Review

Lifestyle Factors and Coronary Artery Calcification

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Lifestyle factors · Coronary artery calcification · Subclinical atherosclerosis

Abstract

The effective prevention of cardiovascular disease (CVD) remains a global health challenge. Adopting a combined primary (prevention of the first episode of coronary heart disease or stroke) and primordial (prevention of the causal risk factors of CVD) prevention strategy is the best approach to prevent CVD. Most importantly, the primordial prevention strategy should in the first place be to promote cardiovascular health across individual and population levels by improving the underlying causal risk factors for CVD (i.e., unhealthy diets, physical inactivity, obesity, and cigarette smoking). Epidemiological evidence indicates that maintaining favorable underlying risk factors (lifestyle factors) is associated with a lower risk of incident CVD. Prevention of early atherosclerotic vascular disease is also an important strategy to prevent CVD. However, there has been limited research on the association between lifestyle factors and early atherosclerotic vascular disease (i.e., coronary or carotid atherosclerosis) across race and gender groups in population-based studies. This article briefly reviews whether lifestyle factors relate to subclinical atherosclerosis as assessed by coronary artery calcification in asymptomatic individuals.

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Introduction

Cardiovascular disease (CVD) is the leading cause of global mortality, leading to more than 17 million deaths annually [1]. With economic development, CVD mortality rates have substantially increased in developing countries [2], while having declined in developed countries over the past 4 decades [3]. Approximately 80% of the CVD burden arises from low- and

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middle-income countries, and continuous efforts are needed to prevent CVD in both developed and developing countries [1]. The establishment of an effective CVD prevention strategy in developed countries may be potentially valuable in preventing CVD in developing countries. As a CVD prevention strategy, most developed countries have adopted primary prevention [prevention of the first episode of coronary heart disease (CHD) or stroke] focusing on treatment of high-risk individuals who already have known risk factors (i.e., hypertension, dyslipidemia, and diabetes) [4]. Identifying high-risk individuals is fundamental to the practice of primary prevention and to prevent the progression of atherosclerotic vascular disease. Guidelines in the US, Europe, and Canada have included traditional CVD risk factors (i.e., hypertension, dyslipidemia, cigarette smoking, and diabetes) to detect coronary disease risk [5–7]. These four traditional CVD risk factors explain about 87% of CHD or 85% of CVD deaths; this also shows that persons with zero risk factors have low CHD or CVD death rates [8, 9]. Most individuals with fatal CHD ($\geq 87\%$) had ≥ 1 elevated traditional CVD risk factor [10]. Thus, maintaining optimal risk factors (i.e., total cholesterol < 200 mg/dl, systolic blood pressure < 120 mm Hg, diastolic blood pressure < 80 mm Hg, no diabetes, not smoking) is important to prevent CVD for a lifetime. This primary CVD prevention strategy has significantly contributed to reducing CHD or stroke mortality in the US by lowering the prevalence of several traditional CVD risk factors including hypertension, high cholesterol, and cigarette smoking [11]. Conversely, the emphasis on this primary prevention approach has also produced a higher prevalence of obesity and diabetes in the US [11]. This increasing trend may significantly influence the burden of CHD or stroke mortality. Notably, the prevalence of optimal risk factors in US communities is low at approximately 3–10% [9, 11]. This clearly documents a tremendous gap between primary prevention strategies and cardiovascular health status. To resolve this issue, adopting primordial prevention in addition to primary prevention is imperative to prevent CVD. In fact, primordial prevention is the ideal approach for improving underlying causal risk factors of CVD (i.e., unhealthy diets, physical inactivity, obesity, and smoking). These underlying risk factors (lifestyle factors) are associated with clinical CVD risk factors [12]. The continuing message is that favorable underlying lifestyle factors are associated with a lower risk of incident CHD and all-cause mortality [13–15]. Thus, increasing healthy populations by promoting healthy lifestyle behaviors at the individual and population level should in the first place be to avoid the burden of traditional CVD risk factors.

To address CVD prevention strategies, it is important to identify causal risk factors associated with early atherosclerotic vascular disease (coronary and carotid atherosclerosis). The American Heart Association (AHA) recently initiated a new approach to improving cardiovascular health, focusing on a healthy diet, regular exercise, not smoking, and managing normal weight [16]. Nonetheless, the health benefits of these favorable lifestyle factors in relation to early atherosclerotic vascular disease remain poorly documented. In this review, we examine whether lifestyle factors relate to subclinical atherosclerosis as assessed by coronary artery calcification (CAC) in population-based cross-sectional and longitudinal studies (table 1).

Subclinical Atherosclerosis: CAC

Approximately 50% of first coronary events occur in healthy men and women without prior symptoms. Of these, about 25% are sudden death or nonfatal myocardial infarction [17]. Therefore, identifying early atherosclerotic vascular disease (i.e., atherosclerosis) and subsequent treatment is an important strategy to prevent CVD. Atherosclerosis is a major cause of CHD and stroke. Monocyte-derived macrophages and other phagocytes are believed to contribute to vascular injury and atherosclerotic progression [18]. The plaque

Table 1. Lifestyle factors and CAC

Study	Year	Study population	Exposure comparison	Outcome (events, n)	OR (95% CI)	p value
<i>Abdominal obesity^a</i>						
Lee et al. [26]	2009	CARDIA study (2,951 US men and women; age 18–30 years)	Waist girth (highest vs. lowest tertile)	CAC >0 (n = 277)	1.90 (1.36, 2.65)	<0.001
Choi et al. [27]	2010	Hospital health care study (1,336 Korean men; age 30–86 years)	Waist girth (quartile 4 vs. quartiles 1–3)	CAC >100 (n = 236)	1.56 (1.12, 2.18)	0.01
			Visceral fat (quartile 4 vs. quartiles 1–3)	CAC >100 (n = 236)	1.42 (1.01, 1.98)	0.043
Fox et al. [28]	2009	Framingham Heart Study (3,130 US men and women; mean age 52 years)	Waist girth (quartile 4 vs. quartile 1)	CAC >0 (n = 457)	1.18 (0.85, 1.64)	0.32
			Visceral fat (quartile 4 vs. quartile 1)	CAC >0 (n = 457)	0.87 (0.61, 1.23)	0.43
Liu et al. [29]	2012	Jackson Heart Study (2,884 African Americans; mean age 60 years)	Visceral fat (per SD)	CAC >0 (n = 1,384)	1.07 (0.9, 1.2)	0.28
<i>Physical fitness^b</i>						
Lee et al. [31]	2009	CARDIA study (2,373 US men and women; age 18–30 years)	High vs. low (quartile 4 vs. quartile 1)	CAC >0 (n = 219)	0.59 (0.36, 0.97)	0.03
DeFina et al. [32]	2014	Cooper center (5,341 US women; age 40–90 years)	MET	CAC >0 (n = 1,062)	0.96 (0.92, 1.01)	0.35
<i>Physical activity^c</i>						
Lee et al. [31]	2009	CARDIA study (2,373 US men and women; age 33–45 years)	High vs. low (quartile 4 vs. quartile 1)	CAC >0 (n = 219)	0.96 (0.63, 1.47)	0.82
Bertoni et al. [33]	2008	MESA study (6,482 US adults; age 45–84 years)	High vs. low (intentional exercise: ≥30 MET h/week vs. none)	CAC >0 (M = 1,900; W = 1,371)	1.05 (M) (0.98, 1.12) 1.02 (W) (0.93, 1.12)	>0.05
<i>Cigarette smoking</i>						
Loria et al. [41]	2007	CARDIA study (2,433 US men and women; age 18–30 years)	Cigarette smoking (>10 vs. <10 cigarettes/day)	CAC >0 (n = 231)	1.25 (1.05, 1.48)	<0.05
Lehmann et al. [42]	2014	Heinz Nixdorf Recall study (1,261 German men and women; age 45–75 years)	Current smoker (yes vs. no)	CAC >0 (n = 317)	1.49 (1.04, 2.15)	<0.05
<i>Alcohol intake</i>						
Pletcher et al. [44]	2006	CARDIA study (3,037 US men and women; age, 33–45 years)	Heavy vs. never (>14 vs. 0 drinks/week)	CAC >0 (n = 260)	1.9 (1.2, 2.9)	0.002
McClelland et al. [45]	2008	MESA study (6,791 US adults; age 45–84 years)	Heavy vs. none (>2 vs. 0 drinks/day)	CAC >0	1.09 (0.66, 1.79)	0.83
Tofferi et al. [46]	2004	US Army Personnel study (731 men and women; age 39–45 years)	Heavy vs. none (≥2 vs. 0 drinks/day)	CAC >0 (n = 135)	1.26 (0.69, 2.59)	>0.05

^a Abdominal obesity was defined as follows: waist girth ≥84.3 vs. <77.5 cm (men) and ≥75.5 vs. <68 cm (women) [26]; waist girth >93.3 vs. ≤93.3 cm (men), visceral fat >173 vs. ≤173 cm² (men) [27]; waist girth >106.7 vs. ≤89.7 cm (men) and ≥101.1 vs. <80.8 cm (men), visceral fat >2,794 vs. ≤1,457 cm³ (men) and >1,804 vs. <681 cm³ (women) [28]; continuous quantity of visceral fat (cm³) [28].

^b Physical fitness was defined as follows: treadmill time ≥13.5 vs. <11 min (men) and ≥10 vs. <7.3 min (women) [31]; MET achieved on treadmill test (1 MET = 3.5 ml O₂/kg/min) [32].

^c Physical activity was defined as follows: physical activity levels ≥688 vs. <272 units (men) and ≥478 vs. <150 units (women) [31]; intentional exercise (≥30 MET h/week vs. none) [33].

formation and calcium deposition is associated with an accumulation of macrophages, smooth muscle cells, fibrosis, necrosis, and lipids in the artery [19]. CAC is a risk marker for atherosclerosis. It is a noninvasive measure of subclinical atherosclerosis and has a superior discriminating power for CVD events compared with other markers of atherosclerosis.

rosis including carotid intima-media thickness or the ankle-brachial index [20, 21]. Significant CAC scores have a greater accuracy in detecting CHD in persons with stenosis >50% [22]. CAC is a strong independent predictor of CVD events and all-cause mortality [23]. Individuals with a CAC score of 0 have a very low rate of CVD events [24]. In general, the established risk factors for CAC are similar to those for clinical CVD.

Adiposity and CAC

Excess adiposity is mainly due to unhealthy diets and sedentary lifestyles. Particularly, abdominal obesity is a significant risk factor for atherosclerosis. The excessive accumulation of visceral fat is related to insulin resistance and hyperinsulinemia, which contribute to atherosclerotic progression [25]. Abdominal obesity is also positively associated with low-density lipoprotein cholesterol (LDL-C) and oxidized LDL-C, which relates to endothelial cell injury and thrombus formation [19]. The Coronary Artery Risk Development in Young Adults (CARDIA) study showed that abdominal obesity measured by waist girth in young adults (aged 18–30 years) was directly associated with early atherosclerotic vascular disease assessed by CAC over 15 years (aged 33–45 years) [26]. At baseline, young adults with the highest tertile of waist girth (men ≥ 84.3 cm; women ≥ 75.5 cm) had twice the risk of developing CAC when compared with young adults in the lowest tertile category (men < 77.5 cm; women < 68 cm) 15 years later. A Korean cross-sectional study also showed that abdominal adiposity measured by waist girth (quartile 4 vs. quartiles 1–3) or visceral fat (quartile 4 vs. quartiles 1–3) was positively associated with CAC in Korean men aged 30–86 years [27]. In contrast, other (cross-sectional) US studies including the Framingham Heart Study and the Jackson Heart Study showed that abdominal obesity measured by waist girth or visceral fat was not related to CAC in US men and women [28, 29]. More longitudinal studies are needed to determine the association between abdominal obesity and CAC across race and gender groups. Further studies are also needed to determine optimal cut points for waist girth or visceral fat associated with the minimum risk of developing CAC. Some investigators have even reported that atherosclerosis does not progress when LDL-C is < 67 mg/dl [30].

Physical Activity or Physical Fitness and CAC

Physical fitness, an objective marker of physical activity determined by behavioral and environmental factors, genetics, and subclinical disease, is a significant predictor of CVD mortality [15]. The CARDIA study showed that physical fitness measured at baseline was inversely associated with early atherosclerotic vascular disease in young adults. High-fitness young adults (treadmill time: men ≥ 13.5 min, women ≥ 10 min; age 18–30 years) had a 41% lower risk of having CAC as compared with low-fitness counterparts (treadmill time: men < 11 min, women < 7.3 min) over 15 years [31]. One cross-sectional study showed a null association between physical fitness, as assessed by continuous metabolic equivalents (MET; 1 MET = 3.5 ml O₂/kg/min), and CAC in US women aged 40–90 years [32]. Interestingly, several population-based studies indicate no association between physical activity and CAC. The Multi-Ethnic Study of Atherosclerosis (MESA) and the CARDIA study have shown that physical activity was not associated with CAC [31, 33]. This may be due to the inaccurate measurement of physical activity in both cross-sectional and observational studies. More studies are needed to determine with a more precise measurement the relation of physical activity to CAC. Further studies are also needed to establish optimal cut points for physical fitness or physical

Fig. 1. Risk of coronary events or CAC by the combination of healthy lifestyle factors: a healthy diet (top 40% of healthy eating scores), regular exercise (moderate-to-vigorous activity >30 min/day), weight control (BMI < 25), tobacco avoidance versus 0 healthy lifestyle factors. Combination of healthy lifestyle factors in CAC was classified as these 4 healthy lifestyle factors or ≥3 versus 0 healthy lifestyle factors. Error bars represent 95% CI for each HR or OR.

activity associated with a minimum risk of developing CAC. Although excessive exercise may be harmful to patients with chronic diseases [34], mounting evidence indicates that improvements in fitness reduce blood pressure and improve lipid profiles, endothelial function, and antioxidant defense systems [35, 36]. To date, the global fitness standards in men and women have not been fully explored. Establishing accurate fitness standards in relation to minimum CVD mortality or CAC risk across age, gender, and race groups is an important strategy for improving cardiovascular health.

Cigarette Smoking and CAC

Cigarette smoking is a potent risk factor for atherosclerosis. Life expectancy in smokers is reduced by an average of 13.2 years for men and 14.5 years for women [37]. Cigarette smoking produces numerous toxic chemicals and free radicals, which induce endothelial cell injury and subsequent atherosclerotic progression. Cigarette smoking is also associated with endothelial dysfunction by elevating platelet aggregability, fibrinogen levels, endothelial permeability and plasma viscosity and by lowering HDL cholesterol [38]. Approximately 50–62% of smokers have CAC scores of >0 [39, 40]. The CARDIA study and the Heinz Nixdorf Recall study have shown that current smoking was positively associated with CAC [41, 42]. Even smokers with a CAC score of 0 had a greater all-cause mortality compared with nonsmokers with a CAC score of 0 [42]. A lifetime of not smoking would show benefit in reducing the risk of developing CAC.

Alcohol Intake and CAC

Moderate alcohol intake is associated with a lower risk of incident CHD, but it still has a potential link to cancer mortality [43]. Thus, recommending moderate alcohol intake to the public requires more careful consideration. The association between alcohol intake and CAC remains controversial. Some investigators found a positive association between heavy alcohol intake (>14 drinks/week) and risk of developing CAC [44]. Other studies have shown no association between heavy alcohol intake (>2 drinks/day) and CAC [45, 46]. More studies are needed to determine whether moderate or heavy alcohol intake relates to CAC.

Combined Effects of Lifestyle Factors and CAC

Few studies have examined the combined impact of healthy lifestyle behaviors on CAC. The MESA showed that persons who exercised regularly (>150 min/week of moderate activity or >75 min/week of vigorous activity), had a healthy diet (Mediterranean diet), never smoked, and maintained a normal body weight ($18.5 \leq \text{BMI} < 25$) had 46% lower odds of having CAC compared with persons with 0 low-risk lifestyle behaviors [47]. Persons with ≥ 3 healthy lifestyle behaviors had approximately 52% lower odds of having CAC as compared with persons with 0 low-risk lifestyle behaviors. Persons who adopted the 4 healthy lifestyles mentioned above also showed a slower annual progression of calcium scores [47]. Several clinical trials including the Lifestyle Heart Trial [48], the Stanford Coronary Risk Intervention Project [49], and the Heidelberg Regression Study [50] also showed that coronary artery disease patients who had exercise training with a low-fat diet [50] or exercise training with other lifestyle modification (not smoking, low-fat diet, and stress management) [48, 49] had a slower progression of coronary atherosclerosis as compared with control patients with coronary artery disease.

Conclusion

Epidemiologic evidence indicates that maintaining a healthy lifestyle (a healthy diet, regular exercise, weight control, and tobacco avoidance) is associated with a lower risk of CVD events (fig. 1). Few studies also show that maintaining these healthy lifestyles is associated with a lower risk of developing CAC. However, whether these lifestyle factors alter early atherosclerotic vascular disease risk is less clear. More longitudinal studies and randomized controlled trials are needed to determine the effect of a single and a combined number of lifestyle factors or novel risk factors on CAC. Further studies are also needed to establish the optimal cut points of lifestyle factors associated with a minimum risk of developing CAC across race, gender, and age groups in population-based studies. The establishment of these cut points will play a fundamental role in preventing early atherosclerotic vascular disease and promoting cardiovascular health worldwide.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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