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5) Abstract:

Cardiovascular disease (CVD) is the largest contributor to global mortality and this trend is expected to continue. Mortality rates have been falling, however adverse developments in obesity and diabetes could 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 cardio-metabolic 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, we propose the hypothesis that plant-based diets in childhood could promote cardio-metabolic health in adults, and thereby reduce CVD and promote longevity and health. However, we also note the need for additional research to establish the safety of predominantly or exclusively plant-based diets in children.

6) Key words: vegetarian diets, children, primordial prevention, cardiovascular disease, cardiovascular disease risk factors

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, two factors threaten to reverse this trend today: ageing of the population (i.e. increased absolute numbers of those aged 70+ and 80+ years) 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 UK, US and Australia.[4, 5,6] 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 cardio-metabolic risk in adulthood is partially determined by 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 cardio-metabolic 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.

Going beyond their potential health benefits, it is notable that 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, as we review in detail below, dietary patterns emphasizing the intake of unprocessed foods of plant origin seem to confer substantial protection against CVD. In particular, fruit and vegetables, whole grains, nuts and legumes consumption has been linked inversely with CVD risk in dose-dependent fashion.[10] In this context, it does not seem surprising that adults systematically pursuing vegetarian and vegan diets have a more favourable 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 non-vegetarians, primarily attributed to their 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 reporting no difference [19]. Moreover, there is currently no evidence that vegetarians/vegans have lower rates of cerebrovascular disease. [17,20, 19]

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 non-vegetarians; 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 counter-balanced by a lack of beneficial effects on non-IHD CVD risk. Further research is required to improve understanding of these scenarios.

While the overt manifestation of cardiovascular disease 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 cardio-metabolic 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.

In this article we therefore review substantial evidence on (a) the association between meat-free diets and CVD risk in adults, and (b) the developmental origins of atherosclerosis, and (c) the tendency for childhood cardio-metabolic 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 towards adult cardio-metabolic health.

Plant based diets and adult CVD 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. It is foods of plant origin that 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 characterised by BMI. A recent systematic review incorporating meta-analysis of 71 cross-sectional studies examining the effect of a vegetarian diet and 19 cross-sectional studies examining the effect of a vegan diet showed that these diets are associated with 1.49 kg/m^2 (95% CI −1.72 - −1.25) and 1.72 kg/m^2 (95% CI −2.21- −1.22) lower BMI, 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 fibre intakes.[28] The association of obesity with CVD risk is mediated by various other risk factors.[22] And these, as well, show a better profile among people following vegetarian diets.

Second, vegetarians, especially vegans, have lower levels of total and non-HDL cholesterol. A recent systematic review with meta-analysis of observational studies showed estimates of effect size ranging from 0.72 mmol/L(95% CI− 0.8 - −0.64) reductions in total cholesterol and 0.55 mmol/L (95% CI −0.62 - −0.47) in LDL cholesterol (LDL-C) associated with vegetarian diets compared to omnivore diets (based on 64 and 46 cross sectional studies respectively) and 0.80 mmol/L (95% CI− 0.90 - −0.70) reductions in total cholesterol and 0.59 mmol/L (95% CI −0.77 -−0.40) in LDL-C associated with vegan 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 randomised 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 significantly lower total cholesterol, LDL-C and non-HDL with pooled estimated effects of -0.36 mmol/L (95% confidence interval (95% CI- 0.55-−0.17), -0.34 mmol/L (95% CI −0.57-−0.11), and -0.30 mmol/L(95% CI −0.50-−0.10) respectively. A 1-mmol/L reduction in TC and LDL-C levels results in a 26.6% to 29.5% decrease for any cardiovascular disease–related event.[31] Therefore, the average reductions of TC and LDL-C concentrations following a vegetarian diet would correspond to a decrease in cardiovascular disease risk of about 9.0% to 10.6%.[14]

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

Third, adults on plant based diets have lower systolic (SBP) and diastolic blood pressures (DBP), and lower risk of hypertension, compared to meat eaters. In the cross-sectional analysis of a sub-set of 592 black women and men enrolled in the Adventist Health Study-2 (25% vegetarian and vegan; 75% non - vegetarian) the risk of hypertension varied among

dietary groups and was lowest for vegans and highest for omnivores. The relative risk (RR) in comparison to omnivores was 0.37 (95% CI 0.19- 0.74) and 0.57 (95% CI 0.36-0.92) 0.53 for vegans and vegetarians respectively in a model adjusted for, age, sex, physical activity.[34] In a matched cohort study of 4109 Taiwanese non-smokers, where each vegetarian was matched with five non-vegetarians by age, sex, and study site, vegetarians had 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 - −3.1) and DBP (−2.2 mm Hg; ; 95% CI −3.5 -−1.0) after application of a vegetarian diet compared with the consumption of omnivorous diets (7 controlled trials, including 311 participants; mean age, 44.5 years) and lower mean SBP (-6.9 mm; CI, −9.1 - −4.7) and DBP (-4.7 mm Hg; 95% CI, −6.3 -−3.1) associated with consumption of vegetarian compared with omnivorous diets (32 observational studies; a total of 21,604 participants; mean age 46.6 years).[15]

Mechanistically, several dietary factors in plant-based diets, other than those affecting BMI, may account for their effects on BP. Vegetarians have higher fibre intakes,[36] which have been shown to lower blood pressure.[37] Other factors, including higher plant protein[38] and potassium intake[39,40] and lower haem 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.[38]

Every 10 mm Hg reduction in SBP significantly reduces the risk of major cardiovascular disease 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] In a systematic review and meta-analysis of observational studies, including 27 studies with 2256 vegetarian and 2192 non-vegetarian participants, and 4 studies of 83 vegans and 125 omnivores, plant-based diets were significantly associated with lower blood glucose levels (vegetarians −5.08 mg/dL, 95% CI −5.98 - −4.19; vegans - 6.39 mg/dL, 95% CI −12.35 - −0.41).[20] Observational studies further show that the prevalence of type 2 diabetes is 1.6 to 2 times lower in vegetarians compared to omnivores, even after controlling for body weight.[46, 47]

Likewise, clinical interventions in subjects 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 to a conventional hypocaloric diet.[47,48] These results confirm substantial protective effects of the portfolio of foods found in plant-based diets, [49] [50,**51**, **52**] along with the avoidance of meat,[53] on glycaemic 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 glycaemic index, increased intake of fibre, higher intake of non-haem 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.[46]

Diabetes confers about a two-fold excess risk for CVD, independently from other conventional risk factors. In people without diabetes, fasting blood glucose concentration is modestly and non-linearly associated with risk of vascular disease.[54]

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),[55] and a decrease in CRP was observed in adults adopting vegan diets (-28.2%; (SE 10.8%), P = .02).[56] Some studies have shown that healthy adult lacto vegetarians have significantly lower carotid intima media thickness (IMT)[57], and the advantage was related to the duration of consuming the vegetarian diet[58], but one study showed no such difference.[59]

Altogether, a lower prevalence of cardio-metabolic risk factors among adults following plant-based diets is likely to be the primary reason why they have ~25% lower risk of developing ischemic heart disease.[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 summarised in Table 1.

However, while 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.[60]

Histological studies indicate that the clinically significant lesions develop from these initially harmless changes in symptomatic individuals.[61]

It was early autopsy studies that first suggested that atherosclerosis begins early in life. Enos et al.[62] showed gross evidence of coronary atherosclerosis among autopsies of 77.3% US soldiers, average age 22 years, killed in the Korean war.[2]

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[63] 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 significant atherosclerotic lesions in a large sample of autopsied persons aged 15–34 years who died in accidents.[60] Other studies reported some degree of fatty streaks in the aorta in all 12-15 year olds,[64] and fatty streaks in the coronary arteries in~30% of children aged 8-11 years and 69% of 12-15 year olds.[61] The clinical significance of these lesions depends on their anatomical location.

While epidemiological studies have not directly confirmed the link between the early presence of aortic fatty streaks and the occurrence of clinically significant atherosclerotic plaques in later life,[65,66] 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.[67] In non-black populations, the extent of involvement of coronary artery with fatty streaks in youth predicts the extent of its involvement with raised lesions in older persons.[68] In an autopsy study of coronary arteries of 565 subjects aged 0 to 29 years, the progressive transformation of fatty streaks in children's coronary arteries to a well-advanced fibrous plaque in young adulthood was observed.[69] In this study, by puberty a small 8%-10% percentage of children

had evidence of more advanced lesions and about 30% of the young adults in their twenties had well-developed raised lesions with large extracellular lipid cores and thick fibromuscular caps.[69]

Overall, the evidence indicates that atherosclerotic process starts in the early years, and this emphasises the importance of understanding the factors contributing to variability between individuals during childhood.

Childhood antecedents of adult atherosclerosis and clinical CVD

The only direct evidence linking cardio-metabolic risk factors other than BMI in youth [70] with overt clinical disease in adulthood comes from genetic disorders related to high cholesterol.

In homozygous familial hypercholesterolemia, a genetic disease whereby LDL cholesterol 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[71]. In heterozygous hypercholesterolemia, in which LDL-C levels usually exceed 5.17 mmol/L and total cholesterol 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.[71]

Furthermore, in familial hypertriglyceridaemia, another genetic disorder resulting in excess triglyceride levels, childhood triglycerides (TG) independently predict CVD in the 4th–5th decade of life.[72]

The substantial genetic component of CVD risk can also be seen among children of patients suffering from premature myocardial infarction (<55 years), who have higher levels of total cholesterol, LDL-C, TG and lower levels of HDL cholesterol (HDL-C) than controls.[73] 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 each mmol/l 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 lifetime exposure. [74]

Most evidence suggesting that childhood cardio-metabolic 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. [61,75]

The Bogalusa Heart Study has demonstrated 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.[76]

The PDAY autopsy study showed strong relationships between atherosclerotic severity and extent with age, non–HDL cholesterol, 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 cholesterol was equivalent to 2 years of 'vascular aging'.[77] 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 subjects in the study.

Analyses from four 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 (total cholesterol, TG, blood pressure, and BMI) were predictive of elevated carotid IMT in adulthood,[78] recognized as a predictive measure of clinical coronary events in middle-aged and elderly populations.[79] Similarly, SBP, DBP, total cholesterol , 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.[80]

Additionally, in the Cardiovascular Risk in Young Finns Study, 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,[81] a marker of pathophysiological changes in the arteries relevant to the development of atherosclerosis later in life.[82] Increased body size, increased blood pressure and decreased HDL-C were associated with coronary artery calcification in young adults in the Muscatine Study.[83]

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.[84] Children with hypercholesterolemia and diabetes showed increased IMTs compared with healthy controls[85] and cumulative exposure to hyperlipidaemia in young adulthood increased subsequent risk of coronary heart disease in a dose-dependent fashion.[86] Other, non diet-related risk factors like smoking[87] and exercise[88]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 cardiovascular disease in adult life. Children with fewer cardio-metabolic risk factors show lower prevalence of atherosclerotic

risk in later life. Dietary-influenced risk factors in childhood and their relation to atherosclerosis are summarised in Table 2.

Tracking of childhood CVD risk factors and their determinants into adulthood

Cardio-metabolic risk factors in childhood deserve attention not only because of their association with atherosclerosis in adulthood, but also because there is evidence that they themselves track (i.e. 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.[89] 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.[90] This could be due both to the direct tracking of body composition, and also due to the tracking of obesity-related behaviours – such as physical inactivity and unhealthy diets- between childhood and adulthood.[91]

Correlation coefficients for cholesterol tracking are in the range of 0.4 and have been reported consistently in numerous studies examining children as young as 5 to 10 years of age and their lipid levels 20 - 30 years later.[71] In the Muscatine Study, 75% of children aged 5-10 years who had total cholesterol concentrations greater than the 90th percentile at baseline had total cholesterol concentrations of >200 mg/dL in their early 20s.[92,93] In the Bogalusa Heart Study, approximately 50% of those children who had total cholesterol levels or LDL-C levels above the 75th percentile at baseline remained elevated 12 years later.[94] In

the same study, adverse glucose levels in childhood not only persisted into adulthood but also predicted adult pre-diabetes and type 2 diabetes.[95]

In a retrospective cohort study of 1058 normoglycaemic, 37 pre-diabetic, 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 HOMA insulin resistance maintained their high rank by being above the 60th percentile in adulthood.[95]

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.[96]

Significant tracking of CRP levels was observed between childhood and adulthood in a cohort of 1617 subjects, aged 3 to 18 years at baseline and re-examined at 24 to 39 years. 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).[97]

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 21-year follow-up, reported some level of tracking of dietary patterns. [98] Similarly, a review of studies published between 2003 and 2013 reported moderate level of tracking for a range of eating behaviours (e.g. food preferences; dietary variety; dietary intake; eating habits) measured before 10 years of age and reassessed in adulthood.[99]

The significance of primordial prevention

As discussed at the outset of this review, the considerable gains made in reducing CVD mortality rates since the 1970-ties through risk factor reductions and better treatment of the disease are increasingly challenged by adverse trends in obesity and diabetes.[100,101]

Better treatment strategies are not expected to offset these adverse trends, [102,7] and would increase exponentially the medical costs given the ageing of most populations. Moreover, they only reduce but do not eliminate the risk of CVD[103,104].

Therefore risk factor reduction strategies are critical for reducing the CVD burden. Numerous modelling studies have estimated that population-wide risk factor reductions can bring substantial decreases of CVD burden[8,105,106,107] 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.[108]

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, i.e. avoiding the development of risk factors before the disease onset, should be embraced as a major component of global CVD prevention policies.[109] This is an approach through which favorable patters for all lifestyle and all major lifestyle-related risk factors can be promoted from conception throughout childhood. Those patterns can then potentially be maintained into adulthood.[110]

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[111] (n=8,816) and the Multiple Risk Factor Intervention Trial Study[112] (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, DBP ≤ 80 and 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 years greater).

So far, CVD prevention strategies targeting early life have primarily been focused on tackling childhood obesity, though success rates are poor.[113] Interest has also focused on factors like birth weight[23] and early catch-up growth,[26] though some of these traits are difficult to target through interventions, due to the need to change maternal physiology. We know, 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,[78] and would therefore benefit from additional interventions. For example, recent evidence from the US suggests that up to 1/3 of pre-pubertal children with normal weight have abnormal lipid levels[114] and that the prevalence of hypertension in the paediatric population has been increasing.[115]

Therefore interventions effectively targeting all classical risk factors in young people could potentially play a key role in preventive strategies. We therefore now link the two components of our review – that adults consuming plant-based diets have lower CVD risk, and that cardio-metabolic risk tracks from childhood into adulthood - by proposing a new testable hypothesis: namely that plant-based diet in childhood could promote cardio-metabolic health in adults, and thereby reduce CVD and promote longevity and health.

Could plant-based diets in childhood promote cardio-metabolic health in adulthood?

Diet in children appears to be one of the strongest determinants of the CVD risk factors.[116] Additionally, childhood diets show some degree of tracking into adulthood, [98,99] associate

with adulthood cardiovascular risk factors and vascular markers of subclinical 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.[27,117] Intakes particularly of plant foods (vegetables, fruits and fibre) and polyunsaturated fatty acids have shown protective effects.[27,117]

Vegan and vegetarian children have lower rates of overweight and obesity.[28] Preliminary evidence suggests that they have lower cholesterol levels[118,114] and higher antioxidant status in the blood.[120] They consume more fruits and vegetables than their omnivore counterparts.[121,122] Moreover, a recent trail showed that an intervention with low-fat vegan diet was more effective at reducing CVD risk factors in obese and hypercholesterolaemic children aged 9 to 18 years old than with the American Heart Associated recommended diet. Children assigned to the vegan intervention had more significant reductions in CVD risk factors from baseline: BMI Z-score (−0.14), systolic SBP (−6.43 mm Hg), total cholesterol (−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), mid-arm circumference (−2.02 cm), weight (−3.05 kg); whereas the significant reductions in the AHA group 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).[123]

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 paediatric populations, through their effects on blood biochemistry, other cardiovascular risk factors and establishing healthy eating patterns, could offer an effective strategy of CVD primordial

prevention. This would present a novel opportunity to promote a healthy childhood trajectory towards cardiovascular health (see Figure 2).

At the same time, data on the safety of vegetarian diets in childhood is sparse, and suggests increased risk of nutrient deficiencies especially in vegan children, including some that can differentially affect CVD risk like vitamin B12, vitamin D, Omega 3 essential fatty acids and iron.[121,124] Therefore two 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 paediatric 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 cardio-metabolic 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 along with offering planetary sustainability benefits. If applied in children, they could potentially offer cardio-metabolic health benefits, via reduction of CVD risk from the early life, a strategy which has been tested to bring the most favourable CVD mortality reductions and increases in life expectancy. At the same time, little is known about the safety and potential cardio-metabolic benefits of these diets applied from childhood and further research in this area is warranted.

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

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

Figure 1 The overall pattern in which vegetarian/vegan diets affect IHD risk factors and incidence.

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

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Table 1. Effects of vegetarian diets on cardiovascular risk factors

Study design	Populations	CVD Risk Factor	Key Findings	Reference group	Ref
Systematic review and meta-analysis of cross - sectional studies	71 studies for vegetarian and 19 studies for vegan diet	BMI	-1.49 kg/m2 (95% CI −1.72 - −1.25) for vegetarians; -1.72 kg/m2 (95% CI −2.21- −1.22) for vegans	Various otherwise similar non-vegetarian populations	Dinu et al. (2016)[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 - −0.64) for vegetarians; -0.80mmol/L (95% CI− 0.90 - −0.70) for vegans	Various otherwise similar non-vegetarian populations	Dinu et al. (2016)[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 - −0.47) for vegetarians -0.59 mmol/L (95% CI −0.77 -−0.40) for vegans	Various otherwise similar non-vegetarian populations	Dinu et al. (2016)[20]
Systematic review and meta-analysis of randomised 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-−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 randomised 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-−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	non-HDL cholesterol	-0.30 mmol/L (95% CI −0.50-−0.10) with	Trial control period	Wang et al. (2015)[14]

	vegan diet and 4 trials of intervention with vegetarian diet		intervention with vegetarian or vegan diet (pooled estimates)		
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	Non -vegetarian 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	Five omnivores matched to one 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	Seven trials, a total of 311 participants, mean age 44.5 years; 32 observational studies, a total of 21,604 participants, mean age, 46.6 years	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; 95% CI, −9.1 to −4.7) for vegetarian diet	Various otherwise similar non-vegetarian populations	
A systematic review and meta-analysis of controlled clinical trials and observational studies	Seven trials, a total of 311 participants, mean age 44.5 years; 32 observational studies, a total of	Diastolic blood pressure	a reduction in mean diastolic blood pressure (−2.2 mm Hg; 95% CI −3.5 -−1.0) for vegetarian diet	Trial control period	Yokoyama et al.(2014)[15]

	21,604 participants, mean age, 46.6 years		lower mean systolic BP (−4.7 mm Hg; 95% CI, −6.3 -−3.1) for vegetarian diet	Various otherwise similar non-vegetarian populations	
Two prospective cohort studies	Adventist Health Study 1(25,698 participants; ca. 50% vegetarians) and 2 (60 903 participants; 52% vegetarians)	Prevalence of diabetes	1.5 to 2 times lower	Non -vegetarian Adventists	Snowdon and Phillips (1985)[125] Tonstad et al. (2009)[45]
Systematic review and meta-analysis of observational studies	Twenty seven studies with 2256 vegetarian and 2192 non-vegetarian participants; 4 studies of 83 vegans and 125 omnivores	Blood glucose levels	−5.08 mg/dL (95% CI −5.98 - −4.19) for vegetarians -6.39 mg/dL(95% CI −12.35 - −0.41) for vegans	Various otherwise similar non-vegetarian populations	Dinu et al. (2016)[20]
Review	Two 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 various measures of diabetes, including body weight, fasting plasma glucose, HbA1c, and hypoglycaemic 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	Thirty long term (≥5 years) vegetarians and 30 age- matched omnivores	C reactive protein (CRP) levels	Lower CRP levels in vegetarians (0.77 mg/L; (1.29), P<0.01) than in omnivores (1.30 mg/L; (1.38))	Matched omnivores	Szeto et al. (2004)[55]
Randomized control trial	Forty-six healthy, hyperlipidaemic	Effect on CRP levels	Vegetarian diet intervention reduced CRP	Control arm of the clinical trial	Jenkins et al. (2003)[126]

	adults randomised to a diet low in saturated fat and a vegetarian diet high in plant sterols		levels by 28.2% (10.8%) (p = .02), whereas control diet by 10% (8.6%) (p = .27)		

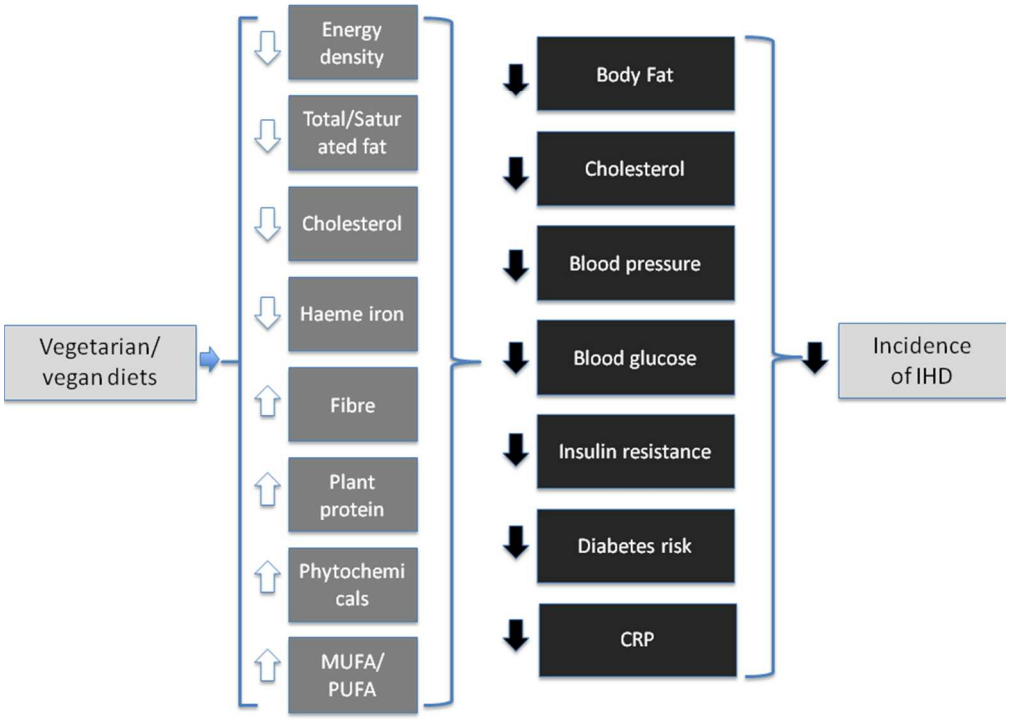
Table 2. Dietary-influenced risk factors in childhood and their relation to atherosclerosis

Study	Population	Findings	Locations of the lesions measured	Additional information	Reference
The Bogalusa Heart Study	Autopsies on 204 young persons 2 to 39 years	A strong association of BMI[1], SBP[2], DBP[3] and serum concentrations of total cholesterol, TG[4], LDL-C[5], and HDL-C[6] 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)[76]
The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study	>3000 autopsies of persons 15 to 34 years	Strong relationships between atherosclerotic severity/extent with age, non–HDL cholesterol, 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)[77]
4 longitudinal cohorts (Cardiovascular Risk in Young Finns Study, Childhood	4380 members of 4 prospective cohorts with cardiovascular risk factor data from childhood (3	Risk factors at 9+ years (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 years and 6 years were weaker and nonsignificant.	Juonala et al. (2010)[78]

[1] Body mass index
[2] Systolic Blood Pressure
[3] Diastolic Blood Pressure
[4] Triglicerydes
[5] LDL cholesterol
[6] HDL cholesterol

Determinants of Adult Health study, Bogalusa Heart Study, and Muscatine Study)	to 18 years) and intima media thickness (IMT) in adulthood (20 to 45 years)				
The Bogalusa Heart Study	1080 black and white subjects (24-43 years; 71% white, 43% male); individuals in the top (n=54) versus 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)[80]
The Cardiovascular Risk in Young Finns Study	2255 healthy white adults aged 24 to 39 years who had risk factor data available since childhood	Childhood LDL cholesterol (≥80th percentile), elevated blood pressure, skinfold thickness, low HDL cholesterol (≤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)[81]
The Muscatine Study	384 subjects (197 men, 187 women) who had coronary risk factors measured in childhood (mean age 15 years) and twice during young adult life (mean ages 27	Increased body size, increased blood pressure and decreased HDL-C were associated with coronary artery calcification in young adults			Mahoney et al.(1996) [83]

	and 33 years)				
Cross-sectional study	88 children (aged 11±2 years)	children with hypercholesterolemia and diabetes showed increased IMTs compared with healthy controls	Aortic and carotid IMT		Järvisalo et al. (2001)[85]



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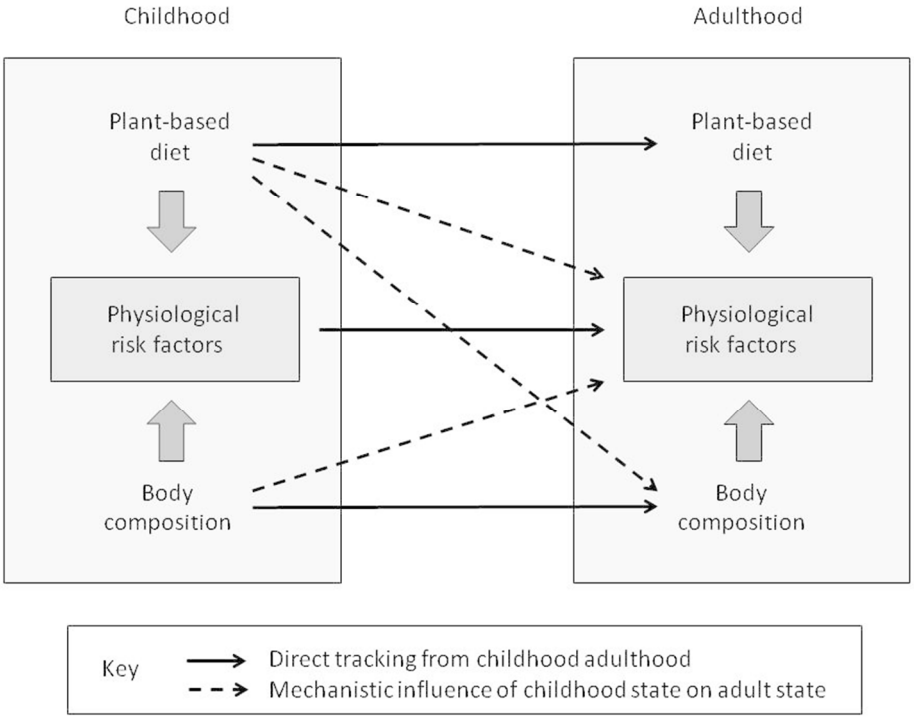

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