Review Article

# Frontiers in subclinical atherosclerosis and the latest in early life preventive cardiology

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## Abstract

Subclinical atherosclerosis underlies most cardiovascular diseases, manifesting before clinical symptoms and representing a key focus for early prevention strategies. Recent advancements highlight the importance of early detection and management of subclinical atherosclerosis. This review underscores that traditional risk factor levels considered safe, such as low-density lipoprotein cholesterol (LDL-C) and glycated haemoglobin (HbA1c), may still permit the development of atherosclerosis, suggesting a need for stricter thresholds. Early-life interventions are crucial, leveraging the brain's neuroplasticity to establish lifelong healthy habits. Preventive strategies should include more aggressive management of LDL-C and HbA1c from youth and persist into old age, supported by public health policies that promote healthy environments. Emphasising early education on cardiovascular health can fundamentally shift the trajectory of cardiovascular disease prevention and optimise long-term health outcomes.

**Keywords:** Life-course approach, preventive cardiology, primary prevention, primordial prevention, subclinical atherosclerosis

## INTRODUCTION

Atherosclerosis is a complex and insidious process that underlies the majority of cardiovascular diseases (CVD), the leading causes of morbidity and mortality worldwide[1] [Figure 1]. There has been a growing recognition of the importance of subclinical atherosclerosis, which refers to the presence of atherosclerotic plaques in the arterial walls before the onset of clinical symptoms.[2-5] The diagnosis of subclinical atherosclerosis through imaging techniques, such as ultrasound of the carotid and femoral arterial systems or computed tomography coronary angiogram (CTCA), is associated with a significantly higher rate of progression to clinical CVD and worse overall outcomes.[1] Detection of early subclinical atherosclerosis and subsequent optimisation of risk factors would be part of a primary prevention approach to reduce the progression of CVD and the risk of cardiovascular events.[6-8] Primordial CVD prevention efforts, on the other hand, would focus on preventing the development of risk factors,[5] through promoting a healthy diet, regular physical activity, tobacco avoidance from early childhood and so on.

The use of advanced imaging modalities, such as CTCA, magnetic resonance imaging, and positron emission tomography, has enabled the visualisation and quantification of subclinical atherosclerosis with unprecedented accuracy and precision.[9,10] For example, the Progression of Early Subclinical Atherosclerosis (PESA) study, conducted in Madrid, Spain, has employed state-of-the-art imaging techniques complemented by a multi-omics approach to characterise the early stages of atherosclerosis in a large cohort of middle-aged adults.[11] The study has provided insights into the natural history of subclinical atherosclerosis and its associations with traditional cardiovascular risk factors, such as hypertension, dyslipidaemia and insulin resistance.

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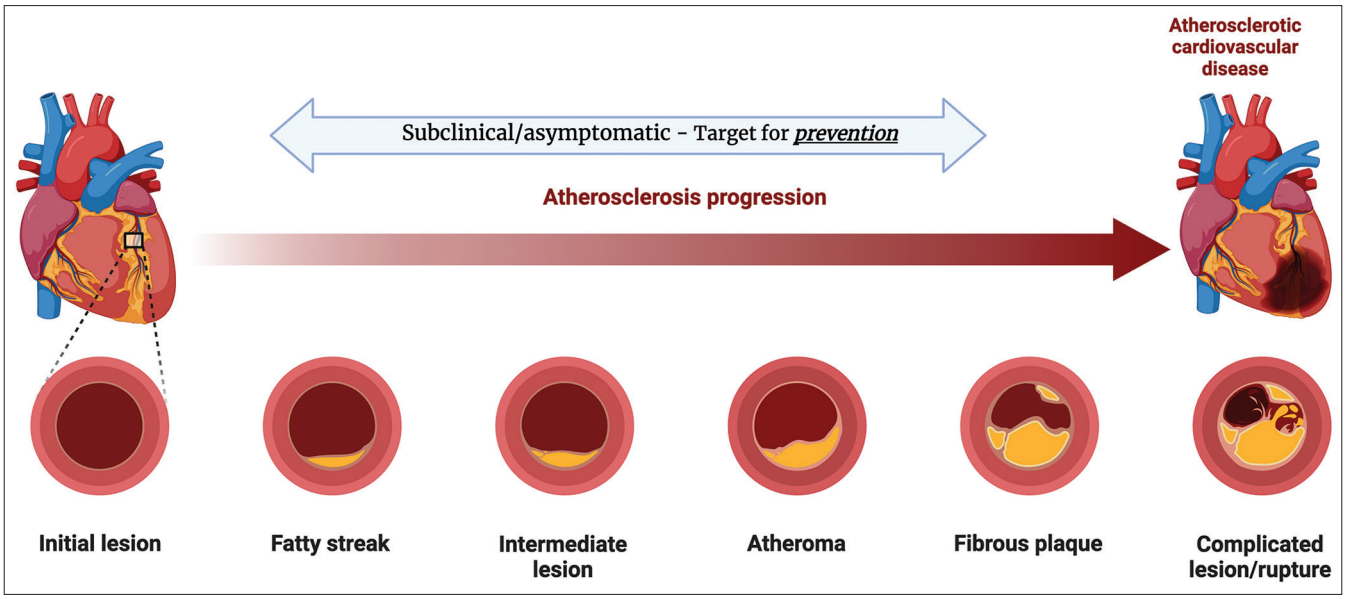


**Figure 1:** Illustration shows the progression of atherosclerosis. Subclinical atherosclerosis represents a target for prevention of progression to atherosclerotic cardiovascular disease. [Created with BioRender.com]

In this review, we explore recent developments in subclinical atherosclerosis and what it can teach us about preventive cardiology. We delve into recent advancements in primary prevention strategies across different age groups, insights from genetics and biological ageing, and the imperative of early intervention, particularly in youth. By understanding and addressing the early stages of atherosclerosis, we can potentially mitigate the burden of CVD and improve cardiovascular outcomes for individuals at risk. A shift is needed from preventing adult CVD to preventing atherosclerosis.

## DEFINING SUBCLINICAL ATHEROSCLEROSIS

Atherosclerotic cardiovascular disease (ASCVD) remains a leading cause of morbidity and mortality. Symptomatic ASCVD manifests clinically as acute coronary syndromes, including myocardial infarction, angina pectoris, peripheral artery disease and ischaemic stroke. These conditions are typically associated with significant luminal narrowing or the presence of a thrombus caused by plaque rupture, erosion or calcified nodules.[12] Given that atherosclerosis is a gradual process, symptomatic ASCVD is preceded by a prolonged asymptomatic phase, referred to as subclinical atherosclerosis.[13,14] In the absence of symptoms, diagnosis is made through imaging modalities such as carotid or femoral artery ultrasound, echocardiography or CTCA for screening purposes. Despite its clinical relevance, a standardised pathological definition of subclinical atherosclerosis remains elusive. At a pathological level, subclinical atherosclerosis is characterised by the absence of ischaemic symptoms, regardless of histological findings. These lesions can be classified into three categories: (1) non-ruptured plaques with mild stenosis (<50%), including various morphologies such as fibroatheromas; (2) thrombus formation following plaque rupture, erosion or calcified nodules that resolve without symptoms and cause less than 50% luminal narrowing; and (3) advanced lesions with 50%–99% stenosis or total occlusion that remain asymptomatic.[15] Epidemiological studies assessing subclinical atherosclerosis have used varying markers of disease. Carotid intima-media thickness was found to be associated with an increased risk of incident myocardial infarction or ischaemic stroke and was used in the Atherosclerosis Risk In Communities study.[16,17] Coronary calcium measured on CT represents a widely validated measure of coronary atherosclerosis and a prognostic marker of ASCVD risk.[18,19] Most recently, the PESA study defined subclinical atherosclerosis as the presence of at least one plaque or a coronary artery calcium score of ≥1.[13] Plaques were defined as localised protrusions extending into the vessel lumen, with a thickness exceeding 0.5 mm or greater than 50% of the surrounding average intimal thickness. Alternatively, subclinical atherosclerosis was identified as diffuse intima-media thickening measuring over 1.5 mm.[13]

## PRIMARY PREVENTION

### Adults aged 20–60 years

The PESA study has shed light on the early origins of subclinical atherosclerosis, demonstrating that atherosclerotic plaques can develop in young adulthood and progress over time, even in the absence of clinical risk factors.[11] Furthermore, the study has shown that traditional cardiovascular risk factors, such as elevated low-density lipoprotein cholesterol (LDL-C), high blood pressure and smoking, are strongly associated with the presence and progression of subclinical atherosclerosis, highlighting the importance of early intervention and risk

factor modification.[2-4] Research from the Coronary Artery Risk Development in Young Adults (CARDIA) study has emphasised the importance of cumulative exposure to multiple risk factors over time. This study found that higher cumulative levels of LDL-C, systolic blood pressure, and triglycerides significantly increased the risk of cardiovascular events later in life.[6-8] In a recent analysis from the PESA study, Mendieta *et al*. used serial multi-site ultrasound of the carotid and femoral arteries to measure global plaque volume as a surrogate for subclinical atherosclerosis.[20] Over six years of follow-up, 32.7% of the cohort of individuals aged 40–55 years at baseline were found to have an increase in global plaque volume and were categorised as progressive subclinical atherosclerosis. Individuals with higher systolic blood pressure and LDL-C at an earlier age were found to progress most rapidly. Interestingly, 8% of individuals with baseline subclinical atherosclerosis were found to have regression in their disease burden over time, indicating that lifestyle intervention can reverse the process of atherosclerosis. Such findings underscore the necessity for sustained primary prevention efforts starting in early adulthood to curb the silent progression of atherosclerosis.

In a large meta-analysis, the presence of subclinical atherosclerosis in asymptomatic individuals, as assessed by arterial ultrasound, CT calcium score and ankle brachial index, was shown to predict worse cardiovascular outcomes, independent of conventional cardiovascular risk factors.[9] However, there remains a paucity of prospective evidence showing a reduction in cardiovascular outcomes from the treatment of subclinical atherosclerosis. The international research initiative, Reversal of Early Atherosclerosis through personalized Curative Treatment, aims to test the identification and aggressive treatment of subclinical atherosclerosis in a randomised controlled trial involving 16,000 participants.[10]

### *Thresholds of LDL-C and HbA1c for assessment and intervention*

Findings from the PESA and CARDIA studies have challenged the traditional thresholds for LDL-C and HbA1c, advocating for lower targets to prevent the early development of subclinical atherosclerosis. The idea that 'lower is better' applies particularly to LDL-C levels, where individuals with LDL-C levels below current guideline recommendations may still benefit from further reduction. For instance, in middle-aged adults, even in the absence of traditional risk factors, individuals with LDL-C levels of 80–100 mg/dL (2.1–2.6 mmol/L) were found to exhibit significant subclinical atherosclerosis.[2] Similarly, emerging data suggest that even subclinical levels of glycaemic control, such as glycated haemoglobin (HbA1c) levels <5.7%, can be associated with an increased risk of subclinical atherosclerosis.[3,4] These findings advocate for a re-evaluation of current thresholds and a more proactive approach in managing these risk factors at the population level.

The American Heart Association's Life's Essential 8 approach emphasises the importance of maintaining optimal levels of key health factors: diet, physical activity, smoking status, body weight, cholesterol, blood pressure, blood sugar and sleep.[21] Adopting the 'as optimal as realistically possible, for as long as possible' philosophy for these health factors may maximise cardiovascular health outcomes.[22] Early intervention to address these parameters and keep them within optimal ranges throughout life may significantly reduce the risk of developing subclinical atherosclerosis and subsequent cardiovascular events.

### Older adults aged 60–100 years

Preventing CVD in older adults presents unique challenges due to the presence of age-related comorbidities and the decline in physiological function. However, primary prevention efforts, even in this population, can reduce the risk of cardiovascular events and improve quality of life.[23] In longitudinal studies, subclinical atherosclerosis is highly prevalent in older adults and is associated with cognitive decline and other age-related conditions.[24] Furthermore, persistent elevation in cardiovascular risk factors over time is associated with an accelerated ageing process, including changes in cerebral blood flow and metabolism.[25] A study by Tristao-Pereira *et al.*[26] published in *The Lancet Healthy Longevity* found that individuals with persistent high cardiovascular risk exhibited significant declines in brain glucose metabolism and elevated levels of neurofilament light chain, a marker of neuronal injury. This suggests that managing cardiovascular risk factors may not only prevent heart disease, but also mitigate the risk of neurodegenerative diseases and preserve cognitive function in older adults.

## PRIMORDIAL PREVENTION

### Children and youth aged 0–20 years

Atherosclerosis begins as early as in childhood. This evidence originated from the data of the Pathobiological Determinants of Atherosclerosis in Youth study. Adolescents and young adults who died of accidental causes were autopsied, and 10%–30% of 15–19-year-olds had fatty streaks in the aorta and 2%–5% had fatty streaks in the coronary arteries.[27] These findings established that atherosclerosis cannot be considered an adult disease alone and identified childhood cardiovascular risk factors such as youth smoking, obesity, elevated blood pressure, hyperglycaemia and dyslipidaemia. Therefore, early intervention in childhood is crucial for preventing the development of subclinical atherosclerosis and reducing the risk of CVD later in adulthood.

Prevention of CVD and cardiometabolic disease starts early in childhood, even prenatally. The Developmental Origins of Health and Disease hypothesis proposes that diseases such as CVD and type 2 diabetes mellitus have their origins in prenatal life and early childhood. Educational interventions

aimed at promoting healthy behaviours from a young age have been shown to be effective in shaping lifelong cardiovascular health trajectories.[28] For example, family-based programmes and community initiatives that focus on promoting a healthy diet, regular physical activity and tobacco cessation have been successful in reducing the prevalence of cardiovascular risk factors in children and adolescents.[29] Additionally, exposure to a healthy environment during childhood and adolescence can have a lasting impact on cardiovascular health outcomes in adulthood, highlighting the importance of early and sustained intervention efforts.

In addition, cardiovascular risk factors detected and managed during childhood may also have sustained benefits. Clinical trials of statins in children with familial hyperlipidaemia, which included measures of subclinical atherosclerosis such as endothelial function and carotid intima-media thickness, showed a positive impact on cumulative LDL-C and projections regarding the age at first CVD event. Individuals who commenced a low-dose statin at the age of 10 and switched to a high-dose statin at the age of 18 were predicted to have a first CVD event at the age of 53, while those who delayed commencing a high-dose statin till the age of 18 were predicted to have a first CVD event at the age of 48; however, untreated patients and individuals with no cardiovascular risks were predicted to have a first CVD event at the age of 35 and 55, respectively.[30]

### Neuroplasticity and habit formation

Neuroplasticity, the brain's ability to reorganise itself by forming new neural connections, plays a pivotal role in habit formation and retention. The brain is particularly receptive to learning and forming new habits during early life stages, from childhood through adolescence.[31,32] During these periods, repeated exposure to certain behaviours and information can lead to long-lasting changes in the brain's structure and function, making early life interventions critically important for establishing lifelong healthy habits. The benefits of healthy behaviours and attitudes developed during youth can be retained into adulthood and influence both disease risk and outcomes. In contrast, changing established habits in adulthood can be challenging due to the brain's reduced plasticity and the entrenchment of long-standing behaviours. Adults often require more intensive and sustained interventions to modify their habits. Therefore, early life intervention may offer a more effective and efficient strategy in promoting lifelong cardiovascular health.[33,34]

## COMPREHENSIVE PREVENTIVE STRATEGY

Preventive cardiology must therefore embrace a comprehensive approach that integrates the latest scientific insights with practical public health strategies. The American Heart Association's Life's Essential 8 provides a robust framework for maintaining cardiovascular health, together with more ambitious targets for lifelong risk factor control. This comprehensive approach may include:

1. Early education and lifestyle interventions: Incorporating cardiovascular health education into school curriculums to promote healthy behaviours from a young age. Community programmes and family-based interventions can reinforce the following messages:
   (a) Diet and nutrition: Teaching children the importance of a balanced diet rich in fruits, vegetables, whole grains and lean proteins. Schools can incorporate nutrition education into their curriculums and provide healthy meal options.
   (b) Physical activity: Encouraging regular physical activity through school sports programmes, physical education classes and community initiatives. Children should be educated about the benefits of staying active and the risks associated with a sedentary lifestyle. Sedentary time should be minimised, with intermittent active breaks, allowing time for at least 1 h of cumulative physical activity daily.[35]
   (c) Tobacco and substance use: Educating children and adolescents on the dangers of smoking or vaping, tobacco and substance abuse. Schools and communities should implement programmes that discourage these behaviours and promote healthy alternatives.
   (d) Mental health and stress management: Addressing the importance of mental health and teaching stress management techniques. Chronic stress is a risk factor for CVD, and early interventions can help children develop healthy coping mechanisms.
   (e) Sleep hygiene: Promoting good sleep hygiene and educating children about the importance of adequate sleep for overall health. Poor sleep can contribute to various health issues, including cardiovascular risk.
2. Regular screening and monitoring: Implementing regular screening for cardiovascular risk factors, including LDL-C and HbA1c, starting in early adulthood. Early identification of at-risk individuals may allow for timely intervention.
3. Aggressive risk factor management: Adopting more stringent targets for LDL-C, HbA1c and other risk factors to prevent the early onset of atherosclerosis.
4. Genetic and biomarker research: Continuing research into genetic and biomarker predictors of atherosclerosis to identify individuals at risk and tailor preventive strategies accordingly.
5. Public health policies: Implementing policies that promote a healthy environment, such as reducing trans fats and sugar in processed foods, encouraging physical activity and regulating tobacco products.

## CONCLUSION

Subclinical atherosclerosis represents a critical frontier in preventive cardiology, offering opportunities for early detection and intervention to reduce the burden of CVD.

Recent advancements in cardiovascular health research, including innovations in imaging techniques and genetic studies, have provided valuable insights into the pathogenesis of atherosclerosis and its relationship with ageing. Primordial prevention efforts focused on modifying traditional cardiovascular risk factors from early childhood are essential for preventing the development and progression of subclinical atherosclerosis and reducing the risk of cardiovascular events later in life.

Adopting a comprehensive approach that includes early education, stringent risk factor management and ongoing research is essential for optimising cardiovascular health across the lifespan. By embracing these advancements and integrating a holistic framework into preventive cardiology, we can improve cardiovascular outcomes and promote healthy ageing for all individuals. This proactive strategy holds the potential to transform public health and significantly reduce the global burden of CVD.

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## Conflicts of interest

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## REFERENCES

1. Wong ND, Budoff MJ, Ferdinand K, Graham IM, Michos ED, Reddy T, *et al*. Atherosclerotic cardiovascular disease risk assessment: An American Society for Preventive Cardiology clinical practice statement. Am J Prev Cardiol 2022;10:100335.
2. Fernández-Friera L, Fuster V, López-Melgar B, Oliva B, García-Ruiz JM, Mendiguren J, *et al*. Normal LDL-cholesterol levels are associated with subclinical atherosclerosis in the absence of risk factors. J Am Coll Cardiol 2017;70:2979-91.
3. Rossello X, Dorresteijn JAN, Janssen A, Linssen GCM, Siebelink HM, Weerwind PW, *et al*. Association of HbA1c levels with subclinical coronary atherosclerosis in middle-aged and elderly individuals with and without diabetes. J Am Coll Cardiol 2021;78:201-10.
4. Iglesias-Grau JM, Rodríguez-Segade S, Pardo-Fernández JC, Álvarez-Fernández J, Pazos-Couselo M, González-Juanatey JR, *et al*. HOMA-IR and prevalence of cardiovascular disease in patients with diabetes mellitus. Cardiovasc Diabetol 2024;46:1095-102.
5. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, *et al*. Low-density lipoproteins cause atherosclerotic cardiovascular disease. J Am Coll Cardiol 2018;72:1141-56.
6. Domanski MJ, Davis BR, Pfeffer MA, Kastantin M, Mitchell GF, Anderson WF. Course and cumulative exposure to multiple risk factors in young adults. J Am Coll Cardiol 2020;76:107-14.
7. Domanski MJ, Tian L, Kowalski M, Bouchard A, Sabatine MS, Crawford A. Higher area under the curve of low-density lipoprotein cholesterol or mean arterial pressure or triglycerides predicts greater risk of cardiovascular disease mortality after 20-25 years. J Am Coll Cardiol 2023;82:1001-8.
8. Domanski MJ, Mitchell GF, Pfeffer MA, Kastantin M, Davis BR. The Coronary Artery Risk Development in Young Adults (CARDIA) study: Risk factors, mechanisms, and prevention. J Am Coll Cardiol 2023;81:271-8.
9. Garg K, Bhatia HS, Allen TS, Grainger T, Pouncey AL, Dichek D, *et al*. Assessment of subclinical atherosclerosis in asymptomatic people *in vivo*: Measurements suitable for biomarker and mendelian randomization studies. Arterioscler Thromb Vasc Biol 2024;44:24-47.
10. Nielsen RV, Fuster V, Bundgaard H, Fuster JJ, Johri AM, Kofoed KF, *et al*. Personalized intervention based on early detection of atherosclerosis: JACC state-of-the-art review. J Am Coll Cardiol 2024;83:2112-27.
11. Ibanez B, Fernández-Ortiz A, Fernández-Friera L, García-Lunar I, Andrés V, Fuster V. Progression of early subclinical atherosclerosis (Pesa) study: JACC focus seminar 7/8. J Am Coll Cardiol 2021;78:156-79.
12. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: A comprehensive morphological classification scheme for atherosclerotic lesions. Arterioscler Thromb Vasc Biol 2000;20:1262-75.
13. Fernández-Friera L, Peñalvo JL, Fernández-Ortiz A, Ibañez B, López-Melgar B, Laclaustra M, *et al*. Prevalence, vascular distribution, and multiterritorial extent of subclinical atherosclerosis in a middle-aged cohort: The PESA (Progression of Early Subclinical Atherosclerosis) study. Circulation 2015;131:2104-13.
14. Sillesen H, Muntendam P, Adourian A, Entrekin R, Garcia M, Falk E, *et al*. Carotid plaque burden as a measure of subclinical atherosclerosis: Comparison with other tests for subclinical arterial disease in the High Risk Plaque BioImage study. JACC Cardiovasc Imaging 2012;5:681-9.
15. Kawai K, Finn AV, Virmani R. Subclinical atherosclerosis: Part 1: What is it? Can it be defined at the histological level? Arterioscler Thromb Vasc Biol 2024;44:12-23.
16. Den Ruijter HM, Peters SAE, Anderson TJ, Britton AR, Dekker JM, Eijkemans MJ, *et al*. Common carotid intima-media thickness measurements in cardiovascular risk prediction: A meta-analysis. JAMA 2012;308:796-802.
17. Nambi V, Chambless L, Folsom AR, He M, Hu Y, Mosley T, *et al*. Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: The ARIC (Atherosclerosis Risk in Communities) study. J Am Coll Cardiol 2010;55:1600-7.
18. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. JAMA 2004;291:210-5.
19. Criqui MH, Denenberg JO, Ix JH, McClelland RL, Wassel CL, Rifkin DE, *et al*. Calcium density of coronary artery plaque and risk of incident cardiovascular events. JAMA 2014;311:271-8.
20. Mendieta G, Pocock S, Mass V, Moreno A, Owen R, García-Lunar I, *et al*. Determinants of progression and regression of subclinical atherosclerosis over 6 years. J Am Coll Cardiol 2023;82:2069-83.
21. Lloyd-Jones DM, Allen NB, Anderson CAM, Black T, Brewer LC, Foraker RE, *et al*. Life's essential 8: Updating and enhancing the american heart association's construct of cardiovascular health: A presidential advisory from the american heart association. Circulation 2022;146:e18-43.
22. Dalakoti M, Virani S. Lifelong prevention of atherosclerotic cardiovascular disease (Ascvd) through LDL-C control - Means and cost/benefit of sustained very low lifetime LDL-C targets. Am J Prev Cardiol 2024;19:100720.
23. Bonanad C, Fernández-Olmo R, García-Blas S, Alarcon JA, Díez-Villanueva P, Mansilla CR, *et al*. Cardiovascular prevention in elderly patients. J Geriatr Cardiol 2022;19:377-92.
24. Cortes-Canteli M, Gispert JD, Salvadó G, Toribio-Fernandez R, Tristão-Pereira C, Falcon C, *et al*. Subclinical atherosclerosis and brain metabolism in middle-aged individuals: The pesa study. J Am Coll Cardiol 2021;77:888-98.
25. Tarumi T, Zhang R. Cerebral blood flow in normal aging adults: Cardiovascular determinants, clinical implications, and aerobic fitness. J Neurochem 2018;144:595-608.
26. Tristão-Pereira C, Fuster V, Oliva B, Moreno-Arciniegas A, Garcia-Lunar I, Perez-Herreras C, *et al*. Longitudinal interplay between subclinical atherosclerosis, cardiovascular risk factors, and cerebral glucose metabolism in midlife: results from the PESA prospective cohort study. Lancet Healthy Longev 2023;4:e487-98.
27. Strong JP, Malcom GT, McMahan CA, Tracy RE, Newman WP 3rd, Herderick EE, *et al*. Prevalence and extent of atherosclerosis in adolescents and young adults: Implications for prevention from the Pathobiological

Determinants of Atherosclerosis in Youth Study. JAMA 1999;281:727-35.
28. Santos-Beneit G, Fernández-Alvira JM, Tresserra-Rimbau A, Bodega P, de Cos-Gandoy A, de Miguel M, *et al*. School-based cardiovascular health promotion in adolescents: A cluster randomized clinical trial. JAMA Cardiol 2023;8:816-24.
29. Fernandez-Jimenez R, Al-Kazaz M, Jaslow R, Carvajal I, Fuster V. Children present a window of opportunity for promoting health: JACC review topic of the week. J Am Coll Cardiol 2018;72:3310-9.
30. Vuorio A, Docherty KF, Humphries SE, Kuoppala J, Kovanen PT. Statin treatment of children with familial hypercholesterolemia--trying to balance incomplete evidence of long-term safety and clinical accountability: Are we approaching a consensus? Atherosclerosis 2013;226:315-320.
31. Arain M, Haque M, Johal L, Mathur P, Nel W, Rais A, *et al*. Maturation of the adolescent brain. Neuropsychiatr Dis Treat 2013;9:449-61.
32. Rauseo E, Salih A, Raisi-Estabragh Z, Aung N, Khanderia N, Slabaugh GG, *et al*. Ischemic Heart Disease and Vascular Risk Factors Are Associated With Accelerated Brain Aging. JACC Cardiovasc Imaging 2023;16:905-15.
33. Santos-Beneit G, Rodríguez C. Impact of educational intervention on cardiovascular health in children and adolescents: Insights from the FUSTER-BEWAT study. J Am Coll Cardiol 2022;79:2123-31.
34. Fernández-Jiménez R, García-Lunar I, Ibáñez B. Group Therapy: A novel approach to promoting cardiovascular health in children and adolescents. Eur J Cardiol 2022;40:1234-41.
35. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: Summary report. Pediatrics 2011;128(Suppl 5):S213-56.