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Lifestyle factors as determinants of atherosclerotic cardiovascular health

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ABSTRACT

A sedentary lifestyle, low levels of physical activity and fitness, poor dietary patterns, and psychosocial stress are strongly associated with increased morbidity and mortality from atherosclerotic cardiovascular disease (ASCVD). Conversely, engaging in regular physical activity, maintaining optimal fitness levels, adhering to a heart-healthy dietary pattern, effectively managing body weight, ensuring adequate sleep, implementing stress-reduction strategies, and addressing psychosocial risk factors are associated with a reduced risk of ASCVD.

This comprehensive review synthesizes current evidence from large observational studies and randomized controlled trials on lifestyle factors as determinants of ASCVD health. It also briefly reviews mechanistic insights into how factors such as low shear stress, increased reactive oxygen species production, chronic inflammation, platelets and coagulation activation, endothelial dysfunction, and sympathetic hyperactivity contribute to the initiation and exacerbation of ASCVD risk factors. These include obesity, hyperglycemia, type 2 diabetes, hypertension, and dyslipidemia, subsequently leading to the development and progression of atherosclerosis, ultimately resulting in chronic ASCVD or acute cardiovascular events. To bridge the translational gap between epidemiologic and trial-based evidence and clinical practice, practical recommendations are summarized to facilitate the translation of scientific knowledge into actionable interventions to promote ASCVD health. Acknowledged is the gap between the evidence-based knowledge and adoption within healthcare systems, which remains a crucial objective in advancing cardiovascular health at the population level.

1. Introduction

Understanding the complex relationship between lifestyle factors that promote atherosclerotic cardiovascular disease (ASCVD) health is critical to the development of effective prevention and treatment strategies, given the significant impact of these factors on global population health. As research continues to unravel the complex interplay between physical activity, diet, and psychosocial stress, it is becoming clear that each of these elements exerts a unique and significant influence on cardiovascular (CV) health, with their combined effects shaping the trajectory of ASCVD risk in healthy individuals and patients at risk. This review summarizes the evidence from several important studies, including large observational studies and randomized controlled trials (RCT), systematic reviews and meta-analyses, presents the underlying physiological mechanisms, and finally summarizes up-to-date practical recommendations for lifestyle approaches to reduce and manage ASCVD risk.

While this review comprehensively addresses physical activity, diet, and psychological stress in relation to ASCVD risk, it is important to note that other lifestyle behaviors such as sleep patterns, night shift work, illicit drug use, and tobacco exposure also significantly impact risk and progression.

2. Physical activity, cardiorespiratory fitness and ASCVD health

2.1. Evidence from large trials, systematic reviews and meta-analyses

Physical activity is defined as any bodily movement that is performed by skeletal muscles and requires energy expenditure. Thus, both the absence of physical activity (sedentarism, physical inactivity) and

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exercise training, which is defined as planned, structured and repetitive exercise with the purpose of improving or maintaining physical fitness, are included in the spectrum of physical activity [1]. However, physical fitness is not only determined by level of physical activity and training, but about 50 % is genetically determined [2]. The intensity of physical activity is typically expressed in MET (metabolic equivalent of task). 1 MET is equivalent to the resting metabolic rate, and a multiple of this to the corresponding intensity of the activity. For example, walking is in a range between 4 and 6 METs and medium intensity running is in a range between 8 and 10 METs [3].

Physical activity is inversely related to the risk of ASCVD in the sense that the risk decreases with increasing volume and intensity of physical activity. In most studies, a steep risk reduction is observed, particularly from the state of physical inactivity up to approximately 5000 MET x minutes per week, corresponding to around 13–14 h of walking per week. This is associated with a risk reduction of approximately 30 %. Beyond this, a plateau is reached and a significant risk reduction of no more than 40–50 % is expected [4–6]. Recent results from the National Health Interview Survey (NHIS) study reported that, for an equivalent amount of physical activity, engaging in regular aerobic activity compared with inactivity resulted in a higher cardiovascular mortality risk reduction in females (36 %) than males (14 %) [7]. These findings are generally consistent with prior findings in terms of sex specific effects of physical activity and CVD risk reduction [8].

This physical activity data, which is usually collected using questionnaires, most commonly the International Physical Activity Questionnaire (IPAQ), is only partially consistent with objectively measured activity data [9]. Accelerometers provide an objective measure of physical activity, but have the disadvantage of not capturing all activities (e.g. cycling or swimming) [9,10], which may play an important role in promoting ASCVD health and cardiac rehabilitation. The independent contribution of questionnaire-based physical activity does not always show an independent contribution to all ASCVD [11], although this is not true for other cohort studies [12,13].

In a recently published systematic review and meta-analysis, objective measurement of physical activity based on daily step count was negatively related to incidence of fatal and non-fatal ASCVD. For example, a reduction in the relative risk of ASCVD of 11 % can be expected around 3000 steps per day, while the incidence of ASCVD is reduced by about 50 % at 7000 steps per day [14]. In another meta-analysis, a 10–15 % risk reduction for CV mortality was found for every 1000 additional steps of physical activity [15]. However, the effect in older people (≥60 years) appears to occur at a step count of 6000–10,000 steps per day, whereas for younger people (<60 years) the effect is seen at 7000–13,000 steps per day [15]. This is all the more remarkable as the position of the pedometer, whether on the wrist or hip, had no significant influence on the results. Also, simple smartphones may be used reliably to measure step counts across a spectrum from very low (1.6 km/h) to high walking velocity (6.0 km/h) [16].

On the contrary, a sedentary lifestyle is positively associated with ASCVD risk. Sedentary behavior of >6 h/day and television viewing >4 h/day is associated with higher risk for CVD mortality, with each additional hour of sedentary behavior above the threshold increasing the estimated RR by 1.04 (1.03–1.04) and for television viewing by 1.08 (1.05–1.12) [17]. Recent data on the cardio-metabolic risk factor profile and physical activity show that a shift from 30 min of sitting, standing or light physical activity to moderate and more intense physical activity has a favorable effect on body mass index, HbA1c and lipid profile [18], suggesting a long term reduction in CV events. In a comparison between moderate and intensive physical activity, intensive physical activity performs significantly better than moderate physical activity in terms of increasing cardiorespiratory fitness [19]. However, there is still no large study, based on hard outcome data, that this translates into ASCVD risk reduction.

Cardiorespiratory fitness is increasingly recognized as the 6th vital sign. The measurement of cardiorespiratory fitness is based on maximal oxygen uptake. As cardiorespiratory fitness increases, the risk of cardiovascular mortality decreases. This was impressively demonstrated years ago, when it was reported that 1 MET higher cardiorespiratory fitness was associated with an approximately 15 % lower cardiovascular mortality risk [20]. On average, 1–2 MET in peak cardiorespiratory fitness can be increased by structured exercise training [2]. In a prospective cohort study with 750,302 participants and a follow-up of 10.2 years, a difference in cardiorespiratory fitness of 1–2 MET from very unfit to below-average fit people was associated with a doubling of the risk of all-cause mortality. In contrast, the risk was "only" increased 1.28-fold in those with pre-existing cardiovascular disease after the follow-up period. There was no discernible disparity in risk reduction between the sexes [21]. Further, the Norwegian HUNT study showed a 48 % smaller incidence of cardiovascular disease in the fittest participants (highest quartile of peak oxygen uptake) compared to the least fit (lowest quartile (multi-adjusted hazard ratio 0.52, 95 % CI 0.33–0.82) [22].

If we compare the most active people with those with the highest cardiorespiratory fitness, we see the highest quintile of cardiorespiratory fitness to be associated with lower risk compared to the highest quintile of physical activity. Hence increasing cardiorespiratory fitness through training should be comparatively more important than increasing physical activity [23,24].

The Generation 100 study stands as the largest and longest RCT examining the effect of structured exercise training on the ASCVD risk profile. Over 5 years, the effect of moderate continuous training was compared to high-intensity interval training and to standard advice (control group). After 5 years, only the high-intensity exercise group showed a significant increase in cardiorespiratory fitness compared to the control group [19]. The results were similar for females and males. This finding is consistent with a recent systematic review and meta-analyses [25]. With regard to the ASCVD risk score, there was no significant difference between the training groups and control group. It remains to be seen to what extent differences in individual risk factors and higher cardiorespiratory fitness of the high-intensity training group prospectively translate into (lower) ASCVD mortality.

A recent Cochrane review of 85 RCTs in 23,430 patients with coronary heart disease undergoing a rehabilitation training with a mean follow-up of 12 months showed a relative risk incidence reduction of 26 % for CV mortality, 23 % for hospitalization and 16 % for myocardial reinfarction [26]. This impressively underlines the effectiveness of an exercise-based cardiac rehabilitation program. For peripheral arterial occlusive disease, better functional performance in the form of a longer distance in the 6-min walk test was associated with lower mortality [27]. In a Cochrane review on the effect of exercise training on mortality in patients after stroke, lack of evidence precluded an assessment. Cardiorespiratory fitness was shown to increase significantly by 3.4 ml/kg/min after low-to-moderate intensity interventions (9 trials with 438 participants), which may result in a reduced risk of CV mortality [28].

The evidence for the effectiveness of strength training on ASCVD is more limited. Based on a few large observational studies, strength training was associated with lower risk of ASCVD in a J-shaped curve [29–31]. The greatest risk reduction was observed with 30–60 min of strength training per week. Durations of 130–150 min/week and more were associated with increase cardiovascular events. A recent large observational study showed an almost 3-fold relative sex difference in relative risk reduction of CV mortality for women (30 %) compared with men (11 %) who performed regular muscle strengthening [7]. However, larger and longer RCTs are warranted to determine the best type and volume of resistance exercise and the most beneficial combination of resistance and aerobic endurance exercise for promoting ASCVD health. The evidence from large studies of physical activity and exercise related to ASCVD risk is summarized in Supplementary Table S1.

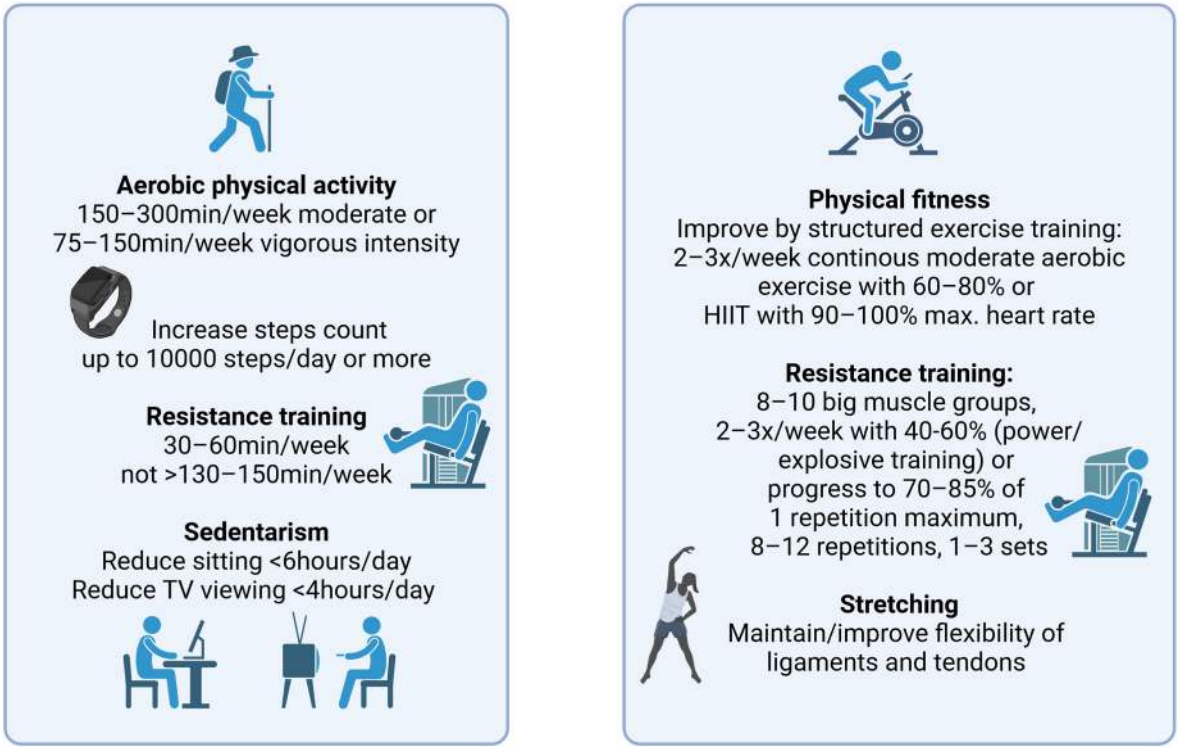

Fig. 1. Recommendations for physical activity and exercise to promote ASCVD health.

2.2. Physical activity mechanisms

The mechanisms by which aerobic physical activity reduces the risk of atherosclerotic manifestations are numerous. First, there is the reduction of sympathetic nervous system activity and promotion of vagal modulation, which is associated with an economization of cardiac work (lower resting and exercise heart rate, better diastolic function, higher stroke volume, smaller myocardial O_2 consumption) [32] and an increased release of nitric oxide [33] and thus better endothelial function [34,35]. Nitric oxide is increased by sudden high-intensity endurance intervals, which, combined with increase in blood flow and thus shear stress, contribute to an increased production of reactive oxygen species (ROS), which in turn play a decisive stimulating role in the initiation of adaptive vascular processes [36]. The reperfusion of transient, exercise-induced ischemia of the muscle tissue and muscle cell damage that occurs also contribute to the production of ROS. This in turn activates antioxidant processes in the liver, muscle and vascular system and thus contributes to the anti-atherosclerotic effect and consequently to the ASCVD risk reducing effect of physical activity [37].

Another key mechanism is the anti-inflammatory effect of aerobic exercise. Interleukin (IL)-6 [38] and its receptor, as well as glycoprotein 130 [39] and other anti-inflammatory cytokines, are increasingly released from the working musculature through exercise with increasing intensity and muscle mass involvement [40]. The as yet poorly understood phenomenon of the anti-inflammatory effect of an inherently pro-inflammatory process when induced by exercise training is only one piece of the puzzle of a multitude of myokines such as IL-10, IL-15, IL-7, which determine the anti-inflammatory effect of exercise [41]. In addition, the adaptive immune system is influenced by physical activity, which contributes decisively to the progression of atherosclerotic processes [42,43].

The mechanisms of resistance training are far more complicated than can be summarized under one umbrella. Inflammatory response, effect on oxidative stress and nitric oxide-mediated endothelial function are highly dependent on the type, intensity and duration of the resistance program [35,44]. In general, more aerobic-type resistance training is similar to aerobic endurance training in terms of physiological mechanisms, whereas high-intensity, low-repetition strength training increases reactive oxidative species [45] and inflammation and tends to stiffen the arterial system [46] via, i.e., increased sympathetic nervous system activity. However, the latter training may induce positive muscular adaptations such as muscle hypertrophy and, in the medium to long term, lead to a reduction in oxidative stress, inflammation [47] and reduce blood pressure and arterial stiffness at moderate intensity (40–70 % 1-repetition maximum) [46,48].

With regard to the reported sex differences in risk reduction for aerobic- and resistance-type physical activity [7], no data were identified to suggest an independent effect of sex hormones in females *vs* males or ovarian or the menstrual cycle in females [49,50]. Another future research topic is the differential effects of physical activity on the micro-*versus* macrovasculature between females and males [51], the finding from which may influence risk reduction recommendations for the respective arteriosclerotic micro- and macrovascular diseases.-

2.3. Recommendations for physical activity and exercise training

To promote ASCVD health, the WHO currently recommends 150–300 min of moderate-intensity aerobic exercise and 75–150 min of higher-intensity exercise per week [52]. In clinical practice, patients may well be advised to increase their step count, with an increase in step count of 1000 steps from any base between 2000 and 5000 steps per day being associated with a risk reduction of 5–10 % up to a step count of 10, 000 [14] (Fig. 1).

Resistance training should be performed 2–3 times per week with a total duration of approximately 30–60 min/week (but not >130–150 min/week) [29–31] with no clear evidence on ASCVD outcomes regarding intensity of resistance training. In general, an intensity of 40–60 % (power/explosive training) or progress to 70–85 % of 1 repetition maximum with 8–12 repetitions to volitional fatigue with 8–10 major muscle groups in 1–3 sets is recommended [53,54]. Stretching is usually recommended to maintain or improve flexibility of ligaments and tendons as part of a broader exercise regimen for promoting

cardiovascular health without a direct link to ASCVD risk reduction [53] (Fig. 1).

All recommendations should be modified based on an individual's age, gender, pre-existing risk factors and CVD status and general level of fitness [52,53]. To operationalize these recommendations it is important to identify and remove potential barriers to the sustained implementation of physical activity guidance, both at the individual level (behavioral change) [55] and societal levels (e.g., natural and built environment) [56].

3. Diet and ASCVD risk

3.1. Background

The relation between diet and ASCVD was first recognized soon after the turn of the 20th century. In 1913 Nikolaj Nikolajewitsch Anitschkow made the seminal observation that feeding cholesterol to rabbits resulted in the development of atherosclerotic plaque similar to that observed in humans [57]. In terms of dietary lipids, subsequent work on the diet-ASCVD axis shifted focused from dietary cholesterol to amount of dietary fat to type of dietary fat [58,59]. Some of the data comes from observational studies and some from interventional studies. Both types of data have been critical to informing the current recommendations for the prevention and treatment of ASCVD (Supplementary Table S2) [60].

Since the first observation, establishing the relationship between dietary fat and ASCVD has progressed in fits and starts, passing through periods where the culprits were thought to be dietary cholesterol, saturated fatty acids, *trans* fatty acids, high fat diets, low fat diets, and then specific foods and food components (e.g., coconut oil). Protectors were thought to be monounsaturated fatty acids, polyunsaturated fatty acids, phytochemicals, specific food components (e.g., polycosanols, alkylresorcinols), and dietary supplements (e.g., vitamin E). In most cases, as individual variables, they have not stood the test of time. This is likely attributable to the multifactorial nature of foods and food combinations that contribute to daily dietary patterns, and synergistically among them. For example, if fats of animal origin (e.g., dairy and meat) replace fats of plant origin (e.g., soybean oil, nuts), multiple other dietary components differ, making it difficult to attribute an outcome to a single factor. One potential approach to address the dilemma is to focus on the unsaturated to saturated fat ratio rather than independent recommendations for saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids. Such an approach is consistent with the evidence base and addresses the underlying issue of the relative balance among types of fatty acids.

3.2. Evidence from large observational studies and randomized controlled trials

Prospective observation studies have provided valuable information with respect to diet and ASCVD risk. Advantages of these types of studies, relative to intervention studies, include (i) large sample size, hence, ability to include a broad strata of clinically relevant subpopulations, (ii) long follow-up times and frequently hard endpoint data, (iii) observations based on habitual diets, not relying on participants adhering to protocol imposed changes, potentially to different degrees, and (iv) availability of prospective data for multiple time points, capturing changes during the observational period [61]. However, interpretation of the data can be difficult because health behaviors frequently co-vary, for example, individuals reporting higher saturated fat intakes frequently have other lifestyle behaviors such as higher rates of physical inactivity and tobacco use [60,61], that likewise contribute to ASCVD risk [58]. Subjective reporting of food intake and estimates of nutrient intake from food composition databases can be subject to biases due to the nature of the data [62].

The Seven Countries study, begun in 1958, established a strong link among dietary saturated fat, plasma cholesterol concentrations and coronary heart disease [63]. Subsequent prospective observational studies involving a wide range of cohorts have been inconsistent in terms of their conclusions about saturated fat and ASCVD outcomes (Supplementary Table S2) [64–67]. Much of the inconsistency can be attributed to focusing solely on saturated fat and lack of consideration to the replacement macronutrient [61]. When the latter is done, diets lower in saturated fat and higher in polyunsaturated fat are associated with lower coronary heart disease relative risk, whereas diets lower in saturated fat and higher in carbohydrates are associated with similar relative risk [65]. To further address this issue, a statistical framework for multivariable regression analysis to compare replacing saturated fat with other macronutrients has been used to estimate relative replacement effects [68]. When applied, replacing saturated fat with polyunsaturated fat results in the largest risk reduction estimate, monounsaturated fat results in a more modest risk reduction estimate, and carbohydrate from whole grains a smaller but statistically significant risk reduction [67]. Substitution of saturated fat with either refined carbohydrate or *trans* fatty acids has no significant benefit for ASCVD risk reduction.

The literature on the effect of diet and ASCVD clinical intervention trials is large. Critical issues to take into consideration when evaluating this vast literature base are related to the (i) magnitude of the intervention (difference between two diets), (ii) study participants compliance rate, (iii) adequacy of the intervention period, and (iv) cost per person [61]. Additional concerns when interpreting the dietary fat and ASCVD literature that, frequently in hindsight, need to be taken into consideration include (i) *trans* fat content of the test fat, (ii) length of the intervention period when hard endpoints are assessed, (iii) availability of objective biomarkers to establish adherence, (iv) use of standard outcome ascertainment methods. An in depth assessment of the available interventional data that reported included event rates identified four studies, termed "core studies", ones that fulfilled four criteria (Supplementary Table S2) [69–72]. A meta-analysis of these intervention trials concluded that replacing saturated fat with plant oil (primarily soybean oil) lowered coronary heart disease by 29 % (RR, 0.71 (95 % confidence interval (CI), 0.61–0.83) [61]. These findings were associated with a reduction in serum cholesterol, suggesting compliance with the intervention. Inclusion of six additional studies that fell short of being included in the group of core studies due to not fulfilling one or more of the criteria likewise resulted in a similar conclusion [61]. Noted was that foods high in saturated fat tend to also be high in cholesterol, both factors may have affected the outcome. An additional trial, published after the in depth review, the PREvención con DIeta MEDiterránea trial, provided extra virgin olive oil or nuts, sources of monounsaturated and some polyunsaturated fatty acids to participants consuming a Mediterranean diet, likewise resulted in significantly lower ASCVD rates (Supplementary Table S2) [73].

3.3. Focus on dietary patterns

An approach which has currently gained favor to avoid challenges around establishing dietary guidance from ASCVD risk reduction is to focus on dietary patterns, the entirety of all foods and beverages consumed during the day, rather than individual dietary components. The advantages of using this approach are that they (i) simultaneously take multiple dietary variables into consideration, (ii) are food based, facilitating implementation, (iii) are adaptable to personal preferences, ethnic and religious practices, and life stages, (iv) eliminate the need to estimate individual dietary component intakes (e.g., % saturated fat, grams added sugar), which can rarely be calculated accurately, (v) meet essential nutrient requirements of most individuals, and (vi) accommodate inclusion of foods with nutrient compositions that covary, potentially confounding data interpretation [60,74].

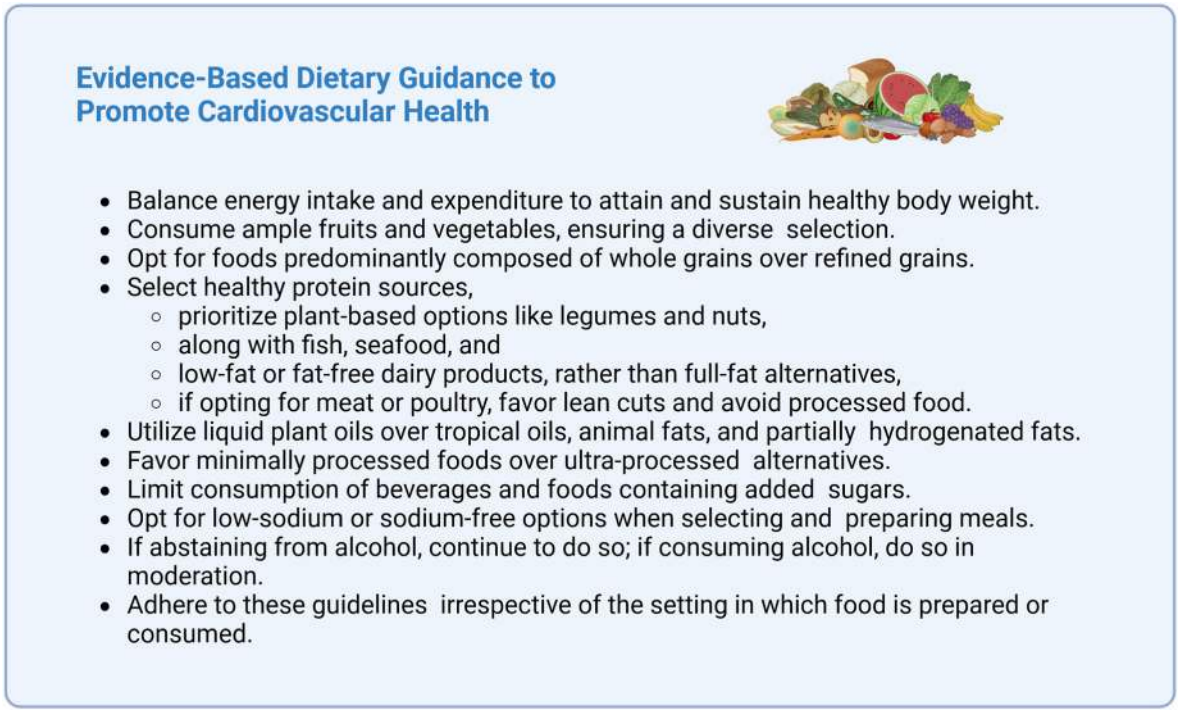

Fig. 2. Dietary guidance to promote cardiovascular health based on scientific evidence, adapted from American Heart Association [60].

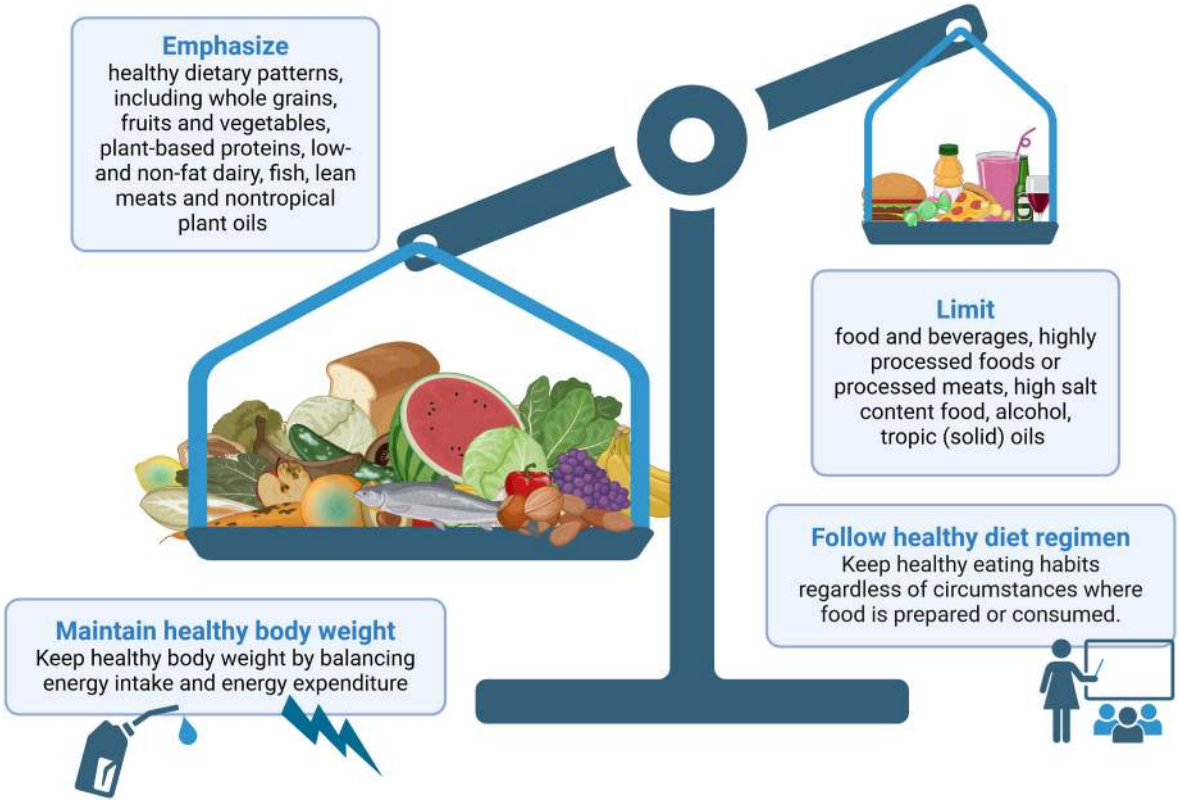

Fig. 3. Dietary patterns to promote cardiovascular health. Adapted from American Heart Association [60].

3.4. Dietary recommendations

In 2021 the American Heart Association (AHA) issued updated dietary guidance to improve CV health [60]. Consistent with concerns about focusing on individual foods or nutrients the emphasis is on dietary patterns. The guidance is organized around 10 basic tenants, which were termed features (Fig. 2).

The emphasis is on energy balance; consuming dietary patterns rich in a variety of fruits and vegetables, whole grain products, protein rich foods from plant sources, fish and seafood, low-fat and fat-free dairy

Diet categories	Common/popular diet names	Defining features			Estimate alignment with 2021 AHA Dietary Guidance
		Emphasize	Include	Limit/avoid	
DASH style	DASH, Nordic, Baltic	Vegetables, fruits, whole grains, legumes, nuts and seeds, low-fat dairy	Lean meats and poultry, fish, nontropical oils	Limit: saturated fat, sodium, fatty meats, refined grains, added sugars, alcohol	Aligned with the 2021 AHA Dietary Guidance; DASH, Mediterranean, vegetarian style (pescetarian, lacto/ovo/lacto-ovo)
Mediterranean style	Mediterranean diet	Vegetables, fruits, whole grains, legumes, nuts and seeds, poultry, fish and seafood (fatty), extra-virgin olive oil	Red wine (moderation)	Limit: dairy, meat, sugar-sweetened beverages, commercial bakery goods, sweets, and pastries	
Vegetarian style	Pescetarian		Fish and seafood, dairy, eggs	Limit: added sugars, refined grains, solid fats, alcohol. Avoid: meat and poultry	
	Lacto/ovo/lacto-ovo-vegetarian	Vegetables, fruits, whole grains, legumes, nuts and seeds	Dairy (lacto/lacto-ovo only). Eggs (ovo/lacto-ovo only)	Limit: refined grains, solid fats, alcohol. Avoid: meat, poultry, fish and seafood	
	Vegan			Limit: added sugars, refined grains, solid fats, alcohol. Avoid: meat, poultry, fish and seafood, dairy, eggs	Mostly aligned with the 2021 AHA Dietary Guidance, ensure vegan pattern includes healthy plant-based proteins and low-fat pattern includes healthy sources of liquid plant oils
Low fat	Low fat (Therapeutic Lifestyle Changes), volumetrics	Vegetables, fruits, whole grains, legumes	Low-fat dairy, lean meats, poultry, and fish	Limit: fat <30% kcal, nuts, oils, fatty meat, poultry, fish, alcohol	
Very low fat	Ornish, Esselstyn, Pritikin, McDougal, PCRM	Vegetables, fruits, whole grains, legumes		Limit: fat <10% kcal, sodium, refined grains, alcohol. Avoid: oils, nuts and seeds, meats, poultry, fish, dairy, eggs.	Contains some elements of the 2021 AHA Dietary Guidance, limited in plant oils and nuts, and some whole grains, legumes and whole fruits
Low carbohydrate	Zone, South Beach, low glycemic load	Vegetables, fruits (nonstarchy), nuts and seeds, fish and seafood, nontropical oils		Limit: carbohydrate 30%–40% kcal, whole and refined grains, legumes, dairy, alcohol. Avoid: added sugars, fatty meat	
Paleolithic	Paleo	Vegetables, fruits, nuts, lean meat, fish	Eggs	Limit: sodium. Avoid: added sugars, whole and refined grains, legumes, oils, dairy, alcohol	Promotes restriction of whole fruit, legumes and whole grain, inclusion of high amounts of animal-sourced foods, hence, the diets are discouraged
Very Low Carbohydrate	Atkins, ketogenic, well-formulated ketogenic diet	Nuts and seeds, red meat, poultry, fish and seafood, eggs, full-fat dairy, oils	Vegetables (nonstarchy), berries. Ketogenic: 3000–5000 mg/d sodium	Limit: carbohydrate <10% kcal, alcohol. Avoid: fruits (except berries), grains, legumes, added sugars	

Fig. 4. Dietary pattern categories, their common/popular names, their defining features and estimate alignment with 2021 AHA Dietary Guidance [60], adapted from Ref. [74].
Colors indicate estimate alignment: Green = aligned, Grey = mostly aligned, yellow = aligned with some elements, orange = mainly not aligned/not recommended.
DASH: Dietary Approaches to Stop Hypertension; PCRM: Physician's Committee for Responsible Medicine.

products and, if desired, lean cuts of unprocessed meat, and liquid plant oils; limited in processed foods, added sugar, salt and, if consumed, alcohol; and importantly applying the guidance regardless of where food is prepared or consumed inside or outside the home (Fig. 3). Alcohol intake has been associated with lower diet quality, even in moderate drinkers [75–77]. This issue may be of particular concern in due to the concomitant positive association between alcohol and energy intake, and higher prevalence of excessive alcohol intake in older adults [77, 78].

Critical to facilitating population-wide adoption to promote ASCVD health is that the guidance be consistent with common dietary practices. In 2023 the American Heart Association published an assessment of the alinement of the guidance with popular dietary patterns [74]. The patterns considered included in the assessment were the DASH (Dietary Approaches to Stop Hypertension)-style, Mediterranean-style, pescetarian, ovo/lacto-vegetarian, vegan, low-fat, very low-fat, low--carbohydrate, Paleolithic (Paleo), and very low-carbohydrate/ketogenic patterns (Fig. 4).

The findings indicated that 4 dietary patterns (Mediterranean-style, DASH style, pescetarian and ovo-lacto-vegetarian dietary) aligned most closely with the 10 features described in Fig. 3. The vegan and low fat diets aligned with most of the 10 features. The low carbohydrate and very low fat dietary patterns aligned somewhat, albeit with limitations. It was recommended that individuals choosing these dietary patterns would benefit from guidance from a registered dietitian. The last group, the Paleo and very low carbohydrate dietary patterns, did not align well with the 10 features of a heart healthy dietary pattern. It was noted that for each dietary pattern there are healthier and less healthy ways of configuring each. A challenge identified was the vast amount of misinformation and oversimplification of how some of these dietary patterns are presented.

3.5. Conclusion

Current dietary guidance to promote ASCVD health was based on both intervention and observational studies. Over the years dietary guidance format has shifted from individual foods and nutrients to dietary patterns encompassing all foods and beverages. There are multiple dietary patterns that are consistent with all or most of the basic features of a heart healthy dietary pattern. The challenge is to increase population-wide adoption of such dietary patterns.

4. Psychosocial stress and risk factors

4.1. Evidence from systematic reviews and meta-analyses

An extensive literature reveals a complex, partially bidirectional association of psychosocial stress and risk factors with ASCVD, with the bulk of research focusing on CHD, followed by cerebrovascular disease and PAD. Psychosocial stress can be defined as a threat to the homeostatic balance arising from taxing psychological and social environmental challenges (i.e., internal and external "stressors") [79]. When time-limited, such stressors result in adaptive physical, emotional and behavioral responses (fight, flight). While acute stress responses may also go awry, leading to acute coronary syndromes (ACS) during times of emotional upset [80], typically in individuals with pre-existing atherosclerosis, chronic stressors are associated with consequences considered as risk factors for ASCVD [81]. These include persistent states of biological perturbation, negative emotions, and unhealthy lifestyle [79]. Personality traits and negative social interactions can increase the level of perceived stress and intensify stress responses with negative consequences for ASCVD [81,82].

Consistent with this viewpoint, Supplementary Table S3 provides a synopsis of commonly investigated psychosocial risk factors (PSRFs) of

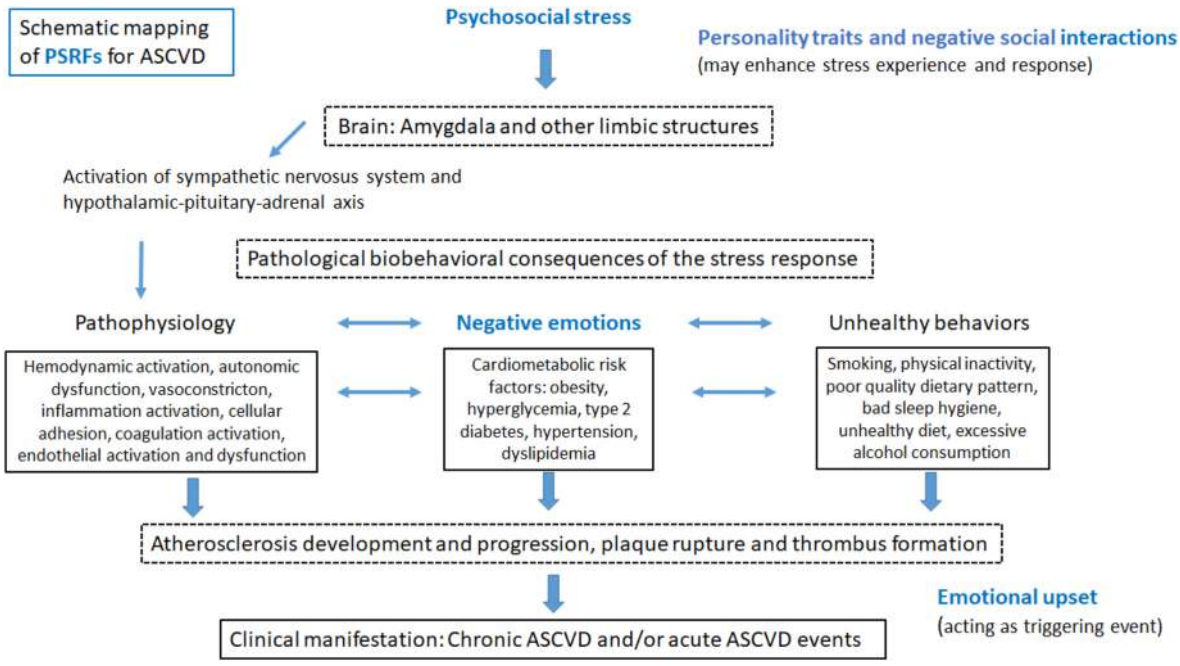

Fig. 5. Biobehavioral mechanisms.
Well-established biobehavioral mechanisms and pathways linking psychosocial risk factors (PSRFs) with the development, progression and clinical manifestation of ASCVD.

ASCVD in healthy populations and patients with ASCVD. These are categorized as chronic stressors [83–88], negative social interactions [89,90], negative emotional states [91–97], and enduring personality traits [98–100], each presented alongside their respective outcomes. A particular PSRF may be implicated in the development of atherosclerosis and the risk of incident ASCVD (e.g., perceived stress [88], loneliness/social isolation [90]), or in the progression and poor prognosis of established ASCVD (e.g., type D personality [100]), or both (e.g., depression [91–94], anxiety [95,96]). Acknowledging the diverse impact of PSRF on CV health throughout the lifespan (e.g., early-life stress *vs.* stress in adulthood), depending on sociodemographics, health behaviors, and comorbidities, is crucial for guiding research on underlying biobehavioral mechanisms and offering clinical recommendations. PSRFs, prevalent in 10–40 % of ASCVD patients [82], exhibit ASCVD risks in a dose-response pattern [101], comparable in magnitude to conventional risk factors (relative risk: 1.2–2.0) [101,102]. This increased ASCVD risk is independent of demographic and conventional risk factors such as body mass index, hypertension, diabetes, smoking and physical activity, e.g. for adverse childhood experiences [83], low socioeconomic status [84], low social support [89] and depression [91,92]. Adjusted effect estimates, while somewhat weaker, suggest conventional risk factors may partially act as confounders or mediators [83,92]. This is further supported by Mendelian randomization studies showing a causal relationship between depression and ASCVD that is partially mediated by cardiometabolic factors and smoking [103].

While PSRFs can co-occur and overlap, especially in the category of negative emotions, they may be partially associated with ASCVD through distinct physiological or behavioral pathways – an area of ongoing research. For example, adjusting for depression retained a significant association of anxiety with major adverse CV events [96], of vital exhaustion with cardiac events [97], and of perceived stress with incident CHD [88]. Controlling for disease severity at baseline did not explain the association of depression and anger-proneness/hostility with poor prognosis in patients with CHD, implying that reverse causality is unlikely [92,98]. While notable publication bias is minimal [91,95–97], some meta-analyses reveal moderate to high heterogeneity among original studies, a common occurrence in PSRF research [95,97]. The association is stronger in shorter-term studies for depression [92] and anxiety [95], whereas for anger-proneness/hostility, it becomes clearer with a longer follow-up [98]. This concurs with the notion that the timing of the clinical manifestation of ASCVD depends on different pathophysiological correlates of acute (e.g. emotional upset), episodic (e.g. depression) or chronic (e.g. hostility) PSRFs [104].

Gender-specific effects [105] and contributions of positive psychology [102] become increasingly important in behavioral cardiology research. For instance, men show an elevated risk of incident CHD related to job strain [106] and a poorer CHD prognosis associated with anxiety and depression compared with women [107]. Dispositional optimism, a tendency to expect positive outcomes, even when facing challenges, has been associated with both a reduced risk of incident ASCVD, independent of sociodemographics, conventional risk factors, and depression [108], and better prognosis in patients with CHD [109].

4.2. *Biobehavioral mechanisms*

Psychosocial stress and risk factors exert their atherosclerotic effects through direct pathophysiological mechanisms, which are integral components of the biological stress response, and unhealthy lifestyle, constituting the behavioral stress response [79,110]. Shared genetic risk variants, including those in the inflammatory system, along with epigenetic programming of glucocorticoid genes, gut dysbiosis, and early life stress, may underlie or contribute to both PSFRs and ASCVD over the lifespan [111–113].

As depicted in Fig. 5 [79,81,82,105,110,114], the orchestrated initiation of the central stress response involves the recruitment of neurobiological areas, primarily the amygdala and other limbic structures. This results in activation of the sympathetic nervous system and the hypothalamic-pituitary adrenal system on the one hand and withdrawal of vagal activity on the other. The subsequent peripheral CV responses, partly mediated by circulating levels of released cortisol, catecholamines and adrenergic receptors, are multifaceted. They encompass hemodynamic alterations (increase in heart rate and blood pressure), autonomic dysfunction (reduced heart rate variability), immune activation with proinflammatory changes and cellular adhesion,

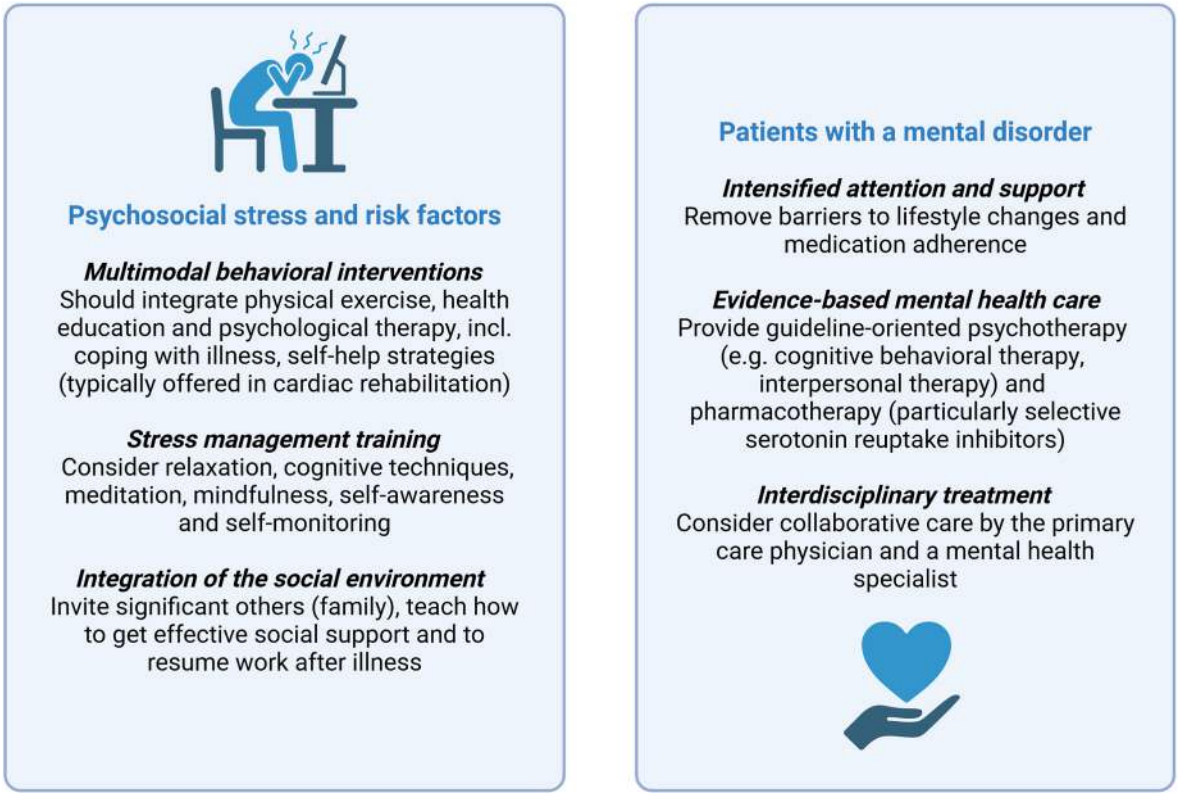

Fig. 6. Recommendations for treatment of psychosocial stress and mental disorders.

platelet and coagulation activation, as well as endothelial dysfunction and damage. These stress-induced biological processes add up to those attributable to an unhealthy lifestyle with a diet rich in cholesterol and sugar, overweight, and physical inactivity - all contributing to atherosclerosis. ASCVD can follow a chronic, progressive course leading to clinical manifestation or have an abrupt onset upon plaque rupture with thrombus formation. Within a critical time interval of 2 h, emotional upset may act as a triggering event, resulting in presentations such as ACS and acute cerebrovascular insult [80]. The pathophysiologic changes initiated by emotional triggers are qualitatively similar but more pronounced than "low-grade" changes associated with episodic and chronic PSRFs. This is evident, for instance, in elevated heart rate and blood pressure, the extent of the prothrombotic response (e.g., D-dimer levels reflecting fibrin formation), and the innate immune response (e.g., circulating IL-6) [110,114].

Unhealthy behaviors, including sleep disturbance, may themselves foster PSRFs. Furthermore, intriguing research suggests that atherosclerosis-related inflammation could signal the brain, inducing neuroinflammation and neurotransmitter dysfunction, thereby kindling negative emotions, including depression [115]. These few examples are representative of the many intricate interactions between biobehavioral mechanisms and pathways that link PSRFs to ASCVD but are often studied in isolation [114]. Notable exceptions include some recent studies showing significant associations between PSRFs, neurobiological activity, inflammatory changes (in bone marrow, arterial wall and circulation) and ASCVD outcomes, in the same study population [105, 116].

4.3. Recommendations

Because PSRFs clearly modify the risk of ASCVD and act as barriers to lifestyle change and adherence to treatment, various guidelines and scientific statements advocate the screening for PSRFs in patients with established ASCVD or at high risk to develop ASCVD [101,107]. Simple single item questions are asked to initiate a conversation about significant PSRFs (e.g., "Are you bothered by any stressful situation?"). These are followed by the use of screening instruments for a more comprehensive assessment of depression (e.g. Patient Health Questionnaire-9) or anxiety (e.g., General Anxiety Disorder-7 scale) [82,101,117]. Fig. 6 provides recommendations and considerations for the treatment of psychosocial stress and risk factors, including mental disorders, in patients with ASCVD [101,117,118].

Multibehavioral interventions, for instance offered in cardiac rehabilitation, should integrate health education, physical exercise to improve mood and alleviate stress, and psychological therapy for PSRFs [117], encompassing the learning of social support and self-help strategies [118]. In addition, in the presence of a mental disorder, evidence-based mental healthcare and interdisciplinary cooperation are advised, with consideration of selective serotonin reuptake inhibitors (SSRIs) for ASCVD patients with moderate-to-severe depression [101]. Note that antidepressants, including SSRIs, are not recommended in patients with heart failure, due to the increased mortality risk associated with their use in this population [101]. Patients who experience stress and PSRFs may benefit from psychotherapy referral to improve ASCVD outcomes [101,117].

Significant findings from systematic reviews and meta-analyses of RCTs support these recommendations. In patients with CHD, psychological interventions improved depressive symptoms, anxiety, and stress [119], reducing CV mortality, events, and ACS compared to usual care [119,120]. Remote cognitive-behavioral therapy, offered by phone or internet, also reduced depressive symptoms [121], and exercise therapy alleviated depression and anxiety [122]. Collaborative care (i.e., coordinated care delivery by a primary care physician and other health professional) for depressed CHD patients reduced major adverse CV events, and improved depressive and anxiety symptoms and quality of life compared to non-active control conditions [123]. SSRI therapy in depressed post-ACS patients was associated with a reduced risk of recurrent ACS [124]. In stroke survivors, psychosocial interventions

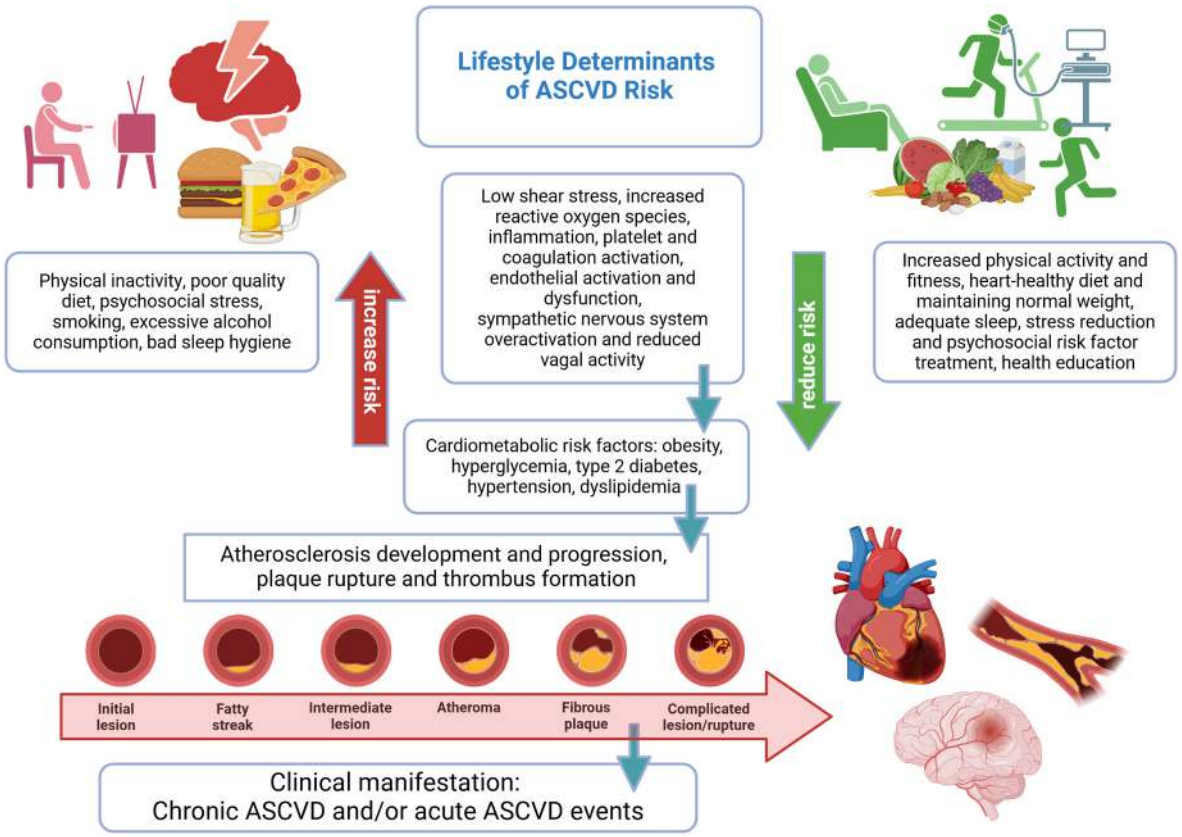

Fig. 7. Lifestyle determinants of ASCVD risk.
Reducing risk by improving healthy lifestyle determinants is the primary goal in reducing atherosclerotic plaque progression and ultimately improving ASCVD health.

reduced depressive symptoms [125], and SSRIs decreased the risk of future depression [126]. Addressing psychosocial issues in exercise-based rehabilitation improved physical activity participation in patients after vascular lower limb amputation in a qualitative meta-analysis [127].

4.4. Perspectives

Understanding the clinically significant role of psychosocial stress and risk factors is crucial for comprehending the lifestyle determinants of ASCVD in a broader context. Addressing psychosocial determinants not only enhances risk stratification but also opens avenues for multi-dimensional, innovative interventions in patients with ASCVD. Further research is warranted to refine therapeutic approaches.

5. Implementation and conclusion

Effective implementation and sustained adherence to lifestyle behaviors that support ASCVD health, including physical activity, diet and psychosocial stress, are critical but challenging goals. Collaboration among policymakers, healthcare professionals, and patients is essential to create an environment that supports adoption and maintenance of healthy lifestyle behaviors. Multidisciplinary healthcare teams including members who are aware of current evidence-based guidance in the areas of exercise physiology, diet and psychiatry/psychology are in the best position to implement comprehensive lifestyle interventions that will support ASCVD health (Fig. 7). Tailored interventions based on specific demographics or risk profiles may further optimize lifestyle change outcomes. However, there is still a gap between evidence-based knowledge from studies of these powerful determinants of ASCVD risk and the implementation in the health care system that needs to be closed. Undoubtedly, this is a goal worth striving towards.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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All figures excluding Fig. 4 were created with BioRender.com.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2024.117577.

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