Minireview Article

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Diet and Cardiovascular Disease: Valvular Heart Disease, Abdominal Aortic Aneurysm, Carotid Artery Disease, Congenital Heart Disease, and Heart Transplant Related Cardiac Problems

Abstract

This manuscript reviews the role of diet in five less common cardiovascular disorders (CVDs) namely, valvular disease, abdominal aortic aneurysm, carotid artery disease, congenital heart disease, and transplanted hearts. Valvular aortic stenosis is the most common valvular heart disease in the West. The 2-year mortality is almost 50% in untreated patients with symptomatic severe aortic valve stenosis. Unfortunately, there is no available pharmacological treatment to halt the disease progression. It is usually treated by open heart or transcatheter aortic valve replacement. Abdominal aortic aneurysm (AAA) is diagnosed when the aorta diameter exceeds 3 cm or increases by more than 50% compared with normal. AAA is estimated to occur in about 8% of males over the age of 65. An effective therapeutic strategy to halt or reverse the disease progression is lacking. Surgical repair is required when the maximum diameter reaches 50–55 mm. Patients with atherosclerotic diseases, including carotid artery disease, have a high long-term all-cause and cardiac-related mortality. An increase in carotid intima-media thickness (CCA-IMT) is usually the first measurable sign of atherosclerosis progression. Carotid ultrasound measurements are considered the method of choice to gauge IMT progression and subclinical atherosclerosis. Congenital heart diseases (CoHDs) are the most common defects presenting at birth, defined as abnormal development of the heart and great vessels. Heart transplantation patients face multiple factors, including the effects of prolonged debilitation prior to surgery and immunosuppression. Several studies have investigated the role of diet in these infrequently seen CVDs. The available data are reviewed in this manuscript.

Keywords: diet, cardiovascular disease, valvular heart disease, congenital heart disease, aortic aneurysm, heart transplantation

Introduction

Cardiovascular disease (CVD) is a major cause of morbidity and mortality worldwide[1]. It is estimated that17.9 million deaths worldwide due to CVDs in 2019 (mostly premature or under the age of 70). Most of these occurred in low- to middle-income countries, indicating that non-communicable CVDs are no longer a disease of the West. The underlying cause has been the increasing spread of the Western diet and lifestyle to these countries. Overall, CVD related deaths represented 32% of all global deaths. The bulk of these CVDs are related to the development and progression of atherosclerosis. Atherosclerosis results from a diseased endothelium, low-grade inflammation, monocyte recruitment, macrophage formation, lipid accumulation, and the development of plaque within the intima layer of the arteries. As they grow, they i\encroach on the inner lumen of the artery and start impeding blood flow. They may further erode or rupture, resulting in platelet activation, superimposed thrombosis, and rapid

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vessel occlusion. The clinical manifestations of arterial blockage are myocardial infarction or an ischemic stroke[1]. Atherosclerosis also plays a role in the morbidity and mortality associated with other major CVDs, namely heart failure, cardiac arrhythmias, peripheral vascular disease and vasculogenic erectile dysfunction.

Many known risk factors for CVD and atherosclerosis are modifiable, including tobacco use, excess alcohol consumption, physical inactivity, and an unhealthy diet[2]. A healthy diet mitigates against the development and progression of atherosclerosis[3]. Although coronary artery disease, stroke, heart failure, cardiac arrhythmias, peripheral artery disease are the major causes of CVD morbidity and mortality and receive the most attention, certain less common CVDs are also affected by lifestyle changes. This manuscript looks at the influence of diet on valvular heart disease, abdominal aortic aneurysm, carotid artery disease, congenital heart disease, and transplanted hearts.

Discussion

Diet plays an important role in the genesis and progression of CVDs. A diet that is high in calories and is not matched by equivalent expenditure via physical activity results in weight gain. A BMI>30 kg/m² (or > 27.5 kg/m^2 in Asians) is considered obese[4]. Obesity, and especially abdominal obesity is harmful to the cardiovascular system. Abdominal obesity can be diagnosed by a WC >102 cm in males and >88 cm in females, a waist hip ratio > 0.85 in women and >0.9 in men. or a waist-height ratio > 0.5 in either male or female[5]. Central or visceral obesity (abdominal obesity) may exist even if the BMI is normal. The adipose tissue is a highly active organ, which influences metabolism, neuro-endocrine activity, systemic inflammation, and immunity[6]. Besides the number of calories consumed, the quality of diet is also extremely important. A Western diet is cardiovascular unhealthy. It is rich in red meat - both processed and unprocessed, saturated fats, ultra-processed foods, refined carbohydrates, fast foods, and sugar-sweetened beverages. It is low in fruits and vegetables and is lacking in fiber, vitamins, and minerals[7]. On the other hand, diets such as the Mediterranean diet (MedD), Dietary Approaches to Stop Hypertension (DASH) diet, and the vegetarian diet are primarily plant-based and are CVD friendly[8]. Several systematic reviews, meta- analyses of prospective cohort studies, and large individual cohort studies have shown a significant reduction in CVDs with these diets[9-11]. The MedD is characterized by a high intake of fruits, vegetables, legumes, wholegrain products, fish, and unsaturated fatty acids (especially olive oil); low to moderate consumption of alcohol (mostly wine, preferably consumed with meals) and low consumption of (red) meat, dairy products, and saturated fatty acids. Several studies have shown the MedD results in a 28%-31% reduction in major vascular events[9]. The DASH eating plan was primarily introduced to reduce hypertension due to its sodium restriction[10]. It is however, also rich in fruits, vegetables, whole grains, legumes, and nuts, moderate in low- fat dairy, seafood, skinless poultry, low to moderate in alcohol (for adults), low in red and processed meats, saturated fats, refined grains, and sugar-sweetened foods and beverages[11]. The Dietary Approaches to Stop Hypertension diet is associated with a 20% reduction in CVD and a 21% reduction in coronary heart disease (CHD) incidence[12]. Vegetarian diets are of numerous types: lacto-vegetarian, ovo-vegetarian, lacto-ovo-vegetarian, vegan, etc. They usually avoid animal products (meat, fish, poultry, eggs, or dairy)

Comment [S4]: Please change it to Body Mass Index (BMI)

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and contain large amounts of fruits, vegetables, whole-grain cereals, legumes/beans, and nuts. Vegetarian diets are associated with a 29% reduction in CVD and a 22% reduction in CHD mortality[13]. Plant-based diets are rich in cardiovascular beneficial ingredients, such as phytochemicals, fibers, folic acid, potassium, magnesium, vitamin E, vitamin C, and carotenoids. Intake of dark chocolate intake, tea, and coffee also impacts CVDs. The role of these dietary patterns in the less frequently encountered CVDs is the topic of this discussion.

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Valvular heart disease

There are several causes of diseased cardiac valves. Rheumatic heart disease (because of beta-hemolytic streptococcal infection of the pharynx) has been a major cause of valvular damage but is gradually decreasing all over the world[14]. Regurgitant lesions are often seen as complications of coronary artery disease (CAD) or heart failure[15-18]. This discussion will focus on stenotic aortic valvular disease, as it is often independent of other cardiovascular problems. Aortic valve stenosis (AVS) is the most common acquired valvular heart disease in the United States and western industrialized countries[19,20]. It is commonly caused by degenerative valve calcification. Bicuspid aortic valve disease is often responsible – it is a congenital anomaly and about 50% of these develop leaflet thickening and fibro-calcific disease of the aortic valve[21]. Valvular stenosis causes gradual obstruction of blood flow from the left ventricle to the aorta, and this results in symptoms[20]. The 2-year mortality is almost 50% in untreated patients with symptomatic severe AVS[22,23]. There is no available pharmacological treatment to inhibit the disease progression. Aortic valve stenosis is commonly treated by open heart or transcatheter aortic valve replacement[24]. These procedures are associated with a high risk of adverse events and substantial healthcare costs[25]. Several dietary interventions have been suggested for preventing or slowing the progression of aortic valvular disease[26-30]. Some researchers have suggested that a low-fat diet[26], a blood pressure-lowering diet[27], or a diet rich in fruits, vegetables, olive oil, and fish[28-30] appears to thwart the development of calcific aortic stenosis. However, Larsson found no objective association between dietary ingredients or special diets and calcific aortic stenosis[31]. Accelerated AVS does occur in patients with type 2 diabetes mellitus (T2DM)[32]. Its presence is associated with a poor prognosis in these patients[33]. Diabetics also demonstrate a faster degeneration of implanted bioprosthetic aortic valves[34]. Dietary control of T2DM may therefore help in slowing down this progressive damage, both in the native diseased valves and in the implanted bioprosthetic valves[35].

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Some studies have found that coffee and alcohol intake may influence the incidence of AVS. In a prospective study of 71,178 men and women (mean follow-up of 15.2 years) Larsson et al. found that the multivariable hazard ratios were 1.11 per 2 cups/day increase of coffee consumption and 1.65 when comparing the highest (≥6 cups/day) with the lowest (<0.5 cup/day) category of coffee consumption[36]. Alcohol appears to have the opposite effect. In another study, Larsson et al. followed 1,249 cases for up to 15.3 hours, found that compared with never drinkers of alcohol, the risk of AVS was significantly lower in current light drinkers (1-6 drinks per week) with a multivariable HR=0.82[37].

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Many weight reducing drugs have been associated with calcific aortic stenosis, the most significant connection has been with appetite suppressant drugs fenfluramine-phentermine (fen-

phen) and dexfenfluramine (up to 23% of cases)[38]. Fortunately, most cases of appetite suppressant-related valve disease were mild or moderate and rarely required valve repair or replacement[39]. Follow-up studies have suggested improvement in valvopathy after discontinuation of the treatment[40]. These drugs have been withdrawn from the US market. Their mechanism of causing harm has, however, never been clearly determined[41].

Abdominal Aortic Aneurysm

Abdominal aortic aneurysm (AAA) is diagnosed when the aortic diameter exceeds 3 cm or increases by more than 50% compared with normal[42,43]. AAA is estimated to occur in about 8% of males over the age of 65[44,45]. An effective non-operative therapeutic strategy to halt or reverse the disease progression is lacking[46,47]. Surgical repair is required when the maximum diameter reaches 50–55 mm[48,49]. However, the mortality of patients undergoing repair surgery is extremely high and exceeds 50%[50]. Unoperated, the mortality from ruptured aneurysms is also very high and can exceed 80%[51,52]. Inflammatory processes and oxidative stress play a major role[53-55]. They bring about protease-mediated degradation of the extracellular matrix and apoptosis of smooth muscle cells in the vascular wall, resulting in AAA[56]. Several studies have looked at the dietary impact on AAA[57,58]. Most studies have found that plant-based diets and omega 3 fatty acids appear to have a protective effect[59]. A retrospective cross-sectional cohort study conducted in the United States, comprising over 3 million individuals, showed that high consumption of fruits, vegetables, and nuts decreased the risk of AAA[60]. Stackelberg et al. in a Swedish cohort study, (80,446 individuals with 1,086 cases of incident AAA) reported that when comparing the highest intake of fruits group (>2 servings/day) with the lowest intake group (<0.7 servings/day), the highest group had a 25% decreased risk of incident AAA[61]. Nordkvist et at. in the Malmö Diet and Cancer Study (a prospective cohort study of 26,133 individuals) examined the incidence of AAA over 20.7 years and found a tendency of decreased risk in individuals adhering to recommendations for fruit and vegetables when compared to those with non-adherence[62]. When comparing the risk of more extreme intake groups, the group with the highest intake of fruits demonstrated a 33% decreased risk. The corresponding group for vegetable intake was associated with 40% decreased risk[62]. A meta-analysis by Takagi et al. (120,055 participants) also found an inverse association of fruit consumption with AAA incidence[63].

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Fruit is the major source (apples 32.0%, followed by chocolate 17.9%, and grapes 17.8%) of procyanidins (polyphenol compounds) in the diet[64]. Polyphenols help by stimulating enzymatic antioxidants and restoring endothelial function[54,65-67]. Vegetables, especially, green leafy vegetables, contain inorganic nitrate which helps by reducing blood pressure and plaque development[68]. Several previous studies have implicated a high-fat diet and increased levels of serum low-density lipoprotein cholesterol, total cholesterol, and triglyceride levels with an increased risk of AAA[69,70]. Arachidonic acid, a long-chain omega-6 polyunsaturated fatty acid (PUFA), can be metabolized to produce prostaglandin E2, thromboxane A2, and leukotriene B4. The latter has been shown to aggravate AAA through their pro-inflammatory effect[71-73]. On the other hand, Omega-3 PUFA intake beneficially affects blood lipid levels[74,75]. They also have anti-inflammatory effects[76] and reduce oxidative stress[77]. Clinically, omega-3 PUFAs improve flow-mediated arterial dilatation[68] and improve aortic stiffness in patients with AAA[79].

Greater adherence to a DASH style dietary pattern is also associated with a lower risk for AAA. Higher consumption of fruits, vegetables, whole grains, low-fat dairy as well as nuts and legumes in this diet may help to decrease the burden of AAAs[80]. Similarly, adherence to the MedD is helpful in reducing the risk of AAA, especially in smokers[81]**.** Individuals with a higher intake of vegetables and fruit often lead a healthier lifestyle in general, decreasing the risk of CVD.

Moderate alcohol consumption is inversely associated with coronary heart disease and stroke[82]. However, the pathogenesis for AAA is different from that causing these CVDs. Stackelberg reported in Circulation that moderate alcohol consumption, specifically wine and beer, was associated with a lower hazard of abdominal aortic aneurysm[83]. A more recent analysis of published studies also showed that lower levels of alcohol consumption were associated with a lower risk of AAA until approximately 15 to 20 g/day, however, the risk increases with higher doses[84]. High levels of alcohol have been shown to upregulate aortic metalloproteases in rats[85] which has been regarded as a mechanism in the pathology of AAAs, along with inflammatory factors, loss of aortic elasticity, and media thickness[86]. This could account for an increased risk of AAA at higher alcohol consumption levels.

Several vitamins have been found to be low in patients with AAA (B6/C/D/E), however, supplementation does not appear to reduce AAA incidence[87]. Lindqvist et al. found a significant inverse correlation between B12 levels and aneurysm diameter in patients with non-ruptured AAA. Their findings suggested that high B12 level intake might protect against AAA progression, indicating a potential beneficial role of B12 supplementation[88]**.**

Carotid Artery Disease

Atherosclerosis in the internal carotid artery is an independent risk factor for CVD events[89,90]. Subclinical atherosclerosis is usually measured by common carotid artery intima- media thickness (CCA- IMT). This measurement is known to predict myocardial infarction and stroke[91-94]. Asymptomatic carotid artery stenosis (>50%) is implicated in 10–15% of all stroke cases[94,95]. Patients with atherosclerotic diseases, including carotid artery disease, have a high long-term all-cause and cardiac-related mortality[96,97]. Several studies have investigated the role of diet in the pathogenesis of CCA-IMT[98,99]. An increase in IMT is usually the first measurable sign of atherosclerosis progression[100]. Blakkenhorst et al. found that women consuming ≥3 servings of vegetables each day had ≈4.6% to 5.0% lower mean CCA-IMT. The effect was more pronounced in those eating more cabbage, brussels sprouts, cauliflower, and broccoli. They estimated that for each 10 g/d higher in cruciferous vegetable intake, there was an associated 0.006 mm (0.8%) lower mean CCA-IMT[101]. A recent systematic review of 20 studies confirmed this data – Bhat et al. found a general trend between diets rich in plant foods and decreased CCA-IMT[102]. Clinically, plant-based diets reduce cerebrovascular disease by 29%[103]. One prospective longitudinal cohort study showed an inverse association of vegetable nitrate intake with carotid atherosclerosis and ischemic cerebrovascular disease in older women after a follow-up of 14.5 years[104]. In a population-based prospective cohort study (25,952 patients with a median follow-up of 21.8 years), there was a trend toward a protective effect of adherence to recommended levels of fruit and vegetable on risk of incident carotid artery disease[105]. Plants

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contain many nutrients and bioactive substances, such as phytochemicals, carotenoids, polyphenols, organosulfur compounds, and nitrogen- containing compounds. that help slow the progression of atherosclerosis[106-108]. One study found that the effect of cruciferous vegetables (such as cabbage, brussels sprouts, cauliflower, and broccoli) intake had a more pronounced on mean CCA- IMT reduction[109]. Wang et al. found a positive association between the Western diet (higher intakes of processed foods, starches, sweetened beverages, and lower consumption of fruits and vegetables) and CCA-IMT in 1,246 midlife women (average age at baseline: 46.3 y) when reviewing data from the Study of Women's Health Across the Nation[110]. The adoption of a diet low in red meat, processed meat, deep-fried products, and sugar-sweetened beverages among midlife women is associated with a lower future risk of atherosclerosis. Diets high in vegetables, such as the MedD- style diet and the vegetarian diet, have also been shown to be associated with a lower CCA- IMT, and demonstrated a delayed progression or even regression of internal carotid artery-IMT, carotid plaques, and atherosclerosis at 2.4 years of follow-up[111].

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Chocolate, coffee, and alcohol consumption have also been associated with CCA-IMT. Several studies have shown that dark chocolate ingestion improves vascular function and helps retard atherosclerosis[112,113]. Wang et al found that in 1,235 midlife women, after adjusting for covariates, women with >0 to <1 cup/day of coffee intake and 1 to <2 cups/day of coffee intake had a 0.031 mm and a 0.027 mm thicker CCA-IMT, respectively than coffee non-drinkers. Women who consumed ≥2 cups/day of coffee did not have significantly different CCA-IMT than non-drinkers[114]. Overall, it appears that habitual intake of coffee >3 cups a day is not harmful and may even have a protective effect on carotid atherosclerosis[115]. The relationship with alcohol has been unclear from epidemiological studies. Moon et al. found a protective role of alcohol on CCA-IMT[116], while Britton et al showed no association[117]. Kesse-Guyot et al. suggested that alcohol intake was harmful[118]. It appears that low to moderate alcohol intake may be beneficial while higher intake may be harmful to carotid artery atherosclerosis. Lee et al. found in their study that alcohol consumption is inversely associated with carotid IMT[119]. These results conform with those found by Xie et al. in a study of13,037 Chinese people[120]. Similarly, in a European study of high-risk CVD individuals, there was an inverse relation between moderate alcohol consumption and carotid subclinical atherosclerosis, and its progression over a 30-month period, independent of several potential confounders[121]. Low-moderate alcohol consumption, corresponding to no more than three standard glasses per day in men and two in women, has anti-inflammatory, antioxidant, fibrinolytic, and lipid-lowering effects – effects that retard arterial atherosclerosis[122]. A higher intake appears to be harmful in most studies[123].

Congenital Heart Disease

Congenital heart diseases (CoHDs) are the most common defects presenting at birth and are characterized by abnormal development of the heart and great vessels[124]. CoHDs also represent the leading cause of neonatal and infant death due to congenital causes[125,126]. Requirements for macronutrients and several micronutrients increase during pregnancy due to the growing needs of the fetus. As a result, certain dietary patterns affect CoHD[127]. The prudent diet (characterized by higher intakes of fruits and vegetables and healthy foods such as yogurt, reduced-fat milk,

whole-wheat bread, fortified cereal, fish, and lower in total and monounsaturated fat) is associated with a reduced risk of CoHDs[128]. Stores-Alvarez et al. reported that a Western diet (characterized by higher intakes of processed foods, starches, sweetened beverages, and lower consumption of fruits and vegetables) intake was associated with increased odds of offspring born with conotruncal and septal defects when compared with the intake of a prudent diet[129]. In a case-control study, Zhang et al. found that excessive consumption of pickled vegetables (adjusted odds ratio or aOR = 1.58), smoked foods (aOR = 1.84), barbecued foods (aOR = 1.62), fish and shrimp (aOR = 0.37), and milk products (aOR = 0.64) had a significant association with a total CoHDs risk[130]. Shaw et al reported evidence for increased risks associated with lower dietary intakes of linoleic acid, total carbohydrate, and fructose for d-transposition of great arteries and a decreased risk for tetralogy of Fallot with lower intakes of total protein and methionine[131], Recently, Paige et al. found that increased maternal fat intake, not adjusted for total energy intake, was associated with decreased odds of double-inlet ventricle[132]. However, the effect was minimal.

Several vitamins taken during pregnancy are extremely helpful in preventing heart defects in the newborn. Smedts and colleagues have shown that low maternal intakes of riboflavin and nicotinamide are associated with ventricular outflow tract defects[128]. Women using vitamins containing folic acid during the early stages of pregnancy notice a significantly reduced risk of offspring with heart defects[133-136]. Dietary intake of B12 is also an independent risk factor for CoHDs[137]. Several studies have found low B12 levels in mothers born with children with CoHD[138,139]. Kapusta et al. reported that median fasting plasma homocysteine was higher and mean plasma B12 levels were lower in mothers of children with CoHD[140]. The deleterious effects of low folate and vitamin B12 status appear to be related to maternal hyperhomocysteinaemia[141]. Shaw et al. implicated several nutrients, including niacin, riboflavin, thiamin, and vitamins B6, B12, C, E, and A, with an increased risk of d-transposition of the great arteries[131]. High maternal vitamin E intake via diet and supplements may increase the risk of CoHD in the offspring[142]. A multivitamin supplement taken during the prenatal and natal period helps reduce CoHD.

Maternal alcohol consumption increases the risk of CoHD[143]. Prenatal alcohol exposure is considered a key factor that leads to teratogenesis in CoHD and its specific phenotypes, especially defects of the cardiac septa, cardiac valves, cardiac canals, and great arteries, adjacent to the chambers, both in animal experiments and clinical retrospective studies[144]. Even paternal alcohol consumption (along with maternal alcohol consumption) in high amounts increases the risk of CoHD in the offspring[145]. A meta-analysis of 55 studies involving 41,747 CoHD cases showed that both maternal (odds ratio (OR) = 1.16) and paternal (OR = 1.44) alcohol exposures were significantly associated with the risk of total CoHDs in offspring[143,145].

Obese pregnant women are more prone to have offspring with CoHD[146]. A systematic review and meta-analysis found a higher risk of congenital cardiovascular anomalies (OR: 1.30) in children born from obese women when compared with non-obese pregnant women[147]. The risk increased with increasing levels of obesity[138]. Children born with excess body weight increase their risk of later life obesity[149]. Offspring with CoHD are living longer and are often

malnourished[150], especially if they have either heart failure or cyanosis[151-154]. Asymptomatic infants are the worst affected[155]. Finally, exposure to a high-fat maternal diet may lead to an increased risk of CVD in the offspring in the future[156]. The intake of a healthy diet, and avoidance of obesity, is therefore important during pregnancy.

Heart Transplantation

Heart transplant patients (HTP) face several problems that make nutritional intervention necessary. A study by Russo et al. of 19,593 orthotopic heart transplant recipients aged >or=18 years, found that those with a BMI<18.5 (underweight) and with BMI=or>30 (obese) demonstrated poor survival[157]. Heart transplant patients tend to gain excessive weight post surgery[158]. Weight gain is also an important driver for the development of post-transplant T2DM in 15.7% to 40.0% HTPs[159]. Immunosuppressive medications also contribute to the development of T2DM. These patients have a poorer prognosis. Obese HTPs also have a higher incidence of HTN and hyperlipidemia. This portends increased mortality, as post-HTPs exhibit an accelerated form of CAD - cardiac allograft vasculopathy[160]. There is some suggestion that supplementation with vitamins C and E after heart transplantation may be beneficial in preventing cardiac allograft vasculopathy, while vitamin D supplementation, in conjunction with calcium, may help in preventing post-transplant bone loss[161]. However, studies on this topic remain scarce.

Conclusion

Diet plays an important role in the development and modulation of cardiovascular diseases. Its relationship with uncommon CVDs such as aortic valvular disease, abdominal aortic aneurysm, carotid artery disease, congenital heart disease, and heart transplantation-related cardiac problems is often ignored. Dietary indiscretion can negatively affect these ailments. MedD and DASH diets are important in mitigating valvular heart disease and atherosclerosis. The latter plays a major role in AAA and carotid artery disease. Preventing CoHD in offspring can be achieved to a large degree with a proper diet and multivitamin supplementation in prenatal and natal mothers. Children born with congenital heart disease often need nutritional assessment and directions for proper growth. Patients post-heart transplantation also need to adhere to dietary recommendations – to avoid obesity and cardiac allograft vasculopathy. This manuscript provides a narrative review of the role of diet in these conditions.

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