0.05
PCI	351 (51.1)	71 (42)	280 (54)	0.004
ACS	172 (25.0)	27 (16)	145 (28)	0.001
SAP	249 (36.2)	82 (48)	167 (32)	0.0002
HA	271 (39.4)	68 (40)	203 (39)	> 0.05
CR	104 (15.1)	19 (11.1)	85 (16.5)	> 0.05

CHD: Coronary heart disease; CABG: Coronary artery bypass surgery; PCI: Percutaneous coronary intervention; ACS: Acute coronary syndrome; SAP: Stable angina pectoris; HA: Hospital admission; CR: Cardiac rehabilitation. *P* value represents differences by sex.

Table 2 Cardiovascular risk factors stratified by sex, *n* (%)

	Total, *n* = 687	Female, *n* = 171	Male, *n* = 516	*P* value
Smoking history				
Current smoker	169 (24.6)	3 (1.8)	166 (32)	< 0.00001
Ex-smoker	169 (24.6)	2 (1.2)	167 (32)	< 0.00001
Never smoked	314 (45.7)	165 (96.5)	149 (29)	< 0.00001
Unknown	35 (5.1)	1 (0.6)	34 (7)	
Physical activity				
Less than below	223 (32.5)	66 (38.6)	157 (30.4)	> 0.05
Moderate	324 (47.2)	74 (43.3)	250 (48.4)	> 0.05
More than above	82 (11.9)	19 (11.1)	63 (12.2)	> 0.05
Unknown	58 (8.4)	12 (7.02)	46 (8.9)	
Family history of premature CVD				
Yes	265 (38.6)	58 (33.9)	207 (40.1)	> 0.05
No	355 (51.7)	96 (56.1)	259 (50.2)	> 0.05
Unknown	67 (9.8)	17 (9.9)	50 (9.7)	
Previous history of				
Hypertension	537 (78.2)	142 (83)	395 (76.6)	> 0.05
Dyslipidaemia	255 (37.1)	60 (35.1)	195 (37.8)	> 0.05
Diabetes	310 (45.1)	95 (55.6)	215 (41.7)	0.002

Less than below physical activity: < 30 min/week; Moderate physical activity: 30 min 3-5 times/week; More than above physical activity: > 30 min/week; *P* value represents differences by sex. CVD: Cardiovascular disease.

isolated SAH in 121 (22.5%), and isolated DAH in 34 (6.3%) patients with AH.

Medication use

The rate of medication use is shown in Table 5. Antiplatelet drugs were used in 84.6%, and beta-blockers in 53.3% of patients, both with an equal rate among female and male participants. Approximately 73.9% of patients were using statins, with a higher usage rate observed among male patients ($P = 0.012$). As for ACE inhibitors, 51.2% of patients were using them, with a higher usage rate observed among female patients ($P = 0.044$). Ca antagonists were used in 29.3%, oral hypoglycaemics in 23%, diuretics in 22.3%, and nitrates in 21.3% of patients. Other groups of medications were used in less than 6% of patients. Oral hypoglycemic drugs, insulin, and nitrate use was higher among female patients ($P = 0.025$, $P = 0.043$, and $P < 0.00001$, respectively).

Table 3 Clinical measurements and laboratory data of the patients (mean ± SD)

	Total	Female	Male	*P* value
Systolic BP (mmHg)	*n* = 663	*n* = 164	*n* = 499	
	138.4 (18.9)	142.4 (1.4)	137.1 (17.9)	0.004
Diastolic BP (mmHg)	*n* = 658	*n* = 162	*n* = 496	
	82.9 (10.7)	82.7 (11.5)	82.8 (10.4)	> 0.05
Heart rate (bmp)	*n* = 649	*n* = 156	*n* = 493	
	77.6 (12.7)	78.5 (12.0)	77.3 (12.9)	> 0.05
BMI (kg/m^2)	*n* = 216	*n* = 50	*n* = 166	
	28.4 (3.02)	29.6 (3.4)	28 (2.8)	0.002
WC (cm)	*n* = 30	*n* = 13	*n* = 17	
	101 (12.9)	100.8 (15.2)	101.0 (11.3)	> 0.05
TC (mg/dL)	*n* = 347	*n* = 86	*n* = 261	
	193.9 (52.4)	200.4 (50.7)	192.3 (53)	> 0.05
LDL-C (mg/dL)	*n* = 371	*n* = 101	*n* = 270	
	111.2 (49.6)	118.3 (49.7)	108.6 (49.3)	> 0.05
HDL-C (mg/dL)	*n* = 185	*n* = 50	*n* = 135	
	53.4 (13.8)	54.4 (13.1)	53 (14.1)	> 0.05
TG (mg/dL)	*n* = 367	*n* = 93	*n* = 274	
	161.0 (76.0)	169.8 (77.8)	158 (75.4)	> 0.05
BG (mg/dL)	*n* = 277	*n* = 73	*n* = 204	
	146.7 (71.5)	162.7 (79.9)	141 (67.5)	0.04
HbA1c (%)	*n* = 137	*n* = 44	*n* = 93	
	7.71 (1.72)	8.1 (2.0)	7.5 (1.5)	> 0.05

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; WC: Waist circumference; TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; TG: Triglycerides; BG: Blood glucose. *P* value represents differences by sex.

Table 4 Rates of uncontrolled blood pressure in different categories of arterial hypertension

BP category, *n* = 658	Total (%)	Female (%)	Male (%)	*P* value
SDH	27.5	27.8	27.4	0.929
ISH	20.9	26.8	18.8	0.029
IDH	6.8	6.8	6.9	0.977

BP: Blood pressure; ISH: Isolated systolic hypertension; IDH: Isolated diastolic hypertension; SDH: Systolic-diastolic hypertension. *P* value represents differences by sex.

DISCUSSION

Summary of main findings

A clinical audit is a 'quality improvement process that seeks to improve patient care and outcomes through a systematic review of care and the implementation of change'[12]. The SURF CHD II clinical audit conducted in Azerbaijan has shown that the prevalence of major cardiovascular risk factors in patients with ASCVD is high. The level of recordings of some risk factors was low, as there was a lack of information on BMI, WC, TC, LDL-C, HDL-C, TG, and HbA1c.

The number of patients involved in the CR program was inadequate (15.1%). The rate of uncontrolled RF was high: SBP (54.6%), DBP (39%), LDL-C (86.8%), DM (60.6%), as well as overweight (66.6%) and obesity (25%). In addition, significant differences in prevalence and control of some risk factors (smoking, BMI, WC, BG, and SBP) between female and male participants have been found.

Table 5 Medication use rate in patients with known coronary artery disease (%)

Medications	Total	Male	Female	*P* value
	n = 687	*n* = 516	*n* = 171	
Antiplatelets	84.6	85.3	82.5	0.377
Beta blockers	53.3	55.2	47.4	0.074
ACE inhibitors	51.2	49.0	57.9	0.044
Ca antagonists	29.3	28.7	31.0	0.565
ARB-s	6.0	5.8	6.4	0.767
Diuretics	22.3	20.5	27.5	0.059
Other antihypertensives	2.3	1.9	3.5	0.238
Nitrates	21.3	7.6	62.6	< 0.00001
Insulin	7.6	6.4	11.1	0.043
Oral hypoglycaemics	23	20.9	29.2	0.025
Statins	73.9	76.4	66.7	0.012
Other lipid lowering	1.3	1.2	1.8	0.555

Ca: Calcium; ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blocker. *P* value represents differences by sex.

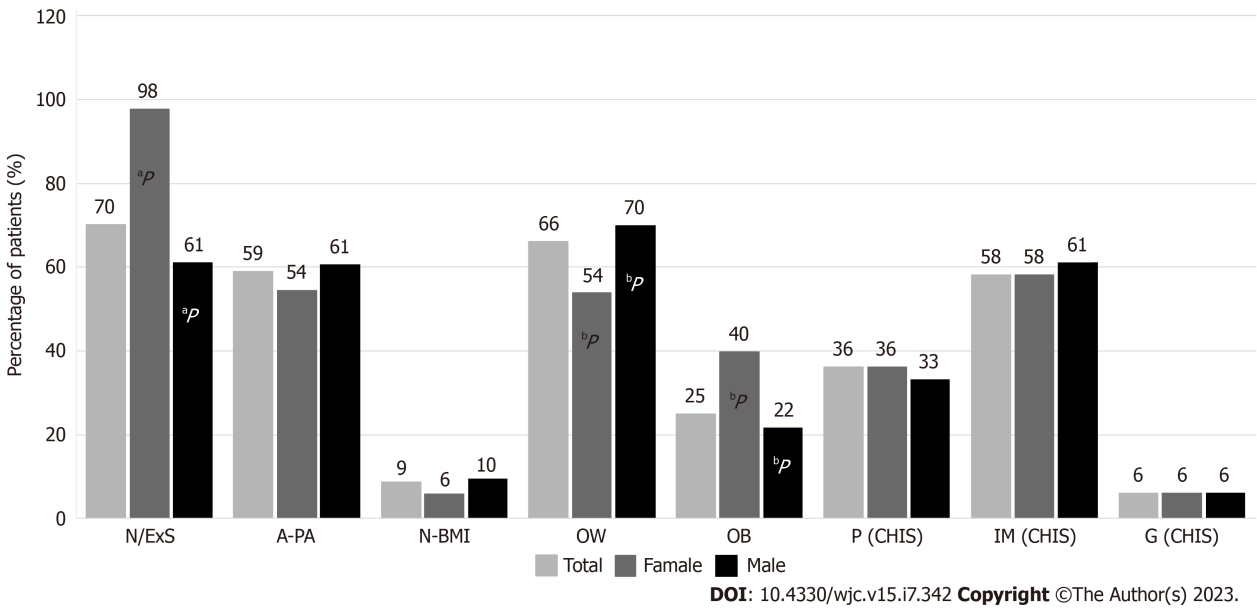

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Figure 1 Lifestyle targets and cardiovascular health index score categories in patients with known coronary artery disease. N/ExS: Non/ex-smoker; A-PA: Adequate physical activity; N-BMI: Normal body mass index; OW: Overweight; OB: Obesity; P, IM, G (CHIS): Cardiovascular health index score categories: Poor, Intermediate, Good. $^{a}P < 0.00001$; $^{b}P < 0.05$.

Cardiovascular risk factors

To effectively manage CVDs, it is vital to recognize their multifactorial nature and implement preventive measures that target modifiable risk factors. These measures should include optimizing physical activity, encouraging smoking cessation, reducing BMI, and treating AH, diabetes, and hyperlipidemia. The positive effects of lifestyle modification and optimal pharmacological interventions on cardiovascular morbidity and mortality have been demonstrated in previous studies[13-15].

Smoking cessation is one of the most effective measures for reversing vascular injury and preventing the development of atherosclerosis and fatal cardiovascular outcomes[16,17].

The information collected in several national surveys conducted in Azerbaijan has shown that there is a high prevalence of risk factors such as smoking, overweight, unhealthy diet, and physical inactivity which are responsible for the great majority of NCD cases. One of the studies conducted to gather information on the health of the population is the WHO-recommended STEPS survey. This survey has been conducted nationwide in both 2011 and 2017[18]. Analysis of

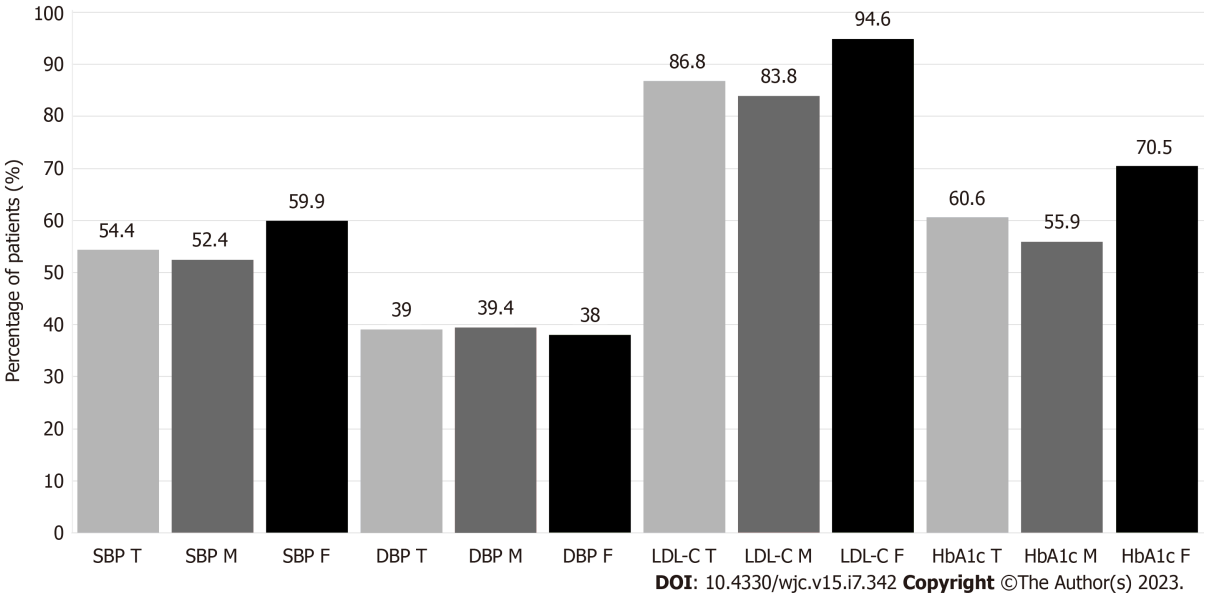

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Figure 2 Rate of uncontrolled risk factors in patients with a previous history of hypertension, dyslipidaemia, and diabetes. SBP: Systolic blood pressure; DBP: Diastolic blood pressure; LDL-C: Low density lipoprotein cholesterol; HbA1c: Glycated haemoglobin; T: Total, M: Males; F: Females. No statistically significant differences between the groups.

the study results, conducted among 3000 adult population aged 18 years and above, has shown that smoking is one of the major problems for Azerbaijani society. Overall, the prevalence of smoking was significantly higher among men (48.8%) than among women (0.2%) who were identified as current smokers. This difference in smoking prevalence can be largely attributed to the social stigma surrounding smoking among women, as it is often viewed negatively within the local culture.

The study also found that 24.9% of all respondents had been exposed to secondhand smoke at home, with men showing a higher incidence of exposure than women. The results of the SURF study are consistent with these data: The smoking rate was 24.6%, and it was significantly high among men than in women (32% *vs* 1.8%, accordingly).

Comorbidities such as hypertension, dyslipidaemia, and diabetes are known risk factors for CHD events and may indicate an increased susceptibility to atherosclerosis development. In the current study, uncontrolled SBP was found in 54.6% of patients with reported AH. According to the STEPS study, the prevalence of AH among the general population was about 30%[18]. Most of the respondents with high BP (65.4%) were not taking any medication. Salt intake was around 10 g per day, with a significant gender difference (11.4% of men *vs* 26.8% of women). The above-mentioned aspects of behaviour and dietary habits could also contribute to the poor management of BP in the participants of the SURF study.

The SURF study has demonstrated that BMI values were high in 91% of participants, which could indicate that BMI is one of the most common risk factors in the development of coronary artery disease (CAD). But it should also be taken into consideration that parameters such as BMI and WC were measured only in a small group of patients and mainly in persons with apparent high body weight and abdominal obesity. This circumstance may have an impact on the data obtained.

The study results have shown that approximately 50% of the patients did not reach even the first target level of lipids [7], despite the fact that the rate of statin usage among this category of patients was 86.4%. These reasons could include discontinuation of statin therapy due to poor adherence and compliance to treatment recommendations, as well as not achieving the target dosage of the medication[19]. A similar pattern was observed with respect to the patients with DM: Despite insulin and oral hypoglycemic drugs use, HbA1c level did not reach the targets in the majority (60.6%) of them.

The cross-sectional study European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) IV was undertaken at 78 centres in 24 European countries with the involvement of 7998 patients < 80 years of age with CAD[20]. While Azerbaijan did not participate in EUROASPIRE, the results acquired from the mentioned study can be compared with the results of the SURF study conducted in our country. It was observed that in Azerbaijani patients with ASCVD, the mean age was younger, the rate of smoking was higher, and the rate of controlled BP level was lower. Uncontrolled LDL-C levels (≥ 70 mg/dL) and BMI greater than 30 kg/m^2 were found to be lower in our study.

Gender-based differences in cardiovascular risk factors

According to the study results, despite that the smoking rate was significantly high among men than in women, higher values of BMI and WC, as well as BG level and history of DM type 2, were found in female participants. Furthermore, the STEPS study has demonstrated that in the general population, approximately 91% of women are not engaging in vigorous physical activity.

These findings comply with the literature data. A systematic review conducted on the distribution by gender of diabetes, risk factors, complications, and disease control in the Caribbean general population has shown that women were more likely than men to have diabetes and obesity. This review also found that women were less physically active than men, but they were less likely to smoke cigarettes[21]. The authors of this review discovered that there was a statistically significant association between gender and diabetes, with women being at a risk of more than one and a half times greater than men.

It could be concluded from the foregoing that the gender differences in the distribution of CV risk factors such as DM, obesity, lack of physical activity, and smoking should be taken into account in the pharmacological management of patients with and without CVD and when designing rehabilitation programmes.

Medication usage and CR

When comparing the rates of medication usage in our study and the results of the cross-sectional study EUROASPIRE IV [20], the rate of cardioprotective medication use was higher in the latter case (anti-platelets 93.8% *vs* 84.6%; statins 85.7% *vs* 73.9%, beta-blockers 82.6% *vs* 53.3%; ACE inhibitors/ARBs 75.1% *vs* 51.2%). According to the data of the SURF CHD II [5] study, the use of statins in the European region was 78.94%, which is broadly comparable to our data.

Adherence and compliance play a major role in all pharmacological therapies. The causes of non-compliance can be classified into the following categories: Patient, physician, and health system-related[22]. Similarly, with dyslipidemia, diabetes, and hypertension, the causes of poor control of risk factors should be carefully analyzed for the effective implementation of the guideline recommendations into clinical practice.

Only 15.1% of patients reported participation in CR in our study, despite this is a recommendation class I and the level of evidence A intervention[3]. The literature indicates that the number of patients who participate in CR programs, especially in low-income countries, is extremely low, and patients' adherence is often scarce[23]. There are several known barriers to the implementation of CR and adherence to such programs. Some of these barriers include limited availability of services, high program costs, long travel distances to access services, low referral rates from healthcare providers, and low levels of patient motivation to participate in rehabilitation programs[23-27], and these reasons may have contributed to the low participation in CR in Azerbaijan.

Another likely reason for the low participation rate in CR could be that these programs are only offered in a limited number of hospitals, and patients are required to cover almost all the costs out-of-pocket. It is expected that reforms in the health system and the financing of medical services, such as the introduction of compulsory health insurance, will help fill this missing gap in the secondary prevention of CVDs.

Context and direction of cardiovascular prevention and rehabilitation in Azerbaijan

In 2015, the 'Strategy for Non-Communicable Diseases' was adopted in order to achieve a significant reduction in premature deaths associated with NCDs in the country. The objectives of the Strategy are to establish an effective intersectoral cooperation mechanism to combat NCDs, to take measures to reduce the main risk factors (tobacco use, alcohol abuse, unhealthy diet, and physical inactivity), and to prevent and control these diseases. Their role does not merely focus on improving the healthcare system and healthcare services, but also on promoting a healthy lifestyle for the population [18].

As a result of the implementation of the project on improving the national legislative framework to combat the tobacco epidemic, the parliament of the country adopted a new law aimed at enhancing limitations on tobacco use in public spaces. This law supports the establishment of tobacco control programs, hotlines, and pharmacotherapy initiatives to assist individuals in smoking cessation[18,28].

Preventive campaigns are the mainstay of activities to combat NCDs in Azerbaijan. The Ministry of Health (MoH) developed a health awareness-raising web portal for the population, which includes articles about non-communicable diseases and their risk factors and prevention strategies. MoH and ASC provide information days and thematic conferences to increase awareness of CVD prevention among the population. Some non-governmental and public organisations also participate in the promotion and popularisation of healthy lifestyles and primary prevention.

Important steps have been taken to improve the rehabilitation services in the country: The new degree programs, which include cardiovascular rehabilitation modules, have been launched[28]. The cardiology curriculum for residents has been updated in line with the ESC standards, and now it contains a chapter on cardiovascular prevention and rehabilitation.

E-training courses for cardiologists from remote areas have been initiated by MoH and ASC. One of the successful programs included the establishment of a portal for specific e-training on cardiovascular risk factors, promotion of physical activity, and tobacco cessation skills for physicians, among others[28].

Despite these measures, the results of the SURF study and previous population-based studies have shown that the rate of risk factors is still high among both the general population and patients with documented CVD. This demonstrates once more the need of consistent training for healthcare professionals, notably primary care physicians, as well as patients, and the need for the healthcare system to pay more attention to this issue. Such measures will undoubtedly help to reduce the frequency of undesirable consequences and rehospitalisations in this category of patients, and hence reduce healthcare costs.

Strengths and limitations

The SURF CHD study uses a one-page, simple questionnaire that allows rapid data collection. It can be completed in a very short period during a routine outpatient visit, requires involving a larger population in the study with minimal effort.

Clinical audits such as SURF also enhance process improvement: In light of the results, changes can be implemented in the procedures to record and manage risk factors, and re-auditing can inform on the effectiveness of these changes to improve risk factor recording and management.

However, it should be mentioned that the current study has several limitations. First, it only included tertiary level hospitals in the capital city (however, it is planned to include primary and secondary health care facilities from the different regions of Azerbaijan at the further stages of the study). Second, for some risk factors such as waist circumference, data were not recorded in all participants. This suggests that some clinicians overlook certain risk factors, and one of the important roles of an audit such as SURF is to stimulate fuller recording of relevant data.

CONCLUSION

Our study has demonstrated that the control of cardiovascular risk factors and lifestyle changes recommended by clinical CVD prevention guidelines in patients with CHD is unsatisfactory. The number of patients involved in CR program is low, and the high level of uncontrolled risk factors among patients who participated in CR indicates the poor adherence and compliance among patients. Monitoring and control of the modifiable risk factors are not at a desired level, and require more organized work and collaboration of healthcare providers from different healthcare facilities.

The above-mentioned trends and individual and gender characteristics of patients should be considered by healthcare organizers when planning secondary prevention activities and public health protection measures.

The strategic needs for prevention and rehabilitation in Azerbaijan are to increase the number of rehabilitation centres and ensure their adequate geographical distribution, with a particular focus on the regions of the country, and to expand indications of CR services and programs for primary and secondary prevention for the population with high and very high cardiovascular risk. More efforts are needed to improve and strengthen the mechanism for education of primary healthcare providers in the field of cardiac prevention and rehabilitation.

It is also suggested that Standard Operating Procedures should be developed for cardiac clinics in regions to facilitate process improvement.

ARTICLE HIGHLIGHTS

Research background

Low level of monitoring and control of modifiable risk factors necessitates better structured effort and coordination of health care specialists from various healthcare facilities. The strategic needs for prevention and rehabilitation in Azerbaijan are to increase the number of rehabilitation centers and ensure their adequate geographical distribution, with a particular focus on the country's regions, and to expand indications of cardiac rehabilitation (CR) services and programs for primary and secondary prevention for the population with high and very high cardiovascular risk, and to expand indications of CR services and programs for primary and secondary prevention for the population with high and very high cardiovascular risk. It is also proposed that cardiac clinics adopt Standard Operating Procedures. More effort is required to improve and reinforce the process for primary health care provider education in the field of cardiac prevention and rehabilitation.

Research motivation

Previous studies have shown that control of major cardiovascular risk factors is generally inadequate in patients with established atherosclerotic cardiovascular disease (CVD) (ASCVD). Azerbaijan is a country in the South Caucasus, a region at very high risk for CVD. The aim of this study was to evaluate compliance with the recommendations of the European Society of Cardiology (ESC) for secondary prevention of CVD based on the measurement of both modifiable major risk factors and their therapeutic management in patients with confirmed coronary heart disease (CHD) in Azerbaijan. We believe that these results will contribute to the improvement of the situation in secondary prevention of CHD in the country.

Research objectives

This study focused on the national results of the Survey of Risk Factors in CHD (SURF CHD) II study in Azerbaijan.

Research methods

SURF CHD II study uses a one-page, standard questionnaire that allows rapid data collection. Information on demographics, risk factors, physical and laboratory data, and medications was collected in consecutive outpatients aged ≥ 18 years with established atherosclerotic CHD. Data from 687 patients (mean age 59.6 ± 9.58 years; 24.9% female) were included in the study.

Research results

The study results show that the control of cardiovascular risk factors and lifestyle modification measures indicated by clinical CVD prevention recommendations in patients with CHD are inadequate. The number of patients with CHD enrolled in a CR program is small as well.

Research conclusions

The findings of the SURF study can be used to improve processes by changing the techniques for documenting and monitoring CVD risk variables, and re-auditing can provide insight into the effectiveness of these modifications in improving the management of patients with ASCVD.

Research perspectives

It is critical to efficiently manage the main cardiovascular risk factors in order to prevent CVD mortality. The international SURF CHD II clinical audit measures modifiable risk factors to assess adherence to ESC recommendations for secondary prevention of CVD in patients with established CHD.

FOOTNOTES

Author contributions: Gabulova R analyzed the data and wrote the manuscript; Marzà-Florensa A was involved in all stages of developing the final version of the manuscript; Rahimov U, Isayeva M, Alasgarli S, Musayeva A, Gahramanova S, Ibrahimov F, Aliyev F, and Imanov G collected the clinical data and contributed equally to this work; Rasulova R analyzed the data; Vaartjes I and Klipstein-Grobusch K critically reviewed the manuscript; Graham I and Grobbee DE designed the research study and critically reviewed the work; all authors have read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Research Ethic Committee of The National Cardiac Society of Azerbaijan (No. 01/2022).

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META-ANALYSIS

Effects of time-restricted eating with different eating duration on anthropometrics and cardiometabolic health: A systematic review and meta-analysis

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Abstract

BACKGROUND

Time-restricted eating (TRE) is a dietary approach that limits eating to a set number of hours per day. Human studies on the effects of TRE intervention on cardiometabolic health have been contradictory. Heterogeneity in subjects and TRE interventions have led to inconsistency in results. Furthermore, the impact of the duration of eating/fasting in the TRE approach has yet to be fully explored.

AIM

To analyze the existing literature on the effects of TRE with different eating durations on anthropometrics and cardiometabolic health markers in adults with excessive weight and obesity-related metabolic diseases.

METHODS

We reviewed a series of prominent scientific databases, including Medline, Scopus, Web of Science, Academic Search Complete, and Cochrane Library arti-

cles to identify published clinical trials on daily TRE in adults with excessive weight and obesity-related metabolic diseases. Randomized controlled trials were assessed for methodological rigor and risk of bias using version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB-2). Outcomes of interest include body weight, waist circumference, fat mass, lean body mass, fasting glucose, insulin, HbA1c, homeostasis model assessment for insulin resistance (HOMA-IR), lipid profiles, C-reactive protein, blood pressure, and heart rate.

RESULTS

Fifteen studies were included in our systematic review. TRE significantly reduces body weight, waist circumference, fat mass, lean body mass, blood glucose, insulin, and triglyceride. However, no significant changes were observed in HbA1c, HOMA-IR, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, heart rate, systolic and diastolic blood pressure. Furthermore, subgroup analyses based on the duration of the eating window revealed significant variation in the effects of TRE intervention depending on the length of the eating window.

CONCLUSION

TRE is a promising chrononutrition-based dietary approach for improving anthropometric and cardiometabolic health. However, further clinical trials are needed to determine the optimal eating duration in TRE intervention for cardiovascular disease prevention.

Key Words: Cardiovascular disease; Cardiometabolic health; Time-restricted eating; Chrononutrition; Intermittent fasting; Obesity

Core Tip: Beneficial effects of time-restricted eating (TRE) on adults with excessive weight and obesity-related metabolic diseases remain under investigation, and results are conflicting. We explored the effectiveness of TRE on anthropometric and cardiometabolic health in adults with excessive weight and obesity-related metabolic diseases. We found that TRE is an effective and sustainable dietary strategy for reducing body weight, body composition, blood glucose, insulin, and triglyceride in individuals with excessive weight or weight-related metabolic disorders. Moreover, the meta-analysis demonstrates the varying effects of fasting duration on the outcomes of interest.

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INTRODUCTION

The global prevalence of overweight and obesity has become a major public health problem. High body mass was responsible for over five million deaths and 160 million disability-adjusted life years worldwide[1]. According to the World Health Organization reports, the number of overweight and obese individuals has doubled globally since 1980, affecting both developed and developing countries. As a result, weight-related diseases, including obesity and related conditions such as type 2 diabetes, cardiovascular disease (CVD), and certain cancers, have become a major public health challenge worldwide and a burden on healthcare systems[2,3]. Researchers and healthcare professionals have explored multiple dietary strategies to improve weight and cardiometabolic health and prevent cardiovascular disease through caloric and macronutrient restriction, specific foods or nutrients, adherence to selected dietary patterns, and fasting. Continuous energy restriction (CER) has been frequently used to manage the body weight of individuals with excessive weight[4]. However, adherence to this diet pattern is challenging due to the daunting task of reducing daily caloric intake [5]. Additionally, CER may promote adaptive responses such as decreased physical activity, increased hunger, and deactivation of the hypothalamic-pituitary-thyroid axis, hindering weight and fat loss[6]. Moreover, CER increases the risk of adverse effects such as hypoglycemia, nutrient deficiencies, and extreme fatigue.

In recent years, intermittent fasting (IF) has emerged as an alternative weight loss and CVD prevention strategy. It refers to a cyclic eating pattern that rotates between periods of abstinence from consuming any caloric-containing food or drinks and periods of eating[7]. Current human research indicates that chrononutrition-based dietary interventions, such as time-restricted eating (TRE), have gained substantial interest from the public as one of the sustainable strategies for CVD prevention[8]. TRE is a lifestyle approach that limits eating duration to a set number of hours per day (typically within 4–12 h) during waking hours, allowing for adequate fasting[9,10]. TRE aims to align dietary intake with daily circadian rhythms. It is considered a more sustainable approach than caloric restriction, as it involves lower-intensity

adaptation for long-term lifestyle modifications to reduce weight[8]. Animal studies have linked TRE to lower body weight, total cholesterol (TC), triglycerides, glucose, insulin, interleukin-6, tumor necrosis factor, and improved insulin sensitivity[11-13].

The effects of TRE with different eating durations, ranging from four to 12 h, have been studied on humans[14]. These studies have reported varying results, with some showing improvements in weight loss, insulin sensitivity, and cardiovascular markers, while others exhibiting no significant changes. Several recent systematic reviews have been conducted to review the effects of TRE interventions on anthropometric and cardiometabolic health[15-23]. The most consistent findings from these reviews were significant weight reduction with TRE intervention, with mixed results for the TRE effects on cardiometabolic health. This inconsistency is mainly due to heterogeneity in subjects and the implemented TRE interventions.

Additionally, combining results from individuals with normal body mass index (BMI) and those with metabolic dysregulation may obscure differences in the effectiveness of the intervention. To our knowledge, no systematic review has evaluated the effects of variation in TRE's eating duration on anthropometric and cardiometabolic health. Therefore, this systematic review and meta-analysis aimed to examine the effects of varying eating durations in TRE interventions on body weight and composition, waist circumference, biomarkers of glucose metabolism, lipid metabolism, inflammatory marker, blood pressure, and heart rate in adults with excessive weight and obesity-related metabolic diseases. The findings of this review will shed light on the overall effectiveness of TRE and its optimal eating duration as a potential dietary approach for weight loss and improved cardiometabolic health in individuals with excessive weight and obesity-related metabolic diseases.

MATERIALS AND METHODS

Protocol and registration

This systematic review was reported according to the updated version of the Preferred Reporting Items for Systematic Reviews and Meta-analyses Statement[24]. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (http://www.crd.york.ac.uk/PROSPERO), with a record number of CRD42022341232. Before conducting the review, PROSPERO and the Cochrane Library were searched to identify existing or ongoing similar work by other researchers.

Search strategy

Multiple electronic databases were queried using selected search terms until May 2022. MEDLINE Complete, Web of Science, Scopus, the Cochrane Library, Academic Search Complete, Food Science Source, OpenDissertations, Education Research Complete, and Psychology and Behavioural Sciences Collection were used for the systematic search (Supplementary Table 1). The search strategy was tailored to each database's keywords to identify literature for the intervention of interest, TRE. The search terms included "time-restricted diet" OR "time-restricted eating" OR "time-restricted feeding" OR "time-restricted fasting" OR "time-restricted meal", which have been identified in previous systematic reviews[19,21,22]. The search was not limited to specific years of publication or languages, and no additional terms were used to avoid filtering out relevant literature. All search outputs were exported to reference manager software (Endnote 20; endnote.com). After removing duplicates, two independent reviewers screened the articles for eligibility based on title, abstract, and full text (Zaman MK and Teng NIMF). A consensus was reached for included articles through discussions after each screening round, and a third reviewer resolved any disagreements (Juliana N).

Study selection

The eligibility criteria for this systematic review were based on the predetermined inclusion and exclusion criteria. We included studies with the following characteristics: (1) Population: Adults with excess weight and obesity-related metabolic diseases; (2) Intervention: TRE, which involves daily (seven days per week) eating window restriction; (3) Comparator: The comparator accepted for this study were dietary intake with ad libitum eating window or eating window of 12 h or more; (4) Outcomes: Changes in body weight, waist circumference, fat mass, lean body mass, fasting glucose, insulin, HbA1c, homeostasis model assessment for insulin resistance (HOMA-IR), lipid profile [total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides], C-reactive protein, blood pressure (systolic and diastolic), and heart rate were identified as outcomes of interest—studies with any reported outcomes of interest were included; and (5) Study design: Only controlled/clinical trials with at least one outcome measurement performed within two weeks to 6 mo of intervention commencement were included in this review.

We excluded studies based on the following characteristics: (1) Population: Studies involving subjects younger than 18 years of age, animal models, or studies including adult subjects with normal BMI were excluded; (2) Intervention: Studies with intermittent TRE (*e.g.*, ad libitum dietary intake during selected days) were excluded; and (3) Study design: Abstracts, and non-original articles such as expert opinions and reviews were excluded from this systematic review.

Risk of bias assessment

Risk of bias (RoB) assessments of the included studies were conducted and graded using version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB-2)[25]. This tool evaluates the RoB across five key domains: Randomization process, deviation from intended interventions, missing outcome data, outcome measurement, and selection of reported

results. Trials were classified as having either low risk, unclear risk, or high RoB for each domain and overall. Two reviewers were involved independently in the RoB assessments of the included studies (Zaman MK and Teng NIMF). Disagreements were resolved through consensus or discussion with a third reviewer (Kasim SS).

Data extraction

Data collection forms were used to extract data from each study. The extraction form was piloted in at least one study included in this review. Two reviewers were involved in the data extraction from included studies (Zaman MK and Teng NIMF). Data extracted include: (1) Information about the trial: Authors, publication year, study design, sample size, and study duration; (2) Study participants: Population characteristics, location, age, gender, and BMI; (3) Intervention characteristics: Description of intervention and control arm, eating window, and timing of intervention; and (4) Outcome measures: Body weight, waist circumference, fat mass, lean body mass, fasting glucose, insulin, HbA1c, HOMA-IR, lipid profile (TC, HDL-C, LDL-C, and triglycerides), C-reactive protein, blood pressure (systolic and diastolic), and heart rate.

Data synthesis and analysis

Standardized mean differences (SMDs), or mean differences (MDs) with 95%CI, were used to report intervention effects for each study based on pre-and post-TRE intervention. Meta-analyses were conducted, if feasible, using a minimum of two included studies with similar outcomes for each outcome of interest. Forest plots were constructed for all studies included in the meta-analysis. A two-sided P value of < 0.05 was considered statistically significant. The heterogeneity was evaluated statistically using the I^2 statistic, with a value greater than 50% indicating substantial heterogeneity. The random-effects model was employed when substantial heterogeneity was present. Publication bias was examined using a funnel plot visualization for outcomes with ten or more studies. Considering the heterogeneity protocol and duration of the eating window in TRE intervention, subgroup analyses were performed by applying a different range of TRE duration. All analyses were conducted using RevMan software, version 5.4.

RESULTS

Search results

The systematic search process identified 2067 articles (Figure 1) from multiple resources, including Medline (n = 425), Scopus (n = 567), Web of Science (n = 483), Academic Search Complete (n = 224), Cochrane Library (n = 216), Food Science Source (n = 126), OpenDissertations (n = 10), Education Research Complete (n = 9), and Psychology and Behavioural Science collection (n = 7). After removing duplicates, 829 records were screened, and 51 were assessed for eligibility after excluding articles not meeting the inclusion criteria. Further screening and quality assessment resulted in 15 studies being selected for the systematic review and meta-analysis, involving 927 subjects[26-40]. The largest study recruited 139 subjects, while the smallest enrolled eight subjects[32,39]. Most studies were conducted in the United States of America (n = 7), followed by Brazil (n = 3), China (n = 3), Switzerland (n = 1), and Germany (n = 1).

Study characteristics

Table 1 displays the characteristics of the participants in the included studies. The participants were adults with overweight/obesity, prediabetes, or Type 2 Diabetes Mellitus. The participants ranged from 27 to 74 years old[26,30], with a BMI above the normal cut-off, ranging from 26.4 to 38.9 kg/m^2. The majority of the included studies were parallel arms randomized controlled trials (RCT) (n = 13), randomized crossover trial (RXT) (n = 1), and non-RCT (n = 1). All studies involved at least one intervention group with a TRE regimen and a comparator group with an unrestricted time of food intake. The interventions were conducted over three weeks to twelve months, with the fasting period lasting between 12 and 20 h per day and the eating period lasting from four to 12 h daily. The timing of the start of the fasting period was either self-selected by participants or predetermined by the study (Table 1). Most TRE interventions in the included studies restricted food intake during the day, with the last meal completed by 20:00[27,29-34,37-39].

Risk of bias assessment

The RoB assessments for the RCTs are summarized in Figure 2. Overall, seven studies posed a high RoB[30-33,35,38,40], and eight studies posed concerns regarding the overall RoB[26-29,34,36,37,39]. In the domain of the randomization process, all included studies were identified as randomized studies except for one. Ten studies had limited or no information on randomization and concealment, leading to concerns in the domain of the randomization process[28-34,37,38,40]. Due to the nature of the intervention of interest, blinding participants may not be feasible. Information on blinding of the participants, carers, and personnel assessing in the laboratory or statistical analyses was often unknown or limited, introducing possible risk of bias due to deviations from the intended intervention. Most studies showed a low RoB due to missing outcome data[26-29,31-34,36,37,40] and outcomes measurement[26-37,39,40]. In the domain of selection of the reported result, most studies were classified as posing concern[26-30,36-39] or high risk[31-33,35,40] due to the limited availability of a prespecified analysis plan (*i.e.*, protocol) or/and missing outcomes measurement.

Effects of TRE on weight and body composition

Body weight: A total of 15 studies were included in the analysis to assess the effect of TRE on body weight (kg) (Figure 3). Individuals assigned to the TRE intervention showed a significant reduction in body weight levels compared to the comparator group [MD -2.26; 95%CI: -3.10 to -1.43, P < 0.00001; I^2 = 93%]. Random-effects subgroup analysis was

Table 1 Characteristics of the participants in the included studies

Ref.	Study design	Sample size	Study duration	Characteristics	Location	Sex	Baseline BMI (kg/m^2)	Age (yr)	Fasting: Eating period (hours)	Timing of intervention
Chair *et al* [26], 2022	Three arm RCT	101	3 wk	Prediabetes	Weight management clinic, Hunan Provincial People's Hospital, Changsha, China	M: 3, F: 64	35.23 ± 6.19	74.30 ± 8.39	16:08	Free to arrange the 8-h eating window based on personal preferences
Che *et al* [27], 2021	RCT	120	14 wk	Overweight adults with type 2 diabetes	Diabetes Clinic, Zhu Xianyi Hospital of Tianjin Medical University, China	M: 65, F: 55	TRE: 26.42 ± 1.96; Comparator: 26.08 ± 2.14	TRE: 48.21 ± 9.32; Comparator: 48.78 ± 9.56	14:10	08:00 to 18:00 and fasted from 18:00 to 08:00 daily
Chow *et al* [28], 2020	RCT	20	12 wk	Adults with BMI ≥ 25 kg/m^2	Minnesota, United States	M: 3, F: 17	TRE: 33.8 ± 7.6; Comparator: 34.4 ± 7.8	TRE: 46.5 ± 9.32; Comparator: 44.2 ± 12.3	16:08	Self-select
Cienfuegos *et al*[29], 2020	RCT (3-arms)	58	10 wk	Adults with BMI of 30-49.9 kg/m^2	Chicago, United States	F: 53 M:5	4-h TRE: 37 ± 1; 6-h TRE: 37.0 ± 1.0; Comparator: 36.0 ± 1.0	4-h: 47 ± 2; 6-h: 47 ± 3; Comparator: 45 ± 2	4-h: 20:04; 6-h: 18:06	4-h TRE: 15:00-19:00; 6-h TRE: 13:00-19:00
Isenmann *et al*[30], 2021	RCT	35	16 wk	Adults with BMI ≥ 25, physically active	Gymnasium, (Windhagen, Germany)	F: 21 M: 21	TRE: 26.3 ± 3.0; Comparator: 25.7 ± 3.3	TRE: 27.9 ± 5.3; Comparator: 27.4 ± 5.8	16:08	12:00-20:00
Kotarsky *et al*[31], 2021	RCT	21	8 wk	Adults with BMI 25.0 and 34.9 kg/m^2	North Dakota State university, United States	F: 18 M: 3	29.6 ± 2.6 kg/m^2	44 ± 7	16:08	12:00-20:00
Liu *et al* [32], 2022	RCT	139	6/12 mo	Adults with BMI of 28-45 kg/m^2	Guangzhou, China	F: 68 M: 71	TRE: 31.8 ± 2.9; Comparator: 31.3 ± 2.6	TRE: 31.6 ± 9.3; Comparator: 32.2 ± 8.8	16:08	08:00-16:00
Lowe *et al* [33], 2020	RCT	116	12 wk	Adults with BMI 27-43 kg/m^2	United States, primarily San Francisco	F: 70 M: 46	32.7 ± 4.2	46.5 ± 10.5	16:08	TRE, 8 h, 12:00-20:00
Peeke *et al* [34], 2021	RCT (Virtual)	60	8 wk	Adults with BMI ≥ 30 kg/m^2	United States	F:69 M: 9	38.9 ± 7.7	44.0 ± 11.0	12:12 (14:10, with fasting snack 12 h post fasting)	Fasting began after dinner (between 17:00-20:00)
Phillips *et al* [35], 2021	RCT	54	6 mo	Adults with at least one component of metabolic syndrome	Switzerland	Not reported	TRE: 28.0 ± 4.1; Comparator: 27.0 ± 4.0	43.4 ± 13.3	12:12	-
de Oliveira Maranhão Pureza *et al* [36], 2021	RCT	58	21/81 d	Adults with BMI 30-45 kg/m^2	Outpatient clinic of the Centro de Recuperação e Educação Nutritional, Brazil	F: 58	TRE: 31.80 (CI: 29.25-34.36); Comparator: 31.03 (CI, 28.20-33.87)	TRE: 33.53 (CI: 32.00-35.50); Comparator: 33.12 (CI: 31.68-34.56)	12:12	Self-select
Ribeiro *et al* [37], 2021	RCT	24	8 wk	Physically active adults with BMI 25 kg/m^2	Brazil	F: 20 M: 4	TRE :30.5 ± 3.5; Comparator: 31.7 ± 5,6	TRE: 32.4 ± 5.5; Comparator: 33.0 ± 8.7	16:08	12:00-20:00

Schroder *et al*[38], 2021	NRCT	40	3 mo	Women with BMI ≥ 30 kg/m^2	Brazil	F: 40	TRE: 32.53 ± 1.13; Comparator: 4.55 ± 1.20	TRE: 36.6 ± 1.6. Comparator: 42.3 ± 3.5	16:08	12:00-20:00
Sutton *et al* [39], 2018	RXT	8	5 wk	Pre-diabetic men with BMI ≥ 25 kg/m^2	Greater Baton Rouge, United States	M: 12	32.2 ± 4.4	56.0 ± 9.0	18:06	Self-select eating window between 06:30-08:30; For early TRE to end eating window by 15:00
Thomas *et al*[40], 2022	RCT	81	12/39 wk	Adults with BMI 27-45 kg/m^2	Colorado, United States	F: 20 M: 4	34.1 ± 5.7	38.0 ± 7.8	14:10	Start eating window 3 h post waking up

RCT: Randomized control trial; NRCT: Non-randomized control trial; RXT: Randomized crossover trial; BMI: Body mass index; M: Male; F: Female; TRE: Time-restricted eating.

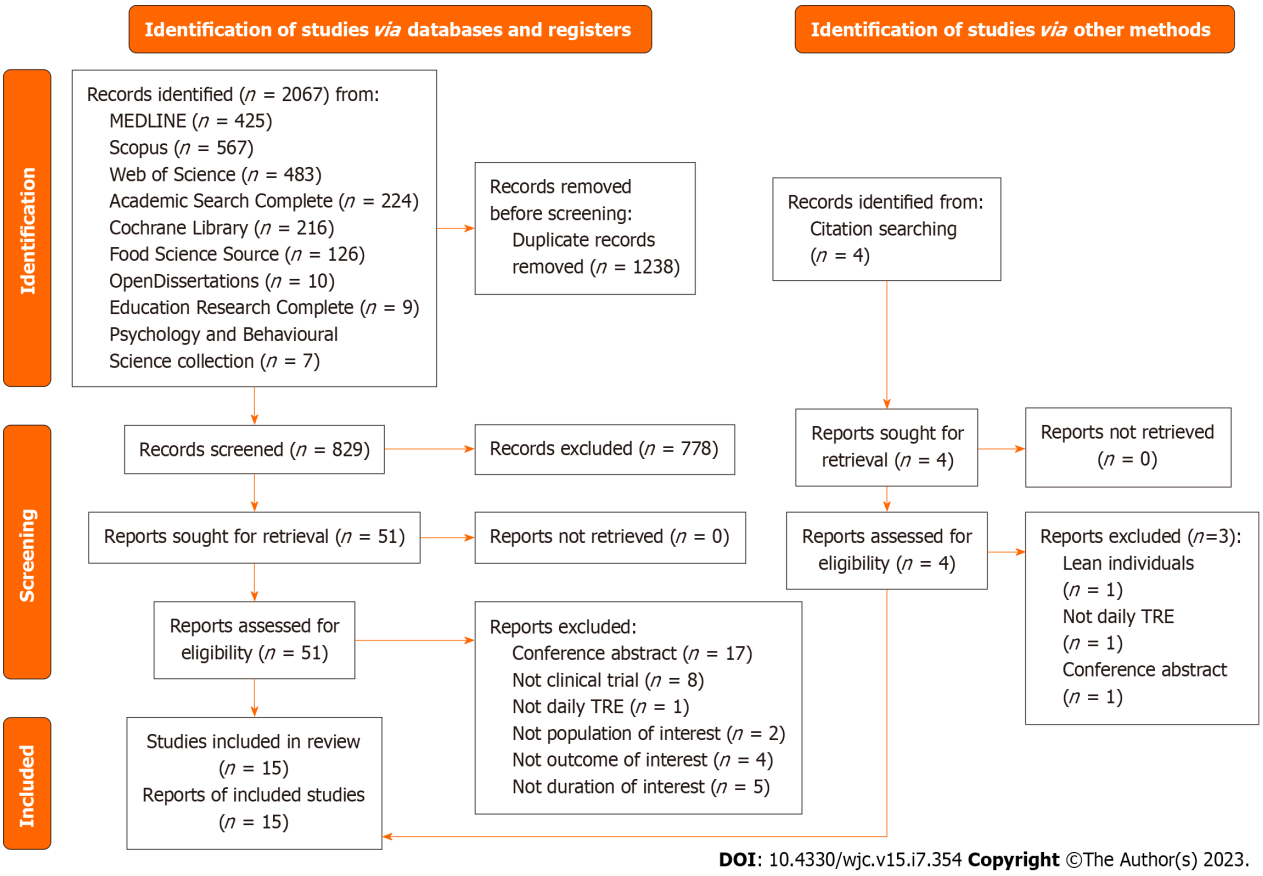

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Figure 1 The preferred reporting items for systematic reviews and meta-analyses 2020 flow diagram for systematic review, which included searches of databases, registers, and other sources. TRE: Time-restricted eating.

conducted based on the duration of TRE intervention revealed no significant changes in body weight in TRE interventions ranging from ten to 12 h [MD -1.11; 95%CI: -2.31 to 0.10, P = 0.07; I^2 = 84%]. Meanwhile, a significant reduction was observed in TRE interventions ranging from seven to nine hours [MD -2.36; 95%CI: -4.37 to -0.35, P = 0.02; I^2 = 79%] and TRE interventions ranging from four to six hours [MD -3.85; 95%CI: -4.29 to -3.41, P < 0.00001; I^2 = 58%].

Waist circumference: A meta-analysis of nine studies demonstrated a significant overall effect of TRE on waist circumference reduction compared to 261 subjects in the comparator group [MD -2.35; 95%CI: -4.43 to -0.27, P = 0.03; I^2 = 81%] (Figure 4). Random-effects subgroup analyses were conducted based on the duration of TRE intervention showed no significant changes in waist circumference following TRE interventions ranging from ten to 12 h [MD -1.11; 95%CI: -2.83 to 0.60, P = 0.20; I^2 = 0%]. However, a significant reduction in waist circumference was observed in TRE interventions ranging from seven to nine hours [MD -2.70; 95%CI: -5.24 to -0.17, P = 0.04; I^2 = 84%]. The effect of TRE ranging from four to six hours on the measured outcome was not reported in any of the included studies.

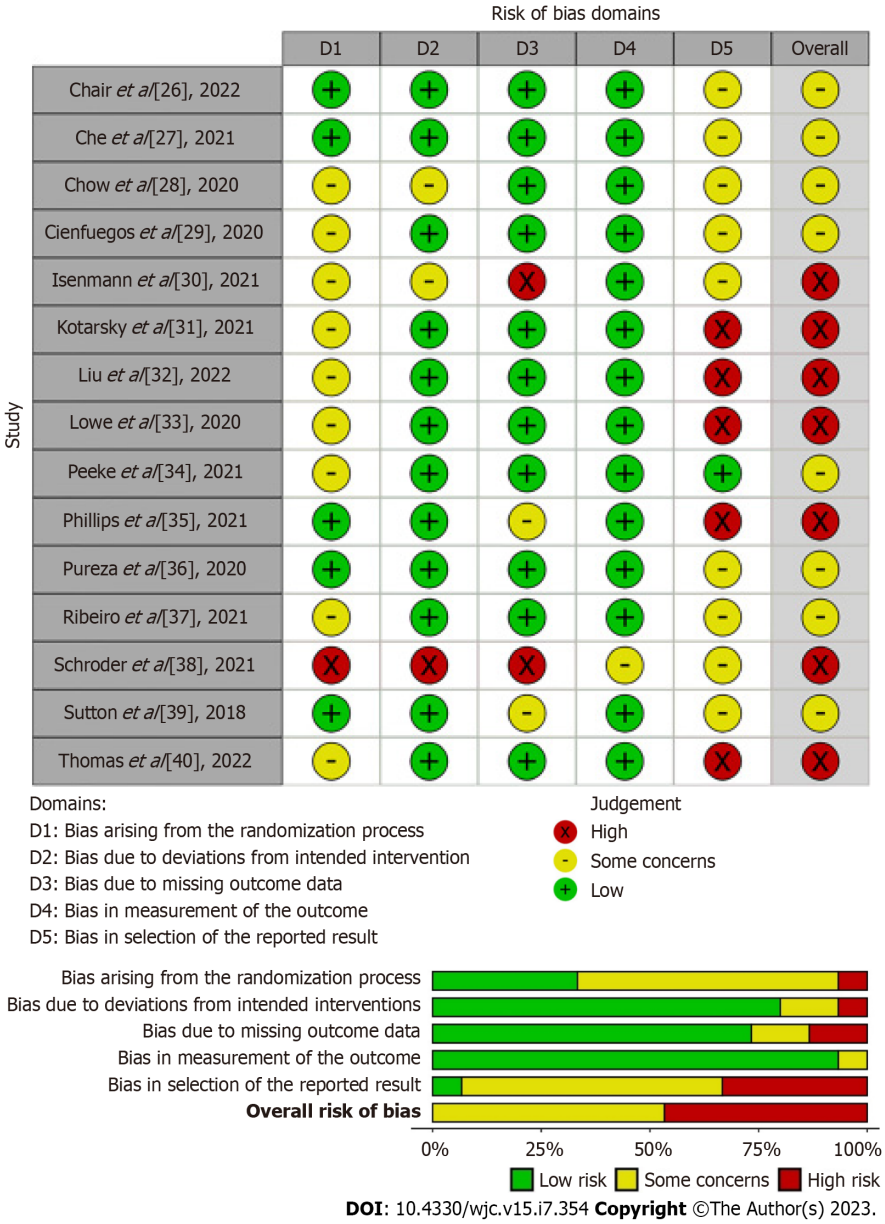

Figure 2 Risk of bias assessment of the studies included in the meta-analyses.

Total fat mass: A meta-analysis of ten studies evaluated the effect of TRE on total fat mass. Individuals assigned to TRE intervention showed a significant reduction in total fat mass levels compared to the comparator group [SMD -0.63; 95%CI: -1.10 to -0.17, P = 0.008; I^2 = 83%] (Figure 5). Random-effects subgroup analyses were conducted based on the duration of TRE intervention, which revealed a significant reduction in total fat mass following TRE interventions ranging from ten to 12 h [SMD -0.41; 95%CI: -0.75 to -0.08, P = 0.02; I^2 = 0%], and TRE interventions ranging from four to six hours [SMD -3.73; 95%CI: -6.76 to -0.70, P = 0.02; I^2 = 91%]. However, no significant changes were observed in TRE interventions ranging from seven to nine hours [SMD -0.13; 95%CI: -0.35 to 0.09, P = 0.25; I^2 = 0%].

Lean body mass: A meta-analysis of nine studies was evaluated the effect of TRE on lean body mass. Individuals assigned to TRE intervention showed a significant overall reduction in lean body mass compared to the comparator group [MD -0.64; 95%CI: -1.11 to -0.16, P = 0.009; I^2 = 75%] (Figure 6). Random-effects subgroup analyses were conducted based on the duration of TRE intervention demonstrated no significant changes in lean body mass following TRE interventions ranging from seven to nine hours [MD -0.23; 95%CI: -0.90 to 0.43, P = 0.49; I^2 = 0%]. A significant reduction in lean body mass was observed in the TRE intervention group compared to the comparator following TRE interventions ranging from four to six hours [MD -0.86; 95%CI: -1.54 to -0.17, P = 0.01; I^2 = 96%]. Subgroup analysis for TRE interventions ranging from ten to 12 h was not calculated since only one study reported this outcome.

Effects of TRE on biomarkers of glucose metabolism.

Glucose: A meta-analysis of eleven studies reported a significant overall effect of TRE on glucose levels reduction compared to the comparator group [MD -4.13; 95%CI: -6.98 to -1.28, P = 0.005; I^2 = 89%] (Figure 7). Random-effects

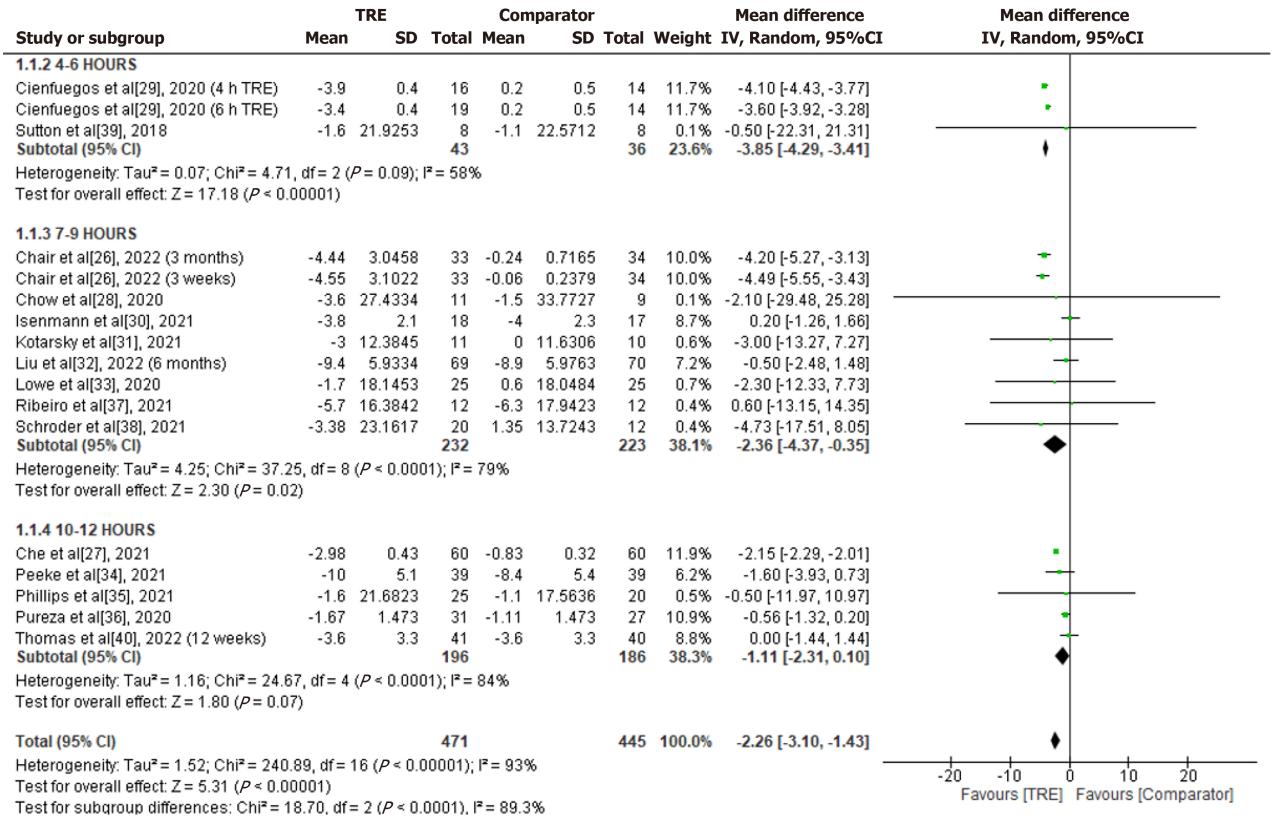

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Figure 3 Meta-analysis of the effects of time-restricted eating *vs* comparator on body weight, kg. TRE: Time-restricted eating.

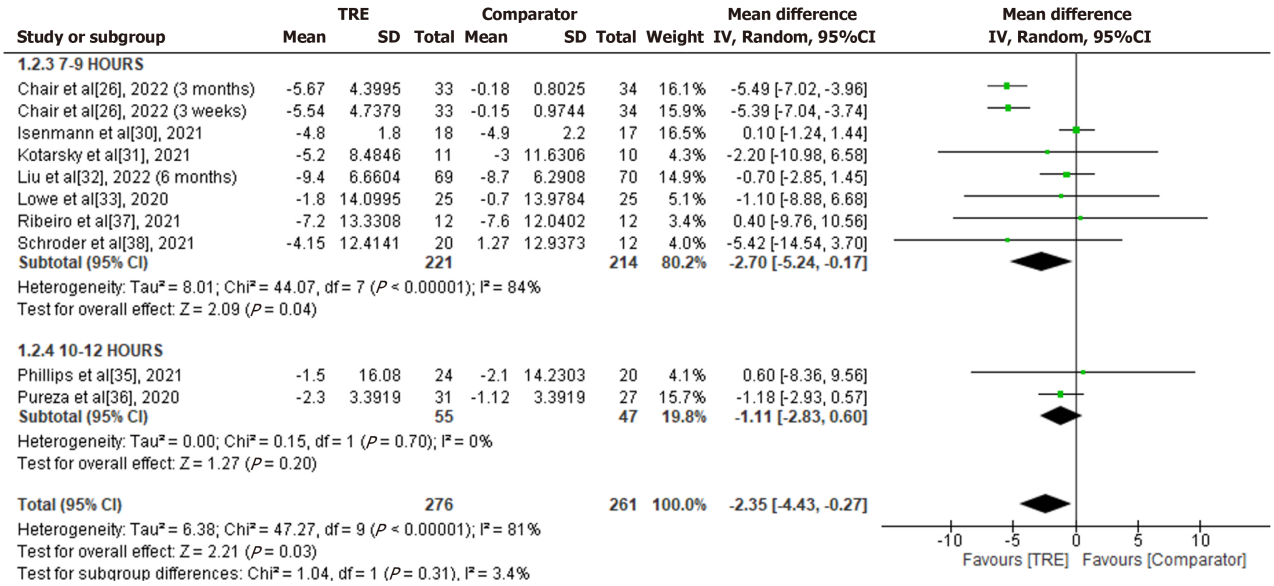

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Figure 4 Meta-analysis of the effects of time-restricted eating *vs* comparator on waist circumference. TRE: Time-restricted eating.

subgroup analyses were conducted based on the duration of TRE intervention showed no significant changes in glucose levels following TRE interventions ranging from ten to 12 h [MD -5.91; 95%CI: -13.29 to 1.48, P = 0.12; I^2 = 82%]. However, a significant reduction was reported in TRE interventions ranging from seven to nine hours [MD -2.20; 95%CI: -3.64 to -0.77, P = 0.003; I^2 = 0%] and TRE interventions ranging from four to six hours [MD -5.79; 95%CI: -8.18 to -3.41, P = 0.00001; I^2 = 54%].

HbA1c: A meta-analysis of six studies revealed the effect of TRE on HbA1c. There was no significant difference in HbA1c levels between the test and comparator groups [MD -0.12; 95%CI: -0.46 to 0.21, P = 0.47; I^2 = 99%] (Figure 8). Random-

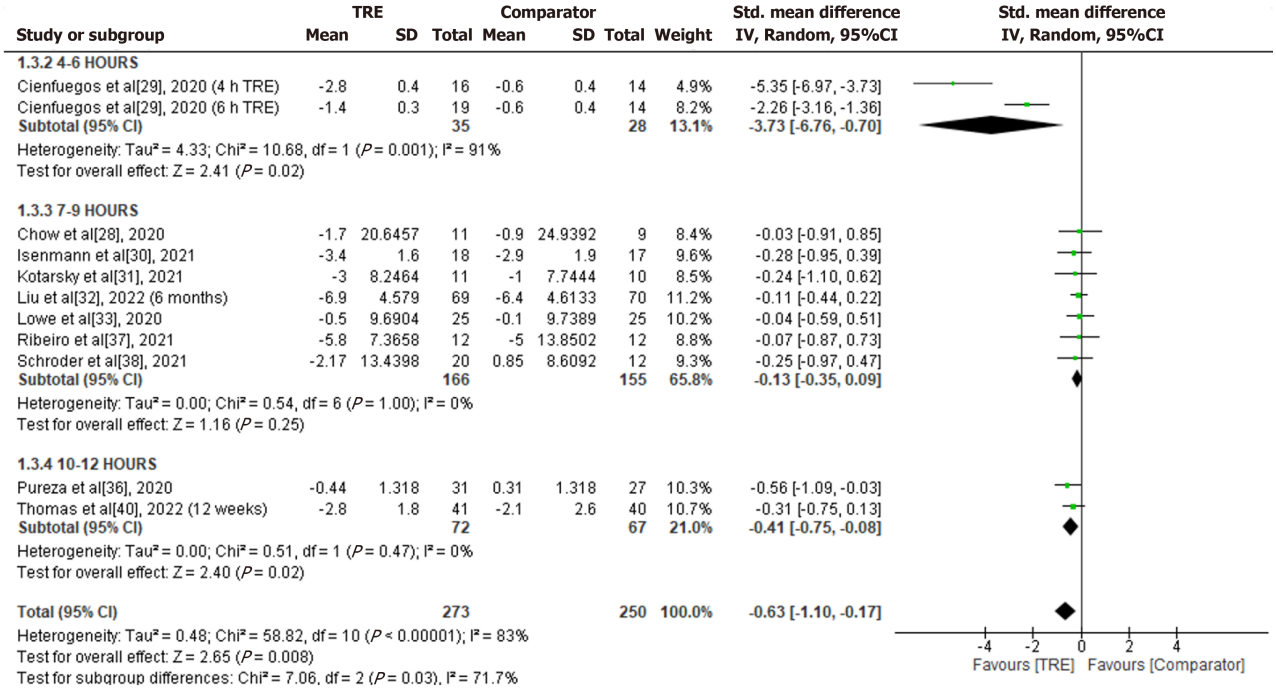

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Figure 5 Meta-analysis of the effects of time-restricted eating *vs* comparator on total fat mass. TRE: Time-restricted eating.

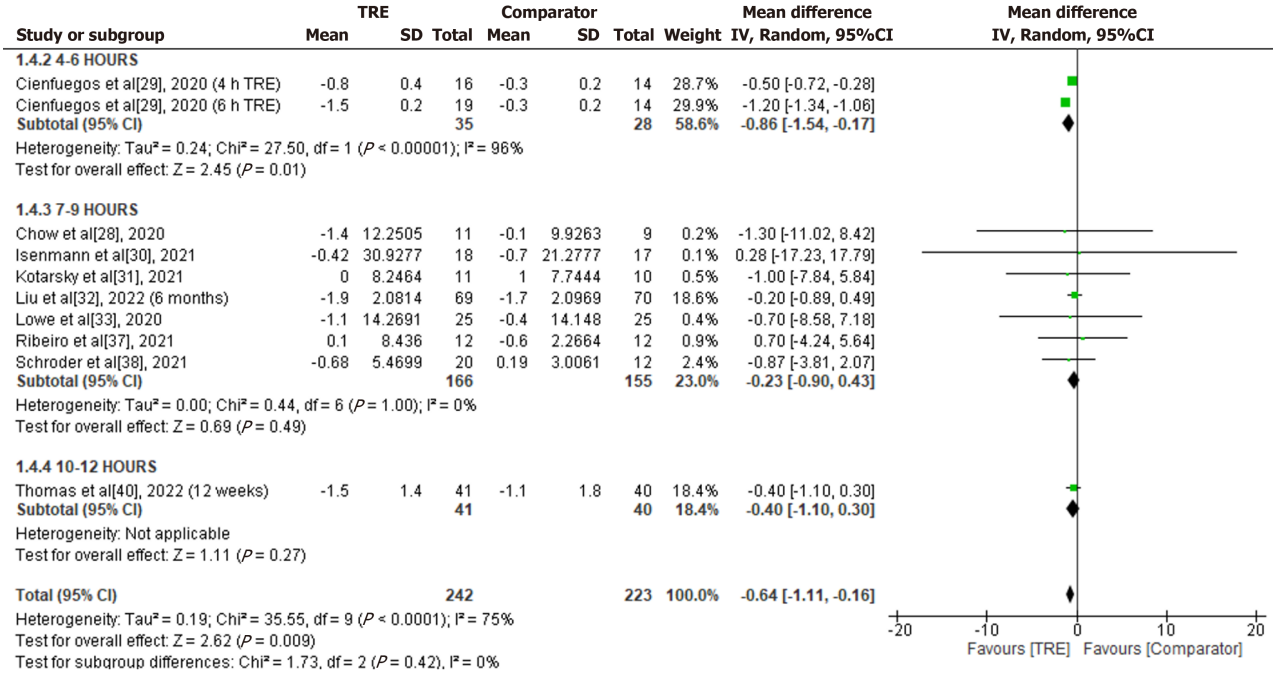

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Figure 6 Meta-analysis of the effects of time-restricted eating *vs* comparator on lean body mass.

effects subgroup analyses were conducted based on the duration of TRE intervention demonstrated no significant changes in HbA1c following TRE interventions ranging from ten to 12 h [MD -0.27; 95%CI: -0.96 to 0.42, P = 0.45; I^2 = 99%] and TRE interventions ranging from seven to nine hours [MD 0.09; 95%CI: -0.28 to 0.47, P = 0.63; I^2 = 0%]. However, a significant reduction was reported in TRE interventions ranging from four to six hours [MD -0.10; 95%CI: -0.15 to -0.05, P < 0.0001; I^2 = 0%].

HOMA-IR: A meta-analysis of seven studies reported the effect of TRE on HOMA-IR. There was no significant difference in HOMA-IR levels compared to the comparator group [MD -0.24; 95%CI: -0.52 to 0.05, P = 0.10; I^2 = 76%] (Figure 9). Random-effects subgroup analyses were conducted based on the duration of TRE intervention showed no significant

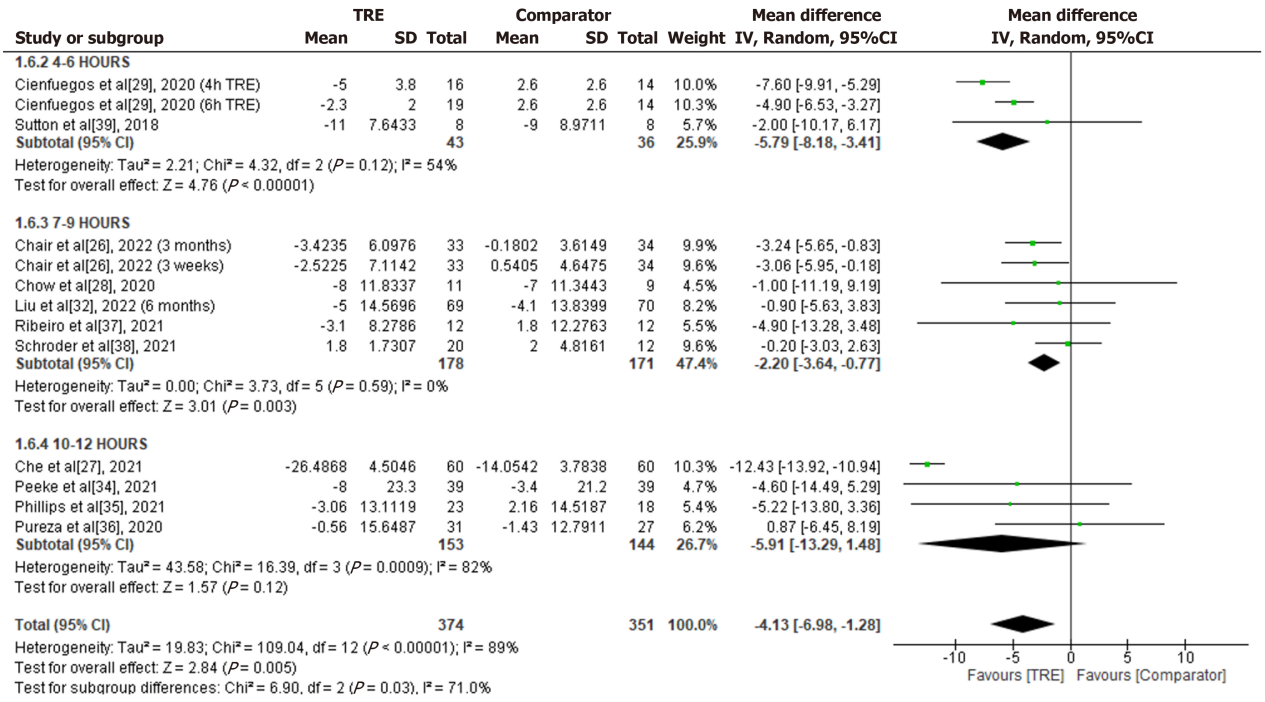

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Figure 7 Meta-analysis of the effects of time-restricted eating *vs* comparator on blood glucose. TRE: Time-restricted eating.

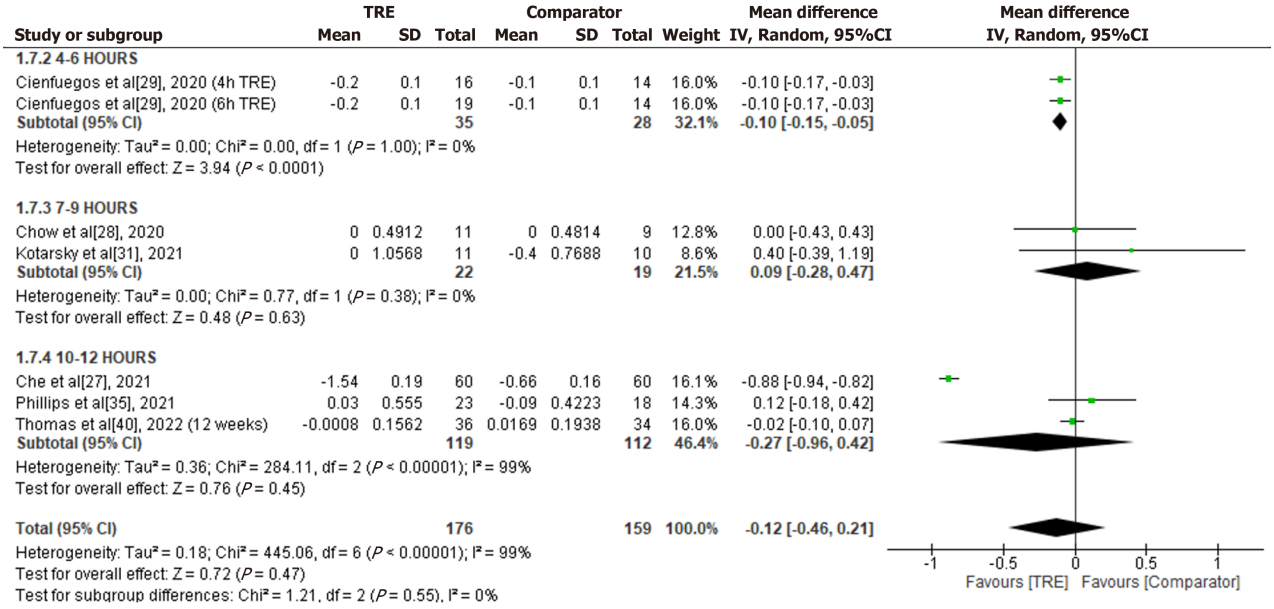

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Figure 8 Meta-analysis of the effects of time-restricted eating *vs* comparator on HbA1c. TRE: Time-restricted eating.

changes in HOMA-IR following TRE interventions ranging from ten to 12 h [MD -0.21; 95%CI: -0.58 to 0.16, P = 0.27; I^2 = 96%] and TRE interventions ranging from seven to nine hours [MD -0.32; 95%CI: -0.84 to 0.20, P = 0.23; I^2 = 0%]. Subgroup analysis for TRE interventions ranging from four to six hours was not calculated since it was reported in only one study.

Insulin: A meta-analysis of eight studies revealed a significant overall reduction of insulin levels with TRE compared to the comparator group (SMD -1.39; 95%CI: -2.54 to -0.25, P = 0.02; I^2 = 95%] (Figure 10). Random-effects subgroup analyses were conducted based on the duration of TRE intervention showed no significant changes in insulin in TRE interventions ranging from ten to 12 h (SMD -1.60; 95%CI: -4.85 to 1.65, P = 0.34; I^2 = 99%] and TRE interventions ranging from seven to nine hours (SMD -0.35; 95%CI: -1.17 to 0.47, P = 0.41; I^2 = 74%]. A significant reduction in insulin level was observed in TRE interventions ranging from four to six hours (SMD -2.75; 95%CI: -5.49 to -0.01, P = 0.05; I^2 = 94%].

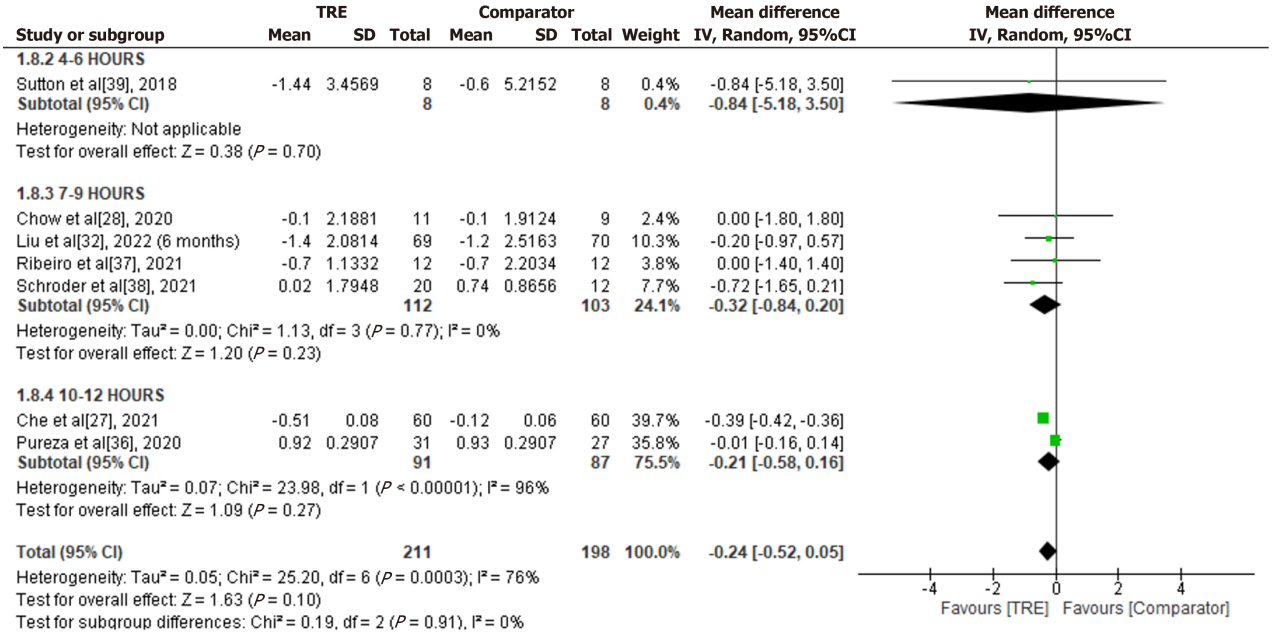

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Figure 9 Meta-analysis of the effects of time-restricted eating *vs* comparator on HOMA-IR. TRE: Time-restricted eating.

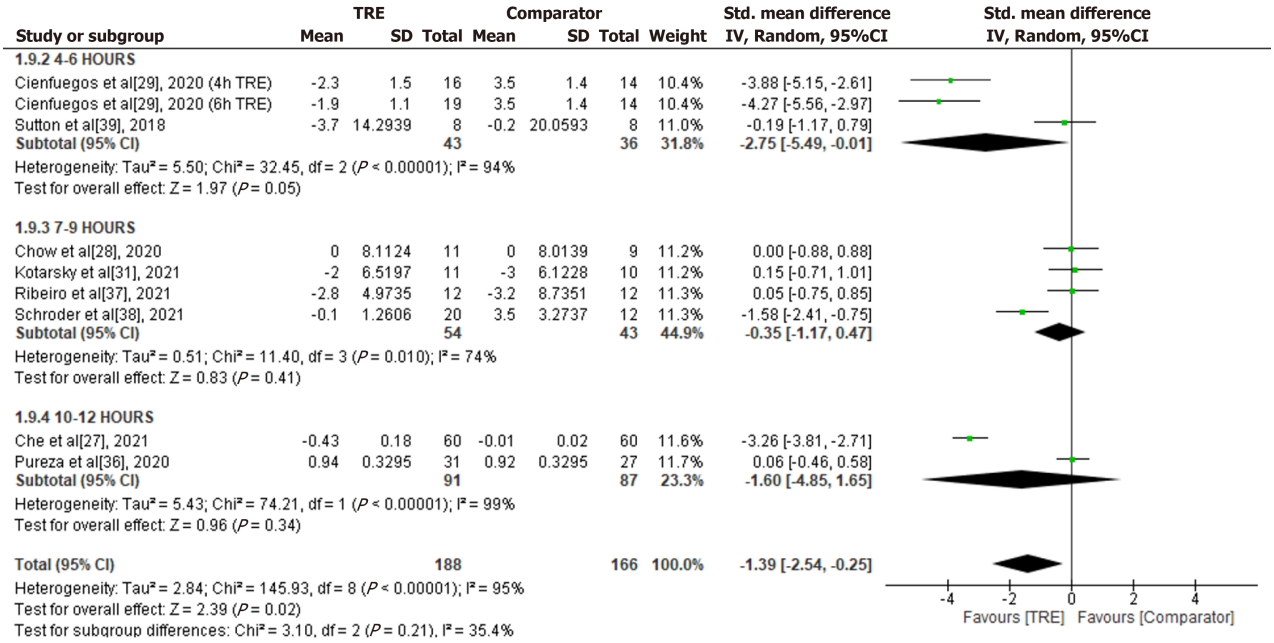

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Figure 10 Meta-analysis of the effects of time-restricted eating *vs* comparator on insulin level. TRE: Time-restricted eating.

Effects of TRE on biomarkers of lipid metabolism

Total cholesterol: A meta-analysis of eight studies evaluated the effect of TRE on TC. There was no significant difference in TC levels between the test and comparator groups [MD 4.08; 95%CI: -4.73 to 12.89, P = 0.36; I^2 = 75%] (Figure 11). Random-effects subgroup analyses were conducted based on the duration of TRE intervention showed a significant reduction in TC following TRE interventions ranging from ten to 12 h [MD -5.63; 95%CI: -9.86 to -1.39, P = 0.009; I^2 = 31%]. Meanwhile, a significant increase in TC was observed in the TRE groups following TRE interventions ranging from seven to nine hours [MD 9.38; 95%CI: 0.59 to 18.18, P = 0.04; I^2 = 22%]. Subgroup analysis for TRE interventions ranging from four to six hours was not calculated since it was reported only in one study.

Triglycerides: A meta-analysis of ten studies evaluated the effect of TRE on triglycerides (Figure 12). Individuals assigned to TRE intervention exhibited significantly reduced triglyceride levels compared to the comparator group [MD -15.79; 95%CI: -28.93 to -2.66, P = 0.02; I^2 = 97%]. Random-effects subgroup analyses were conducted based on the duration

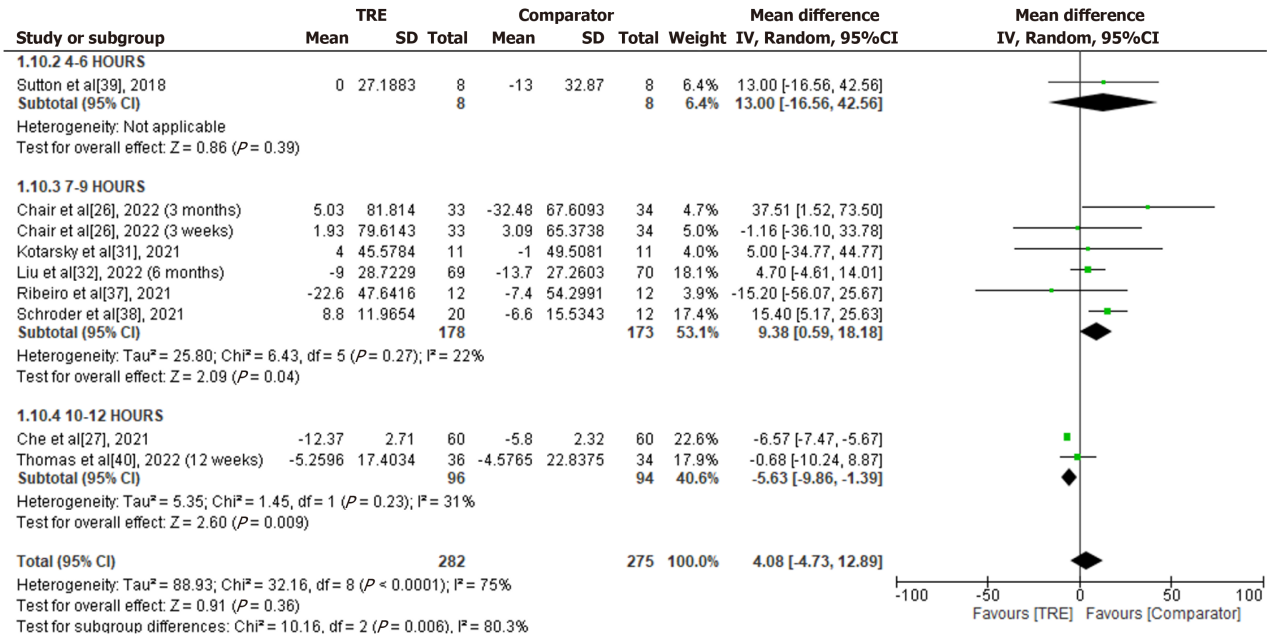

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Figure 11 Meta-analysis of the effects of time-restricted eating *vs* comparator on total cholesterol. TRE: Time-restricted eating.

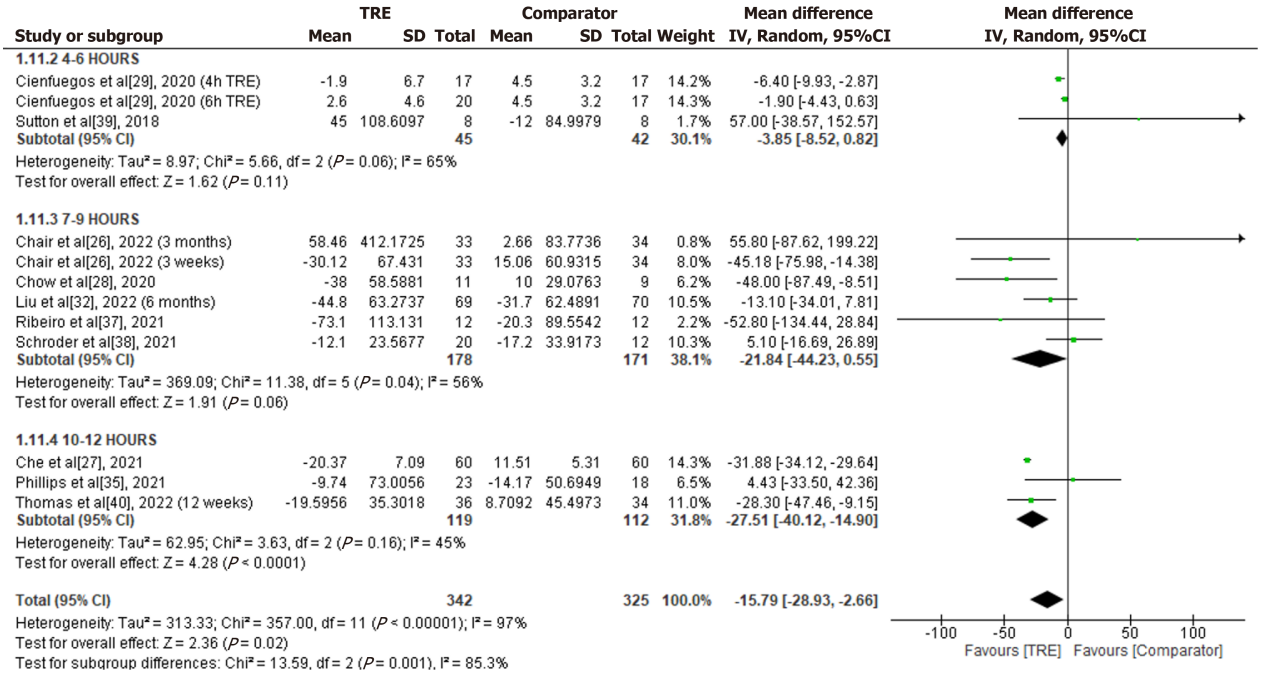

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Figure 12 Meta-analysis of the effects of time-restricted eating *vs* comparator on triglycerides. TRE: Time-restricted eating.

of TRE intervention revealed a significant reduction in triglycerides following TRE interventions ranging from ten to 12 h [MD -27.51; 95%CI: -40.12 to -14.90, $P < 0.0001$; $I^2 = 45\%$]. However, there were no significant changes in triglyceride levels observed following TRE interventions ranging from seven to nine hours [MD -21.84; 95%CI: -44.23 to 0.55, $P = 0.06$; $I^2 = 56\%$] and TRE interventions ranging from four to six hours [MD -3.85; 95%CI: -8.52 to 0.82), $P = 0.11$; $I^2 = 65\%$].

LDL-C: A meta-analysis of nine studies showed no significant overall effect of TRE on LDL-C levels compared to the comparator group [MD 1.26; 95%CI: -3.94 to 6.46, $P = 0.63$; $I^2 = 86\%$] (Figure 13). Random-effects subgroup analyses were conducted based on the duration of TRE intervention, which showed no significant changes in LDL-C following TRE interventions ranging from ten to 12 h [MD -1.56; 95%CI: -15.99 to 12.88, $P = 0.83$; $I^2 = 88\%$] and TRE interventions ranging from four to six hours [MD 0.94; 95%CI: -5.64 to 7.52, $P = 0.78$; $I^2 = 82\%$]. In contrast, a significant increase of LDL-C was observed in TRE interventions ranging from seven to nine hours [MD 5.98; 95%CI: 1.02 to 10.94, $P = 0.02$; $I^2 = 82\%$].

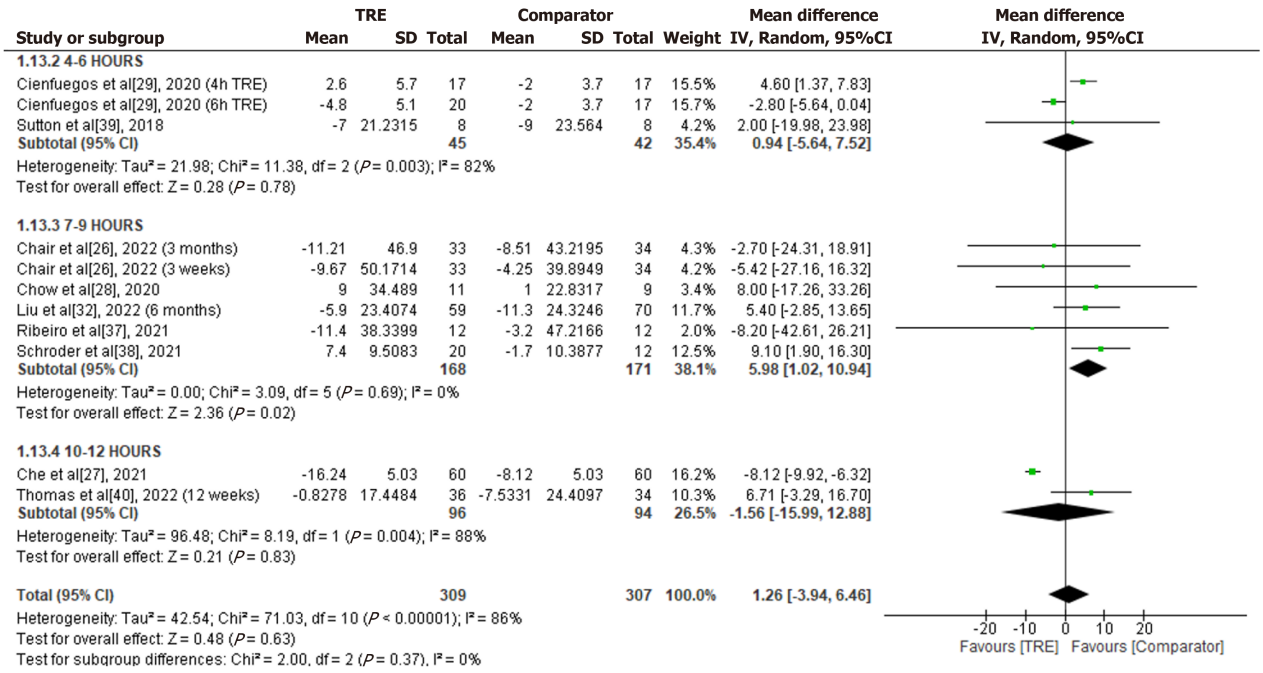

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Figure 13 Meta-analysis of the effects of time-restricted eating *vs* comparator on low-density lipoprotein cholesterol. TRE: Time-restricted eating.

HDL-C: A meta-analysis of ten studies showed no significant overall effect of TRE on HDL-C levels compared to the comparator group [MD -0.17; 95%CI: -1.19 to 0.85, P = 0.74; I^2 = 58%] (Figure 14). Random-effects subgroup analyses were conducted based on the duration of TRE intervention demonstrated no significant changes in HDL-C following TRE interventions ranging from ten to 12 h [MD -0.38; 95%CI: -1.00 to 0.24, P = 0.23; I^2 = 0%], TRE interventions ranging from seven to nine hours [MD 1.62; 95%CI: -2.48 to 5.71, P = 0.44; I^2 = 53%], and TRE interventions ranging from four to six hours [MD -0.88; 95%CI: -2.28 to 0.52, P = 0.22; I^2 = 75%].

Effects of TRE on biomarkers of inflammation

C-reactive protein: A meta-analysis of three studies evaluated the effect of TRE on C-reactive protein (Figure 15). There was no significant difference in C-reactive protein levels between the test and comparator groups [MD -0.35; 95%CI: -1.79 to 1.08, P = 0.63; I^2 = 0%]. No subgroup analysis was conducted due to the limited included studies reporting this outcome.

Effects of TRE on blood pressure and heart rate

Systolic blood pressure: A meta-analysis of eight studies evaluated the effect of TRE on systolic blood pressure (Figure 16). There was no significant difference in systolic blood pressure levels between groups [MD -0.87; 95%CI: -1.90 to 0.16, P = 0.10; I2 = 0%]. Random-effects subgroup analyses were conducted based on the duration of TRE intervention showed no changes in systolic blood pressure following TRE interventions ranging from ten to 12 h [MD 2.08; 95%CI: -1.83 to 5.99, P = 0.30; I^2 = 0%], TRE interventions ranging from seven to nine hours [MD -1.28; 95%CI: -3.74 to 1.18, P = 0.31; I^2 = 0%], and TRE interventions ranging from four to six hours [MD -1.04; 95%CI: -2.23 to 0.14, P = 0.08; I^2 = 0%].

Diastolic blood pressure: A meta-analysis of eight studies evaluated the effect of TRE on diastolic blood pressure (Figure 17). There was no significant difference in diastolic blood pressure levels between the test and comparator groups [MD -1.36; 95%CI: -3.83 to 1.11, P = 0.28; I^2 = 83%]. Random-effects subgroup analyses based on the duration of TRE intervention showed no significant changes in diastolic blood pressure following TRE interventions ranging from ten to 12 h [MD 2.87; 95%CI: -0.79 to 6.52, P = 0.12; I^2 = 0%] and TRE interventions ranging from seven to nine hours [MD 0.25; 95%CI: -1.56 to 2.06, P = 0.79; I^2 = 0%]. In contrast, there was a significant reduction observed in TRE interventions ranging from four to six hours [MD -5.41; 95%CI: -6.25 to -4.57, P = < 0.00001; I^2 = 0%].

Heart rate: A meta-analysis of five studies reported no significant overall effect of TRE on heart rate levels in comparison to the comparator group [MD 0.15; 95%CI: -1.86 to 2.15, P = 0.89; I^2 = 67%] (Figure 18). Random-effects subgroup analyses based on the duration of TRE intervention showed no significant changes in heart rate following TRE interventions ranging from seven to nine hours [MD -1.00; 95%CI: -3.85 to 1.84, P = 0.49; I^2 = 0%] and TRE interventions ranging from four to six hours [MD 1.04; 95%CI: -2.06 to 4.14, P = 0.51; I^2 = 85%]. Subgroup analysis for TRE interventions ranging from ten to 12 h was not calculated since only one study reported the outcome for this particular duration.

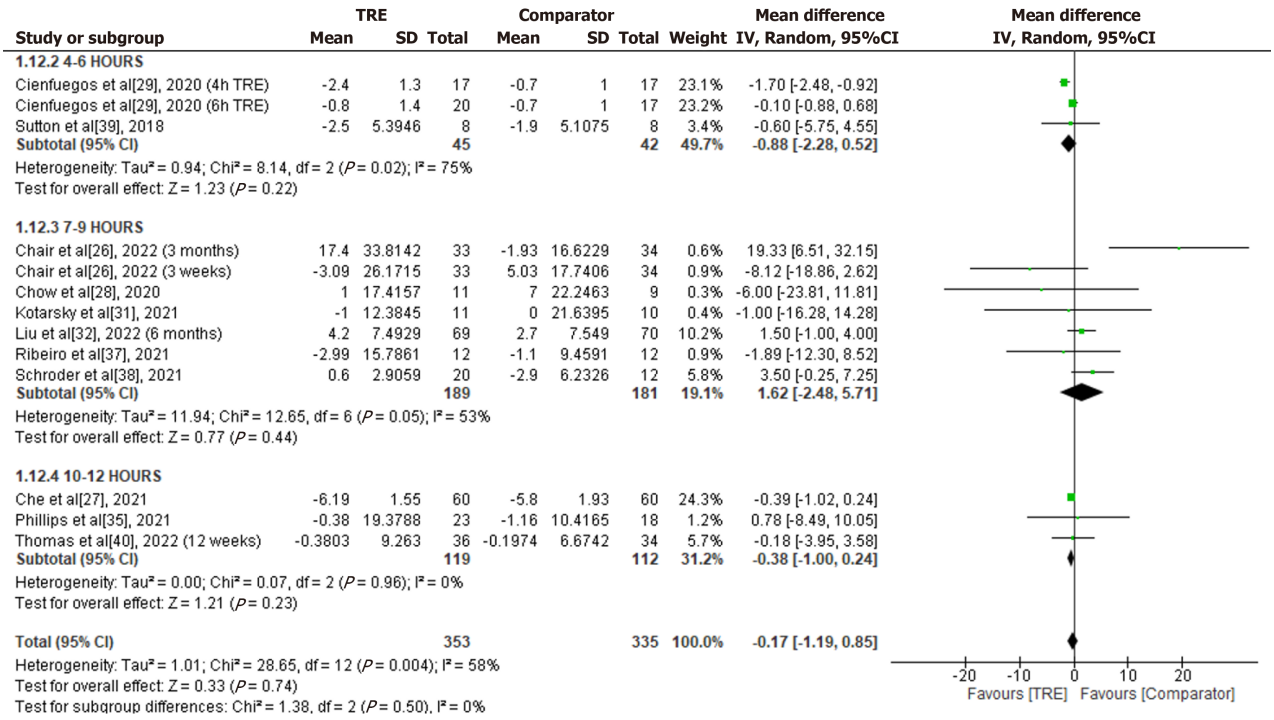

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Figure 14 Meta-analysis of the effects of time-restricted eating *vs* comparator on high-density lipoprotein cholesterol. TRE: Time-restricted eating.

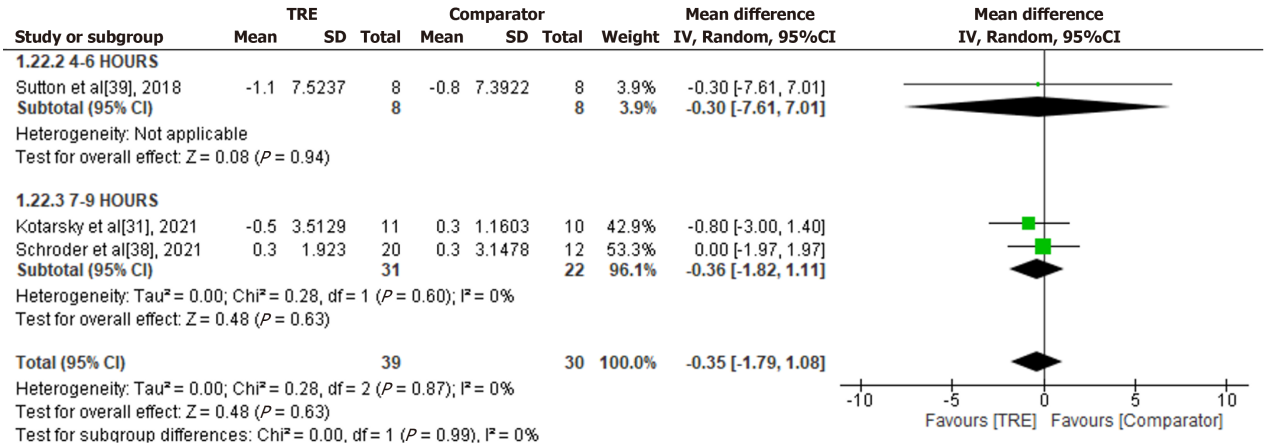

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Figure 15 Meta-analysis of the effects of time-restricted eating *vs* comparator on C-reactive protein. TRE: Time-restricted eating.

Funnel plots

The potential publication biases were assessed using funnel plots based on the outcomes of interest (Supplementary Figure 1). The funnel plots were generally symmetric, indicating a low probability of publication bias in most outcomes. However, the glucose outcome showed an asymmetric funnel plot, suggesting a possible publication bias.

DISCUSSION

Adopting IF, including time-restricted eating interventions, to potentially optimize metabolic health by altering the duration of food consumption is a topic of increasing interest in research and others[41]. The present review analyzed the effects of TRE intervention on anthropometrics and cardiometabolic health markers in adults with excessive weight and obesity-related metabolic diseases. The meta-analysis showed that TRE significantly reduced body weight, waist circumference, fat mass, lean body mass, blood glucose, insulin, and triglyceride. However, no changes were observed in HbA1c, HOMA-IR, TC, LDL-C, HDL-C, heart rate, systolic and diastolic blood pressure. Interestingly, subgroup analyses

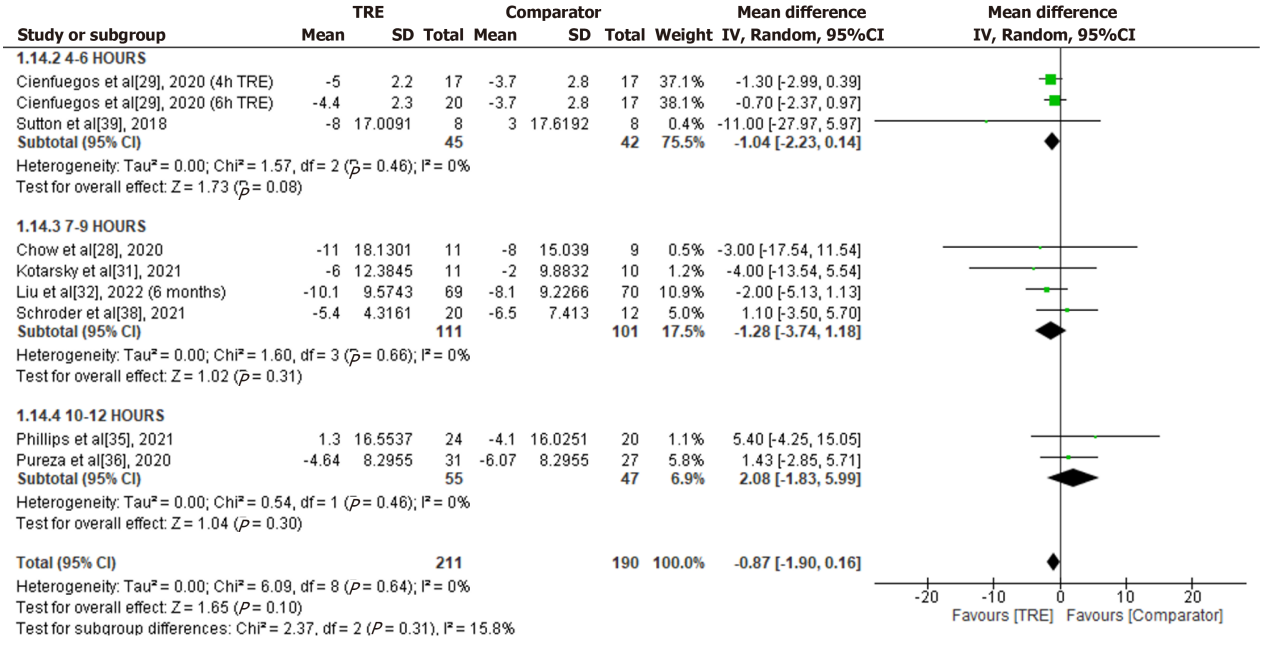

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Figure 16 Meta-analysis of the effects of time-restricted eating *vs* comparator on systolic blood pressure. TRE: Time-restricted eating.

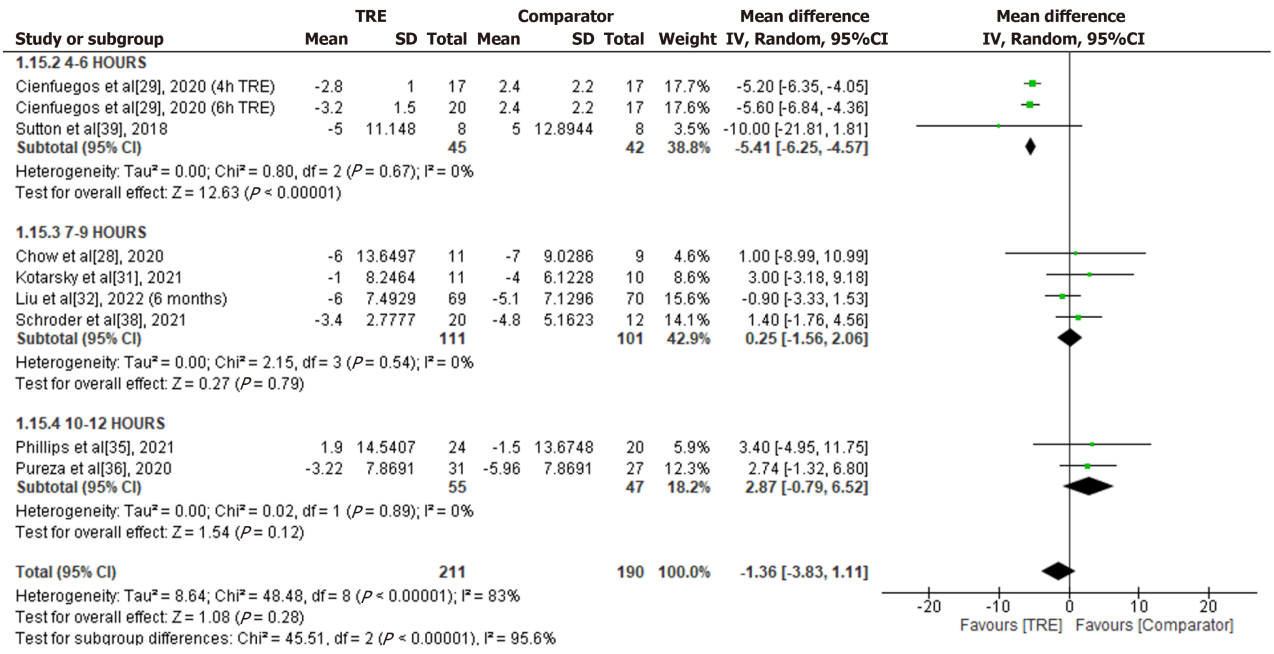

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Figure 17 Meta-analysis of the effects of time-restricted eating *vs* comparator on diastolic blood pressure. TRE: Time-restricted eating.

based on the duration of the eating window revealed that TRE interventions with shorter eating windows (4-6 h) resulted in a more pronounced effect size than longer eating windows as measured for all outcomes. The meta-analysis results suggest that TRE is an effective treatment strategy for adults with excessive weight and obesity-related metabolic diseases as it improves specific metabolic parameters and potentially decreases the risk of atherosclerotic cardiovascular disease.

Limiting food intake to a shorter duration, without explicitly attempting to reduce energy intake, induces fasting physiology. This adaptive mechanism in the human body has evolved to cope with periods of food scarcity and prolonged fasting and is critical for survival[42]. A fasting regime, including TRE, activates metabolic switching from energy production through liver-derived glucose to adipose cell–derived ketones[43,44]. At the molecular level, TRE triggers circadian coordination with nutrient-sensing pathways to regulate metabolic health and protects against metabolic disorders induced by poor dietary intake[45]. Findings from this review are consistent with previous meta-analyses where TRE was shown effective in weight reduction despite mixed findings on body composition[16,18,21,22]. Compared to CER, weight loss achieved through IF is comparable to[46], if not superior to CER[47]. TRE may spontan-

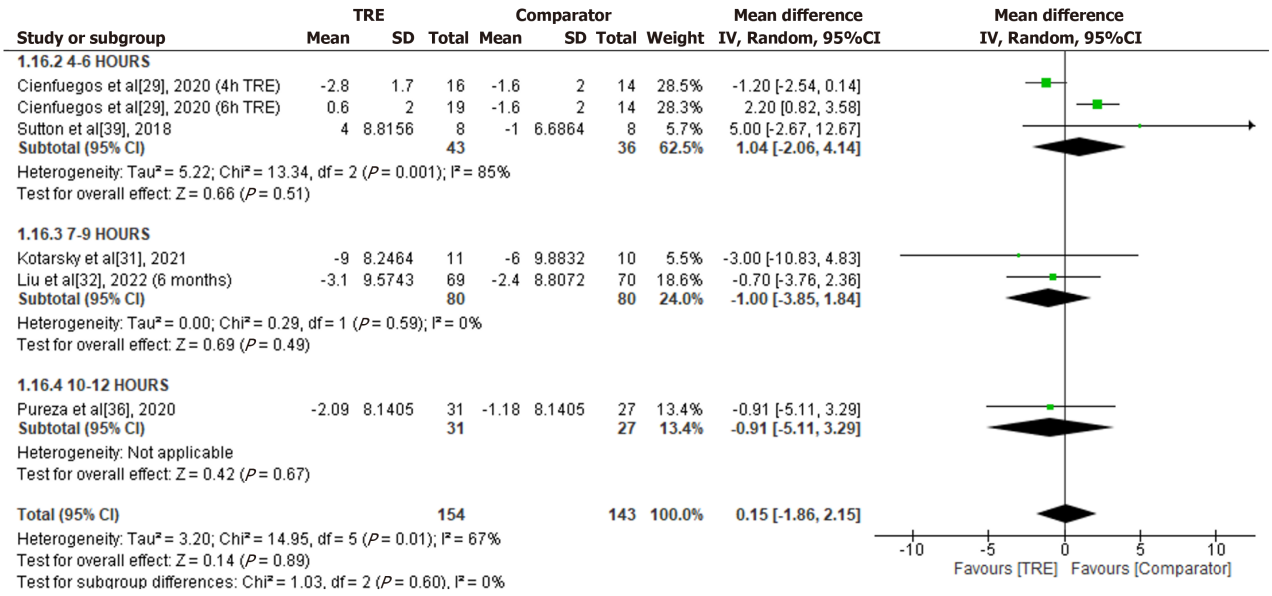

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Figure 18 Meta-analysis of the effects of time-restricted eating *vs* comparator on heart rate. TRE: Time-restricted eating.

eously decrease energy intake by 20%-30% under ad libitum conditions, resulting in weight loss of 1%-4%[48]. During periods of fasting and CER, macro- and micronutrients are less accessible to cells and tissues. Hence, several pathways play comparable roles in mediating CER and IF effects. Decreased glucose levels or decreased protein and amino acid availability, as generated by caloric restriction or fasting, activate AMP-activated protein kinase (AMPK) and inhibit mTOR, resulting in reduced protein synthesis and ribosome biogenesis, as well as the activation of autophagy[49].

Nutrient timing has been proposed as a potential approach to restoring metabolic health by synchronizing dietary intake with the circadian clock[50]. TRE interventions consistently improved glucose metabolism by reducing glucose levels in human studies, as confirmed in the current meta-analysis[16,18,19,21,22]. The glucoregulatory mechanisms of TRE demonstrate that eating within a limited eating window during the day restores cAMP Response Element-Binding Protein phosphorylation, decreases gluconeogenesis, and increases glucogenesis during the fed state *via* enhanced autophagic flux, mild production in ketone bodies, reduced oxidative stress, and promotion of β-cell responsiveness[51]. However, the effects of TRE on lipid profiles, blood pressure, and heart rate have been inconsistent[16,18,19,21,22]. Nonetheless, the meta-analyses revealed that TRE did not worsen any outcomes studied. While it is widely accepted that TRE improves circadian rhythms, it remains unknown whether the metabolic improvements are the result of calorie limitation or time restriction[52].

The duration of the eating window in TRE interventions on humans varies, which has led to heterogeneous results between studies. This systematic review suggests that TRE's beneficial effects may be time-dependent, with a shorter eating window resulting in better weight management and cardiometabolic health than a longer eating duration. The mechanisms by which this occurs have yet to be fully understood. An animal study revealed that a 4-h time-restricted feeding could reprogram the circadian clock by restoring the expression phase of clock genes, despite the high-fat diet [11]. At the cellular level, prolonged fasting leads to increased AMP levels, gene expression, and activation of AMPK, a critical intracellular energy sensor that regulates processes associated with energy metabolism[11,53]. This results in reduced fatty acid synthesis and enhanced fatty acid oxidation in the liver[54]. Similar to AMPK, Sirtuin 1 (SIRT1) activity increases in response to prolonged fasting[55]. SIRT1 regulates numerous biological processes, such as insulin response, glycolysis, apoptosis, antioxidative defense, DNA repair, inflammatory response, metabolism, cancer, and stress, improving cardiometabolic health and CVD prevention[56-58].

Jamshed *et al*[59] conducted a 4-d randomized crossover study to elucidate the possible mechanisms of actions of TRE with short eating duration in humans. This study revealed that TRE with a short eating window improved multiple health aspects *via* circadian and fasting-related mechanisms[59]. The authors postulated that eating earlier in the day and having shorter inter-meal intervals could help minimize glycemic excursions, suggesting that TRE interventions with longer inter-meal intervals may be less effective in lowering glucose levels. Additionally, the study found that TRE may alter diurnal patterns in fasting cholesterol, ketones, cortisol, and circadian clock genes, particularly by increasing ketone levels in the morning and improving the amplitude of the cortisol rhythm. The study also demonstrated that six hours of TRE may produce a favorable effect on hormones and genes related to lifespan and autophagy, such as brain-derived neurotrophic factor, SIRT1, and LC3A, the autophagosome protein.

The findings of this meta-analysis provide evidence to support the hypothesis that longer fasting duration is associated with better weight control[60,61]. Contrary to animal studies, restricting eating duration does not affect 24-h energy expenditure in humans[62,63]. Animal studies have suggested that time-restricted feeding may increase energy expenditure by enhancing oxidative metabolism and expression of the mitochondrial uncoupling protein, which is responsible for non-shivering thermogenesis in brown and white adipose tissue[13,64,65]. Nevertheless, a human study detected an increased thermic effect of food during the early postprandial period[63]. The study demonstrated that short

TRE interventions primarily promote weight loss by decreasing appetite, as evidenced by reduced ghrelin levels and normalized hunger, which tend to promote fullness and reduced appetite. Furthermore, TRE with a short eating window leads to alterations in substrate oxidation, with an increase in 24-h protein oxidation and a decrease in 24-h non-protein Respiratory Quotient (npRQ), indicative of increased fat oxidation. This metabolic alteration is likely attributed to the prolonged daily fasting phase rather than circadian effects[43]. Furthermore, the short TRE group showed higher metabolic flexibility, defined as the difference between the maximum and minimum values of the npRQ, indicating a better ability to switch between different oxidizing substrates than the ad libitum group.

It is important to note that the associations between fasting duration and weight and cardiometabolic health may vary depending on the time of fasting and eating[15]. The early fasting window, characterized by breakfast consumption and early evening meals, may have different metabolic consequences than the late fasting window, characterized by breakfast omission and night-time snacking[60]. Since humans are diurnal organisms, eating closer to daylight is consistent with the 24-h circadian rhythms of metabolism, leading to better metabolic health. The alignment of meals with typical circadian oscillations of hormonal profiles is necessary for TRE to be considered a nutritional strategy utilizing chrononutrition concepts. For example, plasma glucose concentration exhibits diurnal fluctuation, with peak values occurring at the start of the activity phase[66]. Since food intake promotes insulin production, plasma insulin levels reflect the daily rhythm of food intake. Thus, night eating results in a misalignment of central and peripheral endogenous glucose circadian rhythms and impaired glucose tolerance, while restricting meals to the daytime prevents such dysregulation [67]. Accordingly, the current pool of evidence suggests that later or self-selected TRE periods are less effective in improving metabolic health markers[68].

Although the findings of this meta-analysis suggest that short TRE may improve cardiometabolic outcomes, it is crucial to consider the sustainability of a restrictive eating pattern. The primary concern with a short eating window is that it may be too limiting for many individuals, making it challenging to adhere to over the long term. Adherence is a crucial factor in the success of any dietary intervention, as a lack of adherence can lead to the failure of the intervention. Additionally, limiting eating periods may lead to disordered eating patterns or restrictive dieting behaviors. A recent study found that individuals who engaged in TRE were at a higher risk for disordered eating behaviors, such as overeating, losing control, binge eating, vomiting, laxative use, and compulsive exercise[69]. The application of short TRE may not be suitable for all individuals, particularly those with certain medical conditions or who are pregnant or breastfeeding. Alteration in the metabolism and nutrient needs of these individuals may necessitate a more frequent or longer eating duration than the general population.

We have identified several strengths in our meta-analysis. We utilized multiple databases to search existing literature and identify eligible studies related to TRE conducted on individuals with excessive weight or weight-related metabolic diseases while excluding individuals with a normal BMI. This approach ensured the homogeneity of the population of interest, as this group of individuals may have a higher tendency to experience metabolic disturbances than individuals with a normal BMI. Additionally, we performed subgroup analyses based on arbitrary clustering of the eating window duration of TRE intervention to explore methodological heterogeneity. Furthermore, we only included studies involving clinical trials that lasted two weeks up to six months to reduce heterogeneity from short-term interventions (*i.e.*, less than seven days) and studies reporting long-term effects of TRE. However, this meta-analysis has some limitations. Most included studies had small sample sizes, with several posing a high RoB in some domains. Blinding participants was impossible due to the nature of behavioral interventions. Nonetheless, this factor is unlikely to affect the results as outcomes were objectively measured, with some studies executed blinding of assessors. Additionally, there was high heterogeneity in some of the outcomes, which could be due to differences in population, fasting/eating duration, duration of the intervention, meal timing, meal frequency, co-interventions, and level of adherence. Data on such factors, including dietary intake, physical activity, and adherence level, were unavailable in some reports, which might have resulted in biased conclusions. Future large-randomized-controlled trials with rigorous methodology are necessary to elucidate the role of different TRE duration on cardiometabolic health and determine the optimal TRE duration to translate into clinical practice.

CONCLUSION

In conclusion, findings from this meta-analysis demonstrate that TRE is an effective and sustainable dietary strategy for reducing body weight, body composition, blood glucose, insulin, and triglyceride in individuals with excessive weight or weight-related metabolic disorders. Moreover, this study demonstrated that the favorable benefits of TRE on health are dependent on eating duration, with shorter durations resulting in more significant changes in anthropometric and cardiometabolic health markers. However, due to the challenges of adhering to a strict regimen, the TRE interventions with short eating windows may only suit specific individuals and must be monitored vigilantly. Therefore, extensive studies with larger sample sizes and higher quality are required to confirm the findings of this meta-analysis and determine the optimal duration of the eating window for primary and secondary CVD prevention.

ARTICLE HIGHLIGHTS

Research background

There is growing interest in time-based dietary intervention as an alternative to caloric restriction or nutrient-based

dietary intervention for cardiovascular disease prevention.

Research motivation

Time-restricted eating (TRE) is considered a mild form of intermittent fasting and has shown conflicting cardiometabolic health outcomes in humans.

Research objectives

Our study aimed to explore the overall effectiveness of TRE and its optimal duration as a potential dietary approach for weight loss and improved cardiometabolic health in individuals with excessive weight and obesity-related metabolic diseases.

Research methods

Systematic searches were conducted *via* multiple databases (MEDLINE Complete, Web of Science, Scopus, the Cochrane Library, Academic Search Complete, Food Science Source, OpenDissertations, Education Research Complete, and Psychology and Behavioural Sciences Collection) to identify the relevant articles. The methodological quality of the included studies was assessed using the Cochrane risk-of-bias tool for randomized trials (RoB-2). Meta-analyses were conducted depending on feasibility. Analysis was performed using RevMan software.

Research results

TRE significantly decreased body weight, waist circumference, adipose mass, lean body mass, blood glucose, insulin, and triglyceride. HbA1c, homeostasis model assessment for insulin resistance, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, heart rate, systolic and diastolic blood pressure showed no significant changes with the treatment. In addition, subgroup analyses based on the eating duration revealed significant variation in the effects of the TRE intervention on the measured outcomes.

Research conclusions

TRE is an effective and sustainable dietary strategy to improve the anthropometric and cardiometabolic health of individuals with excessive weight or weight-related metabolic disorders.

Research perspectives

A larger sample size and higher quality studies are necessary to corroborate the findings of this meta-analysis and define the optimal duration of the eating window for cardiovascular disease prevention.

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FOOTNOTES

Author contributions: Zaman MK, Teng NIMF, Juliana N, and Kasim SS contributed to the conceptualization of the study, systematic search, and studies selection; Zaman MK and Teng NIMF performed data extraction and risk of bias assessments; data analysis, synthesis, and interpretation were conducted by Zaman MK, and Alshawsh MA; Zaman MK drafted the manuscript; All authors contributed to the manuscript revision and approved the final manuscript.

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