Special Article

Plant-based diets for children as a means of improving adult cardiometabolic health

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Cardiovascular disease (CVD) is the largest contributor to global mortality, and this trend is expected to continue. Although mortality rates have been falling, adverse developments in obesity and diabetes threaten to reverse this. It has been estimated that the only viable strategy to reduce the epidemic is to focus on population-wide risk factor reduction. Primordial prevention, a strategy aimed at avoiding the development of risk factors before the disease onset, has been shown to reduce the CVD epidemic substantially. Plant-based diets appear beneficial for prevention of cardiometabolic diseases, with adult vegetarians and vegans having lower CVD risk than omnivores. Atherosclerosis starts in childhood and progresses in relation to classical CVD risk factors, which, along with dietary habits, track to adulthood. Based on this evidence, it is proposed that plant-based diets in childhood could promote cardiometabolic health in adults and thereby reduce CVD and promote longevity and health. However, the need for additional research to establish the safety of predominantly or exclusively plant-based diets in children is noted.

INTRODUCTION

Cardiovascular disease (CVD) remains the number one cause of premature mortality in the world.[1] In high-income countries, it also contributes the highest percentage of ill health in adults.[2] In most industrialized countries, CVD death rates have been declining since the late 1970s.[3] However, 2 factors threaten to reverse this trend today: aging of the population (ie, increased absolute numbers of those aged > 70 and > 80 y), which increases the lifetime exposure to the risk factors; and global increases in the prevalence of obesity and diabetes[4] and, in some countries, in mean blood pressure and smoking prevalence.[5] These trends may be beginning to cancel out the health gains linked to declines in other risk factors and better care and treatment achieved in recent decades as recently shown for younger adults in the United Kingdom, United States, and Australia.[4–6] The consequence of these antagonistic trends might be an increase in the actual burden of CVD.[4]

It has been postulated that the only strategy capable of substantially reducing the CVD burden in the current scenario is to focus on population-wide reduction of major CVD risk factors, particularly targeting cholesterol levels and blood pressure. This approach has been shown to be more effective than focusing on pharmacological intervention in high-risk individuals.[7] The potential impact of implementing risk-factor reduction policies focused on diet and lifestyle in 9 European countries has been recently quantified, and it was estimated that it would result in up to 29.1% fewer CVD deaths by 2020.[8]

However, there is increasing evidence that cardiometabolic risk in adulthood is partially determined by

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the same risk profile in childhood.[9] Therefore, interventions that target risk factors in young people could potentially be key aspects of preventive strategies in the long-term.

Diet is well established to be one of the most important factors affecting cardiovascular risk in adults.[10] A number of axes of dietary variability have been linked with cardiometabolic risk, including the consumption of saturated and trans-fats, sodium, fruits and vegetables, whole grains, fish, and nuts.[10] However, there is growing interest in one particular axis that may also relate to many of the others: namely, the proportion of the diet obtained from plants. Plant-based diets include vegan diets that exclude products of animal origin, vegetarian diets that rule out meat and fish consumption, and also dietary patterns predominantly based on plant foods with undefined and individually determined levels of animal product consumption. For the purpose of this review, vegetarian and vegan diets will be jointly defined as meat-free diets.

Beyond their potential health benefits, plant-based diets are also considered critical for long-term planetary sustainability,[11] and they are furthermore chosen for ethical reasons by those who sympathize with animal welfare movements.[12] It appears that interest in meat-free diets is growing in many countries[13]; however exact estimates of these trends are yet to be produced. These issues collectively justify greater research into how plant-based diets might be adapted to simultaneously promote health and decrease ecological damage.

In adults, dietary patterns emphasizing the intake of unprocessed foods of plant origin seem to confer substantial protection against CVD. In particular, consumption of fruit and vegetables, whole grains, nuts, and legumes has been linked inversely with CVD risk in a dose-dependent fashion.[10] In this context, it does not seem surprising that adults systematically pursuing vegetarian and vegan diets have a more favorable profile of CVD risk factors,[14,15] translating to lower prevalence of ischemic heart disease (IHD; the predominant form of CVD in Western populations) risk,[16,17] than otherwise similar nonvegetarians, with this difference primarily attributed to diet.[18] However, a note of caution is that studies are inconsistent regarding whether the rate of mortality from IHD differs between vegetarians/vegans and omnivores, with one study showing 26%–34% reductions in risk for different vegetarian diets[17] but another study found no difference.[19] Moreover, there is currently no evidence that vegetarians/vegans have lower rates of cerebrovascular disease.[17,19,20]

Some of this inconsistency in the association of diet and mortality risk could potentially be explained by differences in the uptake of treatment and other health services between vegetarians and nonvegetarians or differences in the duration of consuming the vegetarian diet. Another possibility is that the cardioprotective effects of plant-based diets relating to decreased IHD risk may be counterbalanced by a lack of beneficial effects on non-IHD CVD risk. Further research is required to improve understanding of these scenarios.

Although the overt manifestation of CVD occurs primarily in adult life, the origins of atherosclerosis start well before,[21] and the atherogenic process is influenced by measurable risk factors. So far, research on childhood cardiometabolic risk has placed greatest emphasis on markers of growth and nutritional status, including birth weight,[22,23] childhood body mass index (BMI),[24,25] and catch-up growth.[26] However, these childhood risk factors are potentially influenced by dietary composition, and healthy childhood dietary patterns have been found to be associated with lower adulthood CVD risk.[27] This might be mediated via beneficial effects of prudent diets on the CVD risk factor profile in childhood other than just BMI.

This article reviews substantial evidence on 1) the association between meat-free diets and CVD risk in adults, 2) the developmental origins of atherosclerosis, and 3) the tendency for childhood cardiometabolic risk factors to track into adulthood. This generates a new hypothesis that meat-free or plant-based diets in childhood, through their effects on blood biochemistry and other cardiovascular risk factors, offer a novel opportunity to promote a healthy childhood trajectory toward adult cardiometabolic health.

PLANT-BASED DIETS AND ADULT CARDIOVASCULAR DISEASE RISK

Diet represents a key modifiable direct risk factor for CVD, and it also impacts other components of risk, including obesity, unhealthy lipid profile, hypertension, raised blood glucose, and even physical activity level. Foods of plant origin have the most established protective effect on CVD.[10]

As previously noted, vegetarian diets may decrease the risk of IHD, which is likely to be at least partly mediated via classical CVD risk factors. Descriptive analysis of cardiovascular profile of vegetarians may thus help elucidate mechanisms through which plant-based diets exert their cardioprotective effects.

First, vegetarians and vegans have lower levels of body fat, mainly characterized by BMI. A recent systematic review that incorporated meta-analysis of 71 cross-sectional studies that examined the effect of a vegetarian diet and 19 cross-sectional studies that examined the effect of a vegan diet showed that these diets are associated with a BMI that is 1.49 kg/m^2 (95% confidence interval [CI], −1.72 to −1.25) and

1.72 kg/m^2 (95%CI, −2.21 to −1.22) lower than that of the reference omnivorous population, respectively.[20] These lower BMI values are attributed to the lower energy density of diets high in fruits and vegetables and the satiating effect of increased fiber intakes.[28] The association of obesity with CVD risk is mediated by various other risk factors,[29]which also show a better profile among people following vegetarian diets.

Second, vegetarians, especially vegans, have lower levels of total and non–high-density lipoprotein cholesterol (HDL-C). A recent systematic review with meta-analysis of observational studies showed estimates of effect size ranging from reductions of 0.72 mmol/L (95%CI, −0.8 to −0.64) in total cholesterol (TC) and 0.55 mmol/L (95%CI, −0.62 to −0.47) in low-density lipoprotein cholesterol (LDL-C) associated with vegetarian diets compared with omnivore diets (based on 64 and 46 cross-sectional studies, respectively) to reductions of 0.80 mmol/L (95%CI, −0.90 to −0.70) in TC and 0.59 mmol/L (95%CI, −0.77 to −0.40) in LDL-C associated with vegan diets compared with omnivore diets (based on 19 and 13 cross-sectional studies, respectively).[20] Both total and non-HDL cholesterol concentrations tend to be highest in meat eaters and lowest in vegans, with vegetarians having intermediate values.[30] In another systematic review and meta-analysis of 11 randomized clinical trials (7 included a vegan diet, 2 included a lacto-ovo vegetarian diet, 2 included a lacto vegetarian diet), Wang et al.[14] showed that vegetarian diets were associated with lower TC, LDL-C, and non–HDL-C, with pooled estimated effects of −0.36 mmol/L (95%CI, −0.55 to −0.17), −0.34 mmol/L (95%CI, −0.57 to −0.11), and −0.30 mmol/L (95%CI, −0.50 to −0.10), respectively. A 1–mmol/L reduction in TC and LDL-C levels results in a 26.6%–29.5% decrease in risk for any CVD-related event.[31] Therefore, the average reductions of TC and LDL-C concentrations following a vegetarian diet would correspond to a decrease in CVD risk of approximately 9.0%–10.6%.[14]

Mechanistically, vegetarian diets may reduce blood cholesterol concentrations due to their lower content of saturated fat, total fat, and cholesterol[32] and higher intakes of dietary fiber and numerous phytochemicals, all of which have been linked to lower blood lipids.[33]

Third, adults on plant-based diets have lower systolic blood pressure (SBP) and diastolic blood pressure (DBP), and lower risk of hypertension compared with meat eaters. In the cross-sectional analysis of a subset of 592 black women and men enrolled in the Adventist Health Study 2 (25% vegetarian and vegan; 75% nonvegetarian) the risk of hypertension varied among dietary groups and was lowest for vegans and highest for omnivores. The relative risk (RR) in comparison with omnivores was 0.37 (95%CI, 0.19–0.74) and 0.57 (95%CI, 0.36–0.92) for vegans and vegetarians, respectively, in a model adjusted for age, sex, and physical activity.[34] In a matched cohort study of 4109 Taiwanese nonsmokers, where each vegetarian was matched with 5 nonvegetarians by age, sex, and study site, vegetarians had a 28% lower risk (RR = 0.72; 95%CI, 0.55–0.86) for hypertension adjusting for age, sex, C-reactive protein, waist circumference, and fasting glucose.[35]

Similarly, a systematic review and meta-analysis of controlled clinical trials and observational studies showed a reduction in mean SBP (−4.8 mm Hg; 95%CI, −6.6 to −3.1) and DBP (−2.2 mm Hg; 95%CI, −3.5 to −1.0) after application of a vegetarian diet compared with the consumption of omnivorous diets (7 controlled trials with a total of 311 participants; mean age, 44.5 y) and lower mean SBP (−6.9 mm; 95%CI, −9.1 to −4.7) and DBP (−4.7 mm Hg; 95%CI, −6.3 to −3.1) associated with consumption of a vegetarian diet compared with an omnivorous diet (32 observational studies with a total of 21 604 participants; mean age, 46.6 y).[15]

Mechanistically, several dietary factors in plant-based diets, other than those affecting BMI, may account for the effects on BP. Vegetarians have higher fiber intakes,[36] which have been shown to lower blood pressure.[37] Other factors, including higher plant protein[38] and potassium intakes[39,40] and lower heme iron intake,[41] may improve blood pressure regulation. Potential mechanisms include baroreceptor sensitivity, direct vasodilatory effects, and changes in catecholamine and renin–angiotensin–aldosterone metabolism,[42] along with changes in blood viscosity.[43]

Every 10 mm Hg reduction in SBP reduces the risk of major CVD events (RR = 0.80; 95%CI, 0.77–0.83), coronary heart disease (RR = 0.83; 95%CI, 0.78–0.88), and stroke (RR = 0.73; 95%CI, 0.68–0.77).[44]

Fourth, plant-based diets are associated with lower blood glucose levels, insulin resistance, and diabetes risk.[45,46] In a systematic review and meta-analysis of observational studies, which included 27 studies with a total of 2256 vegetarian and 2192 nonvegetarian participants and 4 studies with a total of 83 vegans and 125 omnivores, plant-based diets were associated with lower blood glucose levels (vegetarians: −5.08 mg/dL, 95%CI, −5.98 to −4.19; vegans: 6.39 mg/dL, 95%CI, −12.35 to −0.41).[20] Observational studies further show that the prevalence of type 2 diabetes is 1.6–2 times lower in vegetarians than in omnivores, even after controlling for body weight.[47]

Likewise, clinical interventions in individuals with type 2 diabetes have demonstrated that adopting a vegetarian diet leads to a greater reduction in fasting plasma glucose, HbA1c, and hypoglycemic medication compared with a conventional hypocaloric diet.[48,49] These results confirm substantial protective effects of

plant-based diets,[50–53] along with the avoidance of meat,[54] on glycemic control and risk of diabetes. Mechanistically, plant-based diets may confer protective effects on diabetes risk through caloric restriction; reduced intake of saturated fatty acids; high intake of polyunsaturated and monounsaturated fatty acids; low glycemic index; increased intake of fiber; higher intake of nonheme iron and reduction in iron stores; increased intake of antioxidants, vitamins, and micronutrients; high intake of vegetable instead of animal protein; and high intake of plant sterols and prebiotics. All of these have been shown to have a positive effect on diabetes prevention.[47]

Diabetes confers an approximately 2-fold excess risk for CVD, independent of other conventional risk factors. In people without diabetes, fasting blood glucose concentration is modestly and nonlinearly associated with risk of vascular disease.[55]

Finally, lower levels of C-reactive protein (CRP) have been reported in adult vegetarians (0.77 mg/L, standard error [SE], 1.29 for vegetarians; 1.30 mg/L, SE, 1.38 for matched omnivores; $P < 0.01$),[56] and a decrease in CRP was observed in adults adopting vegan diets (−28.2%; SE, 10.8%; $P = 0.02$).[57] Some studies have shown that healthy adult lactovegetarians have lower carotid intima media thickness (IMT),[58] with the advantage related to the duration of consumption of the vegetarian diet,[59] but 1 study showed no such difference.[60]

Altogether, a lower prevalence of cardiometabolic risk factors among adults following plant-based diets is likely to be the primary reason why they have an approximately 25% lower risk of developing IHD.[16,20] The overall pattern in which vegetarian or vegan diets affect IHD risk factors and incidence is illustrated in Figure 1. The effects of meat-free diets on cardiovascular risk factors are summarized in Table 1[14,15,20,34,35,45,46,48,56,57]. However, although the main burden of CVD morbidity and mortality occurs in adults, there is compelling evidence that CVD risk is strongly shaped by experience at earlier ages.

ATHEROSCLEROSIS STARTS IN CHILDHOOD

Atherosclerosis comprises arterial lesions that are a fundamental component of adult CVD. These lesions develop over time, starting with the relatively harmless accumulation of lipid-filled macrophages, called fatty streaks, and progressing to more advanced stages where the streaks are raised and vulnerable to rupture, manifesting as fibrous and calcified plaques.[61] Histological studies indicate that the clinically consequential lesions develop from these initially harmless changes in symptomatic individuals.[62]

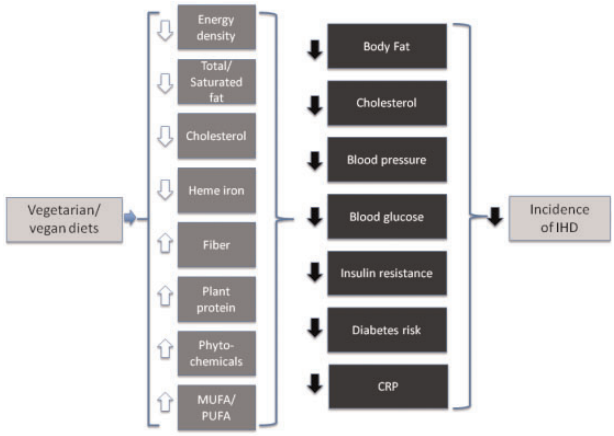

Figure 1 **The overall pattern by which vegetarian/vegan diets affect ischemic heart disease risk factors and incidence.** *Abbreviations:* CRP, C-reactive protein; IHD, ischemic heart disease; MUFA, monounsaturated fatty acid ; PUFA, polyunsaturated fatty acid.

Early autopsy studies first suggested that atherosclerosis begins early in life. Enos et al.[63] showed gross evidence of coronary atherosclerosis among autopsies of 77.3% of US soldiers (average age, 22 years) killed in the Korean war.[3]

Around the same time, Holman et al.[21] demonstrated the presence of fatty streaks in the aortas of children as young as 3 years. Subsequently, McNamara et al.[64] reported atherosclerosis in 45% and severe coronary atherosclerosis in 5% of 105 autopsies of US soldiers killed in Vietnam.

More recently, the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study described the emergence of clinically consequential atherosclerotic lesions in a large sample of autopsied persons aged 15–34 years who died in accidents.[61] Other studies found some degree of fatty streaks in the aorta in all persons aged 12–15 years[65] and fatty streaks in the coronary arteries in approximately 30% of children aged 8–11 years and 69% of persons aged 12–15 years.[62] The clinical importance of these lesions depends on their anatomical location.

Although epidemiological studies have not directly confirmed the link between the early presence of aortic fatty streaks and the occurrence of clinicallyconsequential atherosclerotic plaques in later life,[66,67] there is a relationship between the location of fatty streaks in the coronary arteries in children and atherosclerotic lesions in the same site later in life.[68] In nonblack populations, the extent of involvement of coronary artery with fatty streaks in youth predicts the extent of involvement with raised lesions in older persons.[69] In an autopsy study of coronary arteries of 565 individuals aged 0–29 years, the progressive transformation of fatty streaks in

Table 1 **Effects of vegetarian diets on cardiovascular risk factors**

Study design	Populations	CVD risk factor	Key findings	Reference group	References
Systematic review and meta-analysis of cross-sectional studies	71 studies for vegetarian and 19 studies for vegan diet	BMI	−1.49 kg/m^2 (95%CI, −1.72 to −1.25) for vegetarians; −1.72 kg/m^2 (95%CI, −2.21 to −1.22) for vegans	Various otherwise similar nonvegetarian populations	Dinu et al. (2017)[20]
Systematic review and meta-analysis of cross-sectional studies	64 studies for vegetarian and 19 studies for vegan diet	Total cholesterol	−0.72 mmol/L (95%CI, − 0.8 to −0.64) for vegetarians; −0.80mmol/L (95%CI, −0.90 to −0.70) for vegans	Various otherwise similar nonvegetarian populations	Dinu et al. (2017)[20]
Systematic review and meta-analysis of cross-sectional studies	46 studies for vegetarian and 13 studies for vegan diet	LDL cholesterol	−0.55 mmol/L (95%CI, −0.62 to −0.47) for vegetarians; −0.59 mmol/L (95%CI, −0.77 to −0.40) for vegans	Various otherwise similar nonvegetarian populations	Dinu et al. (2017)[20]
Systematic review and meta-analysis of randomized clinical trials	7 trials of intervention with vegan diet and 4 trials of intervention with vegetarian diet	Total cholesterol	−0.36 mmol/L (95%CI, 0.55 to −0.17) with intervention with vegetarian or vegan diet (pooled estimates)	Trial control period	Wang et al. (2015)[14]
Systematic review and meta-analysis of 11 randomized clinical trials	7 trials of intervention with vegan diet and 4 trials of intervention with vegetarian diet	LDL cholesterol	−0.34 mmol/L (95%CI, −0.57 to −0.11) with intervention with vegetarian or vegan diet (pooled estimates)	Trial control period	Wang et al. (2015)[14]
Systematic review and meta-analysis of 11	7 trials of intervention with vegan diet and 4 trials of intervention with vegetarian diet	non-HDL cholesterol	−0.30 mmol/L (95%CI, −0.50 to −0.10) with intervention with vegetarian or vegan diet (pooled estimates)	Trial control period	Wang et al. (2015)[14]
Adventist Health Study 2, a cohort study	96 000 participants (7% vegan, 29.2% vegetarian)	Risk of hypertension	RR = 0.86 (95%CI, 0.51– 1.45) for vegetarians; RR = 0.53 (95%CI, 0.25–1.11) for vegans	Nonvegetarian Adventists	Orlich et al. (2014)[34]
Matched cohort study	4109 Taiwanese nonsmokers	Risk of hypertension	RR = 0.72 (95%CI, 0.55–0.86) for vegetarians	5 omnivores matched to 1 vegetarian by age, sex, and study site	Chuang et al. (2016)[35]
A systematic review and meta-analysis of controlled clinical trials and observational studies	7 trials, a total of 311 participants, mean age of 44.5 y; 32 observational studies, a total of 21 604 participants, mean age of 46.6 y	Systolic blood pressure	A reduction in mean systolic blood pressure (−4.8 mm Hg; 95%CI, −6.6 to −3.1) for vegetarian diet	Trial control period	Yokoyama et al. (2014)[15]
			Lower mean systolic blood pressure (−6.9 mm Hg; 95%CI, −9.1 to −4.7) for vegetarian diet	Various otherwise similar nonvegetarian populations	
A systematic review and meta-analysis of controlled clinical trials and observational studies	7 trials, a total of 311 participants, mean age of 44.5 y; 32 observational studies, a total of 21 604 participants, mean age of 46.6 years	Diastolic blood pressure	A reduction in mean diastolic blood pressure (−2.2 mm Hg; 95%CI, −3.5 to −1.0) for vegetarian diet	Trial control period	Yokoyama et al. (2014)[15]

(continued)

Table 1 **Continued**

Study design	Populations	CVD risk factor	Key findings	Reference group	References
			Lower mean systolic BP (−4.7 mm Hg; 95%CI, −6.3 to −3.1) for vegetarian diet	Various otherwise similar nonvegetarian populations	
Two prospective cohort studies	Adventist Health Study 1 (25 698 participants; approximately 50% vegetarians) and 2 (60 903 participants; 52% vegetarians)	Prevalence of diabetes	1.5–2 times lower	Nonvegetarian Adventists	Snowdon and Phillips (1985)[46] Tonstad et al. (2009)[45]
Systematic review and meta-analysis of observational studies	27 studies with 2256 vegetarian and 2192 nonvegetarian participants; 4 studies of 83 vegans and 125 omnivores	Blood glucose levels	−5.08 mg/dL (95%CI, −5.98 to −4.19) for vegetarians; −6.39 mg/dL (95%CI, −12.35 to −0.41) for vegans	Various otherwise similar nonvegetarian populations	Dinu et al. (2017)[20]
Review	2 randomized clinical trials of interventions with vegetarian diet in diabetes including 43 and 74 participants with diabetes	Effect on various diabetes markers	A greater reduction in various measures of diabetes, including body weight, fasting plasma glucose, HbA1c, and hypoglycemic medication and greater increase in insulin sensitivity with vegetarian diet	Hypocaloric diet or a diet recommended by American Diabetes Association	Kahleova et al. (2015)[47]
Cross-sectional study	30 long-term ($\geq$ 5 years) vegetarians and 30 age- matched omnivores	CRP levels	Lower CRP levels in vegetarians (0.77 mg/L; SD, 1.29; $P < 0.01$) than in omnivores (1.30 mg/L; SD, 1.38)	Matched omnivores	Szeto et al. (2004)[56]
Randomized control trial	46 healthy, hyperlipidemic adults randomized to a diet low in saturated fat and a vegetarian diet high in plant sterols	Effect on CRP levels	Vegetarian diet intervention reduced CRP levels by 28.2% (SE, 10.8%; $P = .02$), whereas control diet reduced CRP by 10% (SE, 8.6%; $P = 0.27$)	Control arm of the clinical trial	Jenkins et al. (2003)[57]

Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; CRP, C-reactive protein; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RR, relative risk; SD, standard deviation; SE, standard error.

children's coronary arteries to a well-advanced fibrous plaque in young adulthood was observed.[70] In this study, by puberty a small 8%–10% percentage of children had evidence of more advanced lesions, and approximately 30% of the adults in their 20s had well-developed raised lesions with large extracellular lipid cores and thick fibromuscular caps.[70]

Overall, the evidence indicates that the atherosclerotic process starts in the early years. This emphasizes the importance of understanding the factors contributing to variability of its severity among individuals during childhood.

CHILDHOOD ANTECEDENTS OF ADULT ATHEROSCLEROSIS AND CLINICAL CARDIOVASCULAR DISEASE

The only direct evidence linking cardiometabolic risk factors other than BMI in youth[71] with overt clinical disease in adulthood comes from genetic disorders related to high cholesterol. In homozygous familial hypercholesterolemia, a genetic disease whereby LDL-C clearance is impaired, LDL-C levels exceed 20.68 mmol/L already in infants, CVD events begin in the first decade of life, and life span is reduced.[72] In heterozygous hypercholesterolemia, in which LDL-C levels usually exceed 5.17 mmol/L and TC levels exceed 6.5 mmo/L beginning in infancy, 50% of men and 25% of women experience clinical coronary events by the age of 50 years.[72] Furthermore, in familial hypertriglyceridemia, another genetic disorder resulting in excessive triglyceride (TG) levels, childhood TG levels independently predict CVD in the 4th–5th decade of life.[73]

The substantial genetic component of CVD risk can also be seen among children of patients suffering from premature myocardial infarction (<55 y), who have higher levels of TC, LDL-C, and TGs and lower levels of HDL-C than controls.[74] Another piece of evidence linking childhood blood lipids with CVD risk in adulthood in the context of genetic predisposition stems from Mendelian randomization studies. Meta-analysis of such studies found a 54.5% (95%CI, 48.8%–59.5%) reduction in the risk of IHD per millimole-per-liter reduction in LDL-C (effect size 3-fold greater than that achieved via treatment with statins in later life) due to genetic polymorphism, and thus relating to lower low-density lipoprotein cholesterol lifetime exposure.[75]

Most evidence suggesting that childhood cardiometabolic physiology affects adult arterial pathology is indirect and comes from autopsy and imaging studies linking childhood risk factors with atherosclerosis and its surrogate markers. The extent to which the artery surface is involved in individual children with lesions varies; however, it is influenced by the same classical risk factors that predict adult coronary heart disease.[62,76] The Bogalusa Heart Study has demonstrated a strong association of BMI, SBP, DBP, and serum concentrations of TC, TGs, LDL-C, and HDL-C with vascular lesions in children and young adults on autopsy.[77]

The PDAY autopsy study showed strong relationships between atherosclerotic severity and extent with age, non–HDL-C, HDL-C, hypertension (determined by renal artery thickness), tobacco use (thiocyanate concentration), diabetes mellitus (glycohemoglobin), and (in men) obesity. It also showed that a 30 mg/dL incremental increase in non–HDL-C was equivalent to 2 years of "vascular aging."[78] The severity and extent of the lesions were positively associated with age and increased in association with the number of risk factors. At the same time, an absence of risk factors was associated with a virtual absence of advanced atherosclerotic lesions, even in the oldest individuals in the study.

Analyses from 4 longitudinal cohorts (Cardiovascular Risk in Young Finns Study, Childhood Determinants of Adult Health Study, Bogalusa Heart Study, and Muscatine Study) showed that risk factors measured at age 9 years or after (TC, TGs, blood pressure, and BMI) were predictive of elevated carotid IMT in adulthood,[79] which is recognized as a predictive measure of clinical coronary events in middle-aged and elderly populations.[80] Similarly, SBP, DBP, TC, LDL-C, HDL-C, and smoking status were linked to IMT of the femoral artery, a surrogate measure of coronary and peripheral atherosclerosis, in asymptomatic young individuals in the Bogalusa Heart Study.[81]

Additionally, in the Cardiovascular Risk in Young Finns Study, childhood LDL-C ($\geq$80th percentile), elevated blood pressure, skinfold thickness, low HDL-C ($\leq$20th percentile), and smoking were inversely associated with artery elasticity in adulthood,[82] a marker of pathophysiological changes in the arteries relevant to the development of atherosclerosis later in life.[83] Increased body size, increased blood pressure, and decreased HDL-C were associated with coronary artery calcification in young adults in the Muscatine Study.[84]

Other studies have examined the relationship of isolated childhood risk factors to various measures of atherosclerosis and CVD risk. Dietary fat quality reflected in the serum cholesterol ester fraction in childhood was associated with carotid IMT in adult women.[85] Children with hypercholesterolemia and diabetes showed increased IMTs compared with healthy controls,[86] and cumulative exposure to hyperlipidemia in young adulthood increased subsequent risk of coronary heart disease in a dose-dependent fashion.[87] Other, nondiet-related risk factors such as smoking[88] and exercise[89] in childhood were also associated with

adult atherosclerosis in a pattern similar to that in adulthood.

Collectively, all of these studies indicate that modifiable phenotypic traits in childhood, including diet and body fatness, are associated with the early emergence of atherosclerotic progression to calcified plaque, manifesting as overt CVD in adult life. Children with fewer cardiometabolic risk factors show lower prevalence of atherosclerotic risk in later life. Dietary-influenced risk factors in childhood and their relation to atherosclerosis are summarized in Table 2[77–79,81,82,84,86].

TRACKING OF CHILDHOOD CARDIOVASCULAR DISEASE RISK FACTORS AND THEIR DETERMINANTS INTO ADULTHOOD

Cardiometabolic risk factors in childhood deserve attention not only because of their association with atherosclerosis in adulthood but also because there is evidence that they track (ie, persist) into adult life, therefore generating a cumulative impact on the process of disease. Evidence for tracking is strongest for obesity, with childhood BMI levels predictive of adult obesity.[90] A recent systematic review of 13 prospective or retrospective longitudinal studies published after 2001 showed that the risk of an overweight child becoming an overweight adult is at least twice as high compared with normal-weight children, and it is even higher for obese children.[91] This could be due to both the direct tracking of body composition and the tracking of obesity-related behaviors—such as physical inactivity and unhealthy diets—between childhood and adulthood.[92]

Correlation coefficients for cholesterol tracking are in the range of 0.4 and have been found consistently in numerous studies examining children as young as 5–10 years of age and their lipid levels 20–30 years later.[72] In the Muscatine Study, 75% of children aged 5–10 years who had TC concentrations > 90th percentile at baseline had TC concentrations > 200 mg/dL in their early 20s.[93,94] In the Bogalusa Heart Study, approximately 50% of those children who had TC levels or LDL-C levels above the 75th percentile at baseline had elevated levels 12 years later.[95] In the same study, adverse glucose levels in childhood not only persisted into adulthood but also predicted adult prediabetes and type 2 diabetes.[96]

In a retrospective cohort study of 1058 normoglycemic, 37 prediabetic, and 25 type 2 diabetic adults aged 19–39 years followed on average for 17 years since childhood, at least 50% of the individuals who ranked in the top childhood quintile for glucose, insulin, and homeostatic model assessment (HOMA) insulin resistance had measurements above the 60th percentile in adulthood.[96]

Elevated blood pressure in youth predicts adult hypertension, and a systematic review and meta-analysis of 50 cohort studies reported degree of tracking with correlation coefficient at 0.38 for SBP and 0.28 for DBP.[97]

Tracking of CRP levels was observed between childhood and adulthood in a cohort of 1617 individuals aged 3–18 years at baseline and reexamined at 24–39 years of age. The age- and sex-specific correlations were the highest in the group aged 18 years at baseline ($r = 0.47$ in females, $r = 0.32$ in males).[98]

Of particular relevance to this review, diet itself, one of the strongest correlates of cardiometabolic risk, also tracks from childhood into adulthood. The Cardiovascular Risk in Young Finns Study, a prospective cohort study with a 21-year follow-up, found some level of tracking of dietary patterns.[99] Similarly, a review of studies published between 2003 and 2013 reported moderate level of tracking for a range of eating behaviors (eg, food preferences, dietary variety, dietary intake, eating habits) measured before 10 years of age and reassessed in adulthood.[100]

IMPORTANCE OF PRIMORDIAL PREVENTION

As discussed at the outset of this review, the considerable gains made in reducing CVD mortality rates since the 1970s through risk factor reductions and better treatment of the disease are increasingly challenged by adverse trends in obesity and diabetes.[101,102] Better treatment strategies are not expected to offset these adverse trends[7,103] and would increase exponentially medical costs given the aging of most populations. Moreover, treatment strategies reduce but do not eliminate the risk of CVD.[104,105]

Therefore, risk factor reduction strategies are critical for reducing the CVD burden. Numerous modeling studies have estimated that population-wide risk factor reductions can bring substantial decreases of CVD burden,[8,106–108] even taking into account current trends of obesity and diabetes. It has also been shown that mortality trends respond very rapidly to changes in risk factors at the population level.[109]

Given compelling evidence that the atherosclerotic process starts in childhood and is linked to well-defined, modifiable risk factors that track into adulthood, there is increasing recognition that primordial prevention (ie, avoiding the development of risk factors before the disease onset) should be embraced as a major component of global CVD prevention policies.[110] This is an approach through which favorable patterns for all lifestyle (eg, physical activity, avoidance of smoking) and all

Table 2 **Dietary-influenced risk factors in childhood and their relation to atherosclerosis**

Study	Population	Findings	Locations of the lesions measured	Additional information	References
Bogalusa Heart Study	Autopsies on 204 young persons aged 2–39 y	A strong association of BMI, SBP, DBP, and serum concentrations of total cholesterol, TG, LDL-C, and HDL-C with vascular lesions in children and young adults on autopsy	Coronary arteries, aorta	The association between less advanced lesions (fatty streaks) and more advanced ones (fibrous plaques) was much stronger in the coronary arteries than in the aorta	Berenson et al. (1998)[77]
Pathobiological Determinants of Atherosclerosis in Youth study	> 3000 autopsies of persons aged 15–34 y	Strong relationships between atherosclerotic severity/extent with age, non–HDL-C, HDL-C, hypertension, tobacco use, diabetes mellitus, and (in men) obesity on autopsy	Left anterior descending coronary artery, right coronary artery, and abdominal aorta	Severity and extent of lesions positively associated with age and with number of risk factors	McMahan et al. (2006)[78]
4 longitudinal cohorts (Cardiovascular Risk in Young Finns Study, Childhood Determinants of Adult Health study, Bogalusa Heart Study, and Muscatine Study)	4380 members of 4 prospective cohorts with cardiovascular risk factor data from childhood (aged 3–18 y) and IMT in adulthood (aged 20– 45 y)	Risk factors at age > 9 y (total cholesterol, TG, blood pressure, and BMI) were predictive of elevated carotid IMT in adulthood	Carotid IMT	The associations with risk factors measured at age 3 y and 6 y were weaker and nonsignificant	Juonala et al. (2010)[79]
Bogalusa Heart Study	1080 black and white individuals (aged 24–43 y; 71% white, 43% male); individuals in the top (n = 54) vs bottom fifth (n = 54) percentiles distribution of femoral IMT were compared for traditional cardiovascular risk factors profile	SBP, DBP, total cholesterol, LDL-C, HDL- C, and smoking status were linked to IMT of the femoral artery	Femoral artery IMT		Paul et al. (2005)[81]
Cardiovascular Risk in Young Finns Study	2255 healthy white adults aged 24–39 y who had risk factor data available since childhood	Childhood LDL-C (≥80th percentile), elevated blood pressure, skinfold thickness, low HDL-C (≤20th percentile), and smoking were inversely associated with artery elasticity in adulthood	Carotid artery elasticity comprising carotid artery compliance, Young's elastic modulus, and stiffness index	Associations remained highly significant after adjustment for the number of risk factors identified in adulthood	Juonala et al. (2005)[82]

(continued)

Table 2 **Continued**

Study	Population	Findings	Locations of the lesions measured	Additional information	References
Muscatine Study	384 individuals (197 men, 187 women) who had coronary risk factors measured in childhood (mean age, 15 y) and twice during young adult life (mean ages, 27 and 33 y)	Increased body size, increased blood pressure, and decreased HDL-C were associated with coronary artery calcification in young adults			Mahoney et al. (1996)[84]
Cross-sectional study	88 children (aged 11 ± 2 y)	Children with hypercholesterolemia and diabetes showed increased IMTs compared with healthy controls	Aortic and carotid IMT		Järvisalo et al. (2001)[86]

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; IMT, intima media thickness; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglicerydes.

major lifestyle-related risk factors (eg, cholesterol, hypertension, glucose levels) can be promoted from conception throughout childhood. Those patterns can then potentially be maintained into adulthood.[111]

The concept of primordial prevention is strongly backed by data. Two prospective studies from the late 1960s and 1970s—the Chicago Heart Association Detection Project in Industry Study[112] (n = 8816) and the Multiple Risk Factor Intervention Trial Study[113] (n = 12 866)—showed that favorable levels of all readily-measured major CVD risk factors in young adulthood (TC < 5.17 mmol/L; SBP ≤ 120 mm Hg; DBP ≤ 80 mm Hg; BMI < 25.0 kg/m^2) lead to substantially reduced CVD mortality rates (76%–89% for men and 60%–67% lower in women) and sizable increases in life expectancy (8–12 y greater).

So far, CVD prevention strategies targeting early life have primarily been focused on tackling childhood obesity, although success rates are poor.[114] Interest has also focused on factors like birth weight[23] and early catch-up growth,[26] although some of these traits are difficult to target through interventions because of the need to change maternal physiology. It is known, however, from the Cardiovascular Risk in Young Finns Study, Childhood Determinants of Adult Health Study, Bogalusa Heart Study, and Muscatine Study, that other classical CVD risk factors relate to adult atherosclerosis independently from BMI[79] and would therefore benefit from additional interventions. For example, recent evidence from the United States suggests that up to one third of prepubertal children with normal weight have abnormal lipid levels[115] and that the prevalence of hypertension in the pediatric population has been increasing.[116]

Therefore, interventions effectively targeting all classical risk factors in young people could potentially play a key role in preventive strategies. Linking the 2 components of this review—that adults consuming plant-based diets have lower CVD risk and that cardiometabolic risk tracks from childhood into adulthood—a new testable hypothesis is now proposed: namely, that a plant-based diet in childhood could promote cardiometabolic health in adults, thereby reducing CVD and promoting longevity and health.

PLANT-BASED DIETS IN CHILDHOOD AS A MEANS TO PROMOTE CARDIOMETABOLIC HEALTH IN ADULTHOOD

Diet in children appears to be one of the strongest determinants of the CVD risk factors.[117] Additionally, childhood diets show some degree of tracking into adulthood[99,100] and associate with adulthood cardiovascular risk factors, vascular markers of subclinical

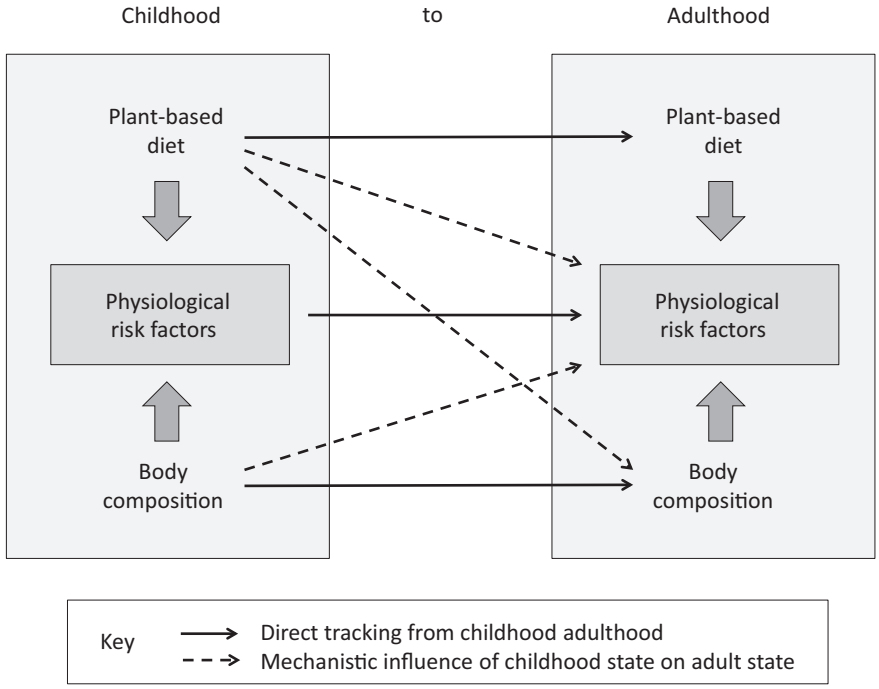

Figure 2 **Potential direct and indirect mechanisms through which plant-based diets in children could benefit cardiometabolic health in adults.**

atherosclerosis, and CVD risk.[27] The few available studies in this area suggest that healthy childhood dietary patterns are associated with lower adulthood CVD risk.[27,118] Intakes of plant foods (vegetables, fruits, and fiber) and polyunsaturated fatty acids have shown protective effects.[27,118]

Vegan and vegetarian children have lower rates of overweight and obesity.[28] Preliminary evidence suggests that they have lower cholesterol levels[119,120] and higher antioxidant status in the blood.[121] They consume more fruits and vegetables than their omnivore counterparts.[122,123] Moreover, a recent trial showed that an intervention with low-fat vegan diet was more effective than the American Heart Association–recommended diet at reducing CVD risk factors in obese and hypercholesterolemic children aged 9–18 years old. Children assigned to the vegan intervention had more significant ($P < 0.05$) reductions in CVD risk factors from baseline—BMI *Z*-score (−0.14), systolic SBP (−6.43 mm Hg), TC (−22.5 mg/dL), LDL-C (−13.14 mg/dL), high sensitivity CRP (−2.09 mg/L), insulin (−5.42uU/ml), myeloperoxidase (−75.34 pmol/L), midarm circumference (−2.02 cm), weight (−3.05 kg)—whereas in the American Heart Association group significant ($P < 0.05$) were noted only for the last 3 risk factors (−69.23 pmol/L,/−1.55 cm, −1.14 kg, respectively) and waist circumference (−2.96 cm).[124]

Therefore, vegetarian and vegan children might have a better CVD risk profile than omnivore children, and if the diet and risk profile tracks into adulthood, plant-based diets in pediatric populations, through their effects on blood biochemistry, other cardiovascular risk factors, and the establishment of healthy eating patterns, could offer an effective strategy of CVD primordial prevention. This would present a novel opportunity to promote a healthy childhood trajectory toward cardiovascular health (see Figure 2).

At the same time, data on the safety of vegetarian diets in childhood are sparse and suggest increased risk of nutrient deficiencies, especially in vegan children, including some deficiencies that can differentially affect CVD risk, such as deficiencies in vitamin B12, vitamin D, n-3 essential fatty acids, and iron.[122,125] Therefore 2 issues are of importance. First, further research is required to comprehensively assess the safety, along with the CVD-protective potential, of vegetarian and vegan diets in childhood. Second, preventive strategies should potentially consider not only promoting vegatarian diets per se but also increasing the percentage of plant foods within omnivore diets in children.

CONCLUSION

The population-wide reduction of CVD risk factors seems currently to be the only feasible strategy to combat the CVD epidemic. More attention should be given to pediatric populations in this context to take advantage of primordial prevention. Atherosclerosis starts in

early life and progresses in relation to the same classical risk factors in children that influence the course of the disease in adults. Moreover, these risk factors, along with dietary habits, track into adulthood. Children with fewer cardiometabolic risk factors show lower prevalence of atherosclerotic risk in later life. Plant-based diets have been shown to substantially reduce CVD risk factors, morbidity, and mortality in adults and also offer planetary sustainability benefits. If applied in children, they could potentially offer cardiometabolic health benefits through reduction of CVD risk beginning in early life, a strategy that has been shown to bring the most favorable CVD mortality reductions and increases in life expectancy. At the same time, little is known about the safety and potential cardiometabolic benefits of these diets applied from childhood, and further research in this area is warranted.

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