1 **1) Article type: special article**

2 **2)Title: Childhood antecedents of adult cardiovascular risk: could plant-based diets for**

3 **children improve adult cardio-metabolic health?**

4 **3) Authors:**

5

6 **Małgorzata A. Desmond**

7 1. UCL Great Ormond Street Institute of Child Health. University College London. United
8 Kingdom. 2. Department of Paediatrics, Nutrition and Metabolic Diseases. Children's
9 Memorial Health Institute. Warsaw. Poland.

10 **Jakub Sobiecki**

11 1. School of Public Health. Imperial College London. United Kingdom. 2. Department of
12 Paediatrics, Nutrition and Metabolic Diseases. Children's Memorial Health Institute.
13 Warsaw. Poland.

14 **Mary Fewtrell**

15 UCL Great Ormond Street Institute of Child Health. University College London. United
16 Kingdom

17 **Jonathan C.K. Wells**

18 UCL Great Ormond Street Institute of Child Health. University College London. United
19 Kingdom.

20 **4) Corresponding author:**

21 Malgorzata Desmond; Childhood Nutrition Research Centre; Population, Policy and Practice;

22 UCL Great Ormond Street Institute of Child Health; 30 Guilford Street; London WC1N 1EH,

23 United Kingdom; +44207 905 2104, malgorzata.desmond.11@ucl.ac.uk;

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.

71   Diet is well established to be one of the most important factors affecting cardiovascular risk

72   in adults.[10] A number of axes of dietary variability have been linked with cardio-metabolic

73   risk, including the consumption of saturated and trans-fats, sodium, fruits and vegetables,

74   whole grains, fish and nuts.[10] However, there is growing interest in one particular axis, that

75   may also relate to many of the others: namely the proportion of the diet obtained from plants.

76   Plant- based diets include vegan diets that exclude products of animal origin; vegetarian diets

77   that rule out meat and fish consumption, and also dietary patterns predominantly based on

78   plant foods with undefined and individually determined levels of animal product

79   consumption. For the purpose of this review, vegetarian and vegan diets will be jointly

80   defined as meat-free diets.

81   Going beyond their potential health benefits, it is notable that plant-based diets are also

82   considered critical for long-term planetary sustainability[11] and they are furthermore chosen

83   for ethical reasons by those who sympathize with animal welfare movements.[12] It appears

84   that interest in meat-free diets is growing in many countries,[13] however exact estimates of

85   these trends are yet to be produced. These issues collectively justify greater research into how

86   plant-based diets might be adapted to simultaneously promote health and decrease ecological

87   damage.

88   In adults, as we review in detail below, dietary patterns emphasizing the intake of

89   unprocessed foods of plant origin seem to confer substantial protection against CVD. In

90   particular, fruit and vegetables, whole grains, nuts and legumes consumption has been linked

91   inversely with CVD risk in dose-dependent fashion.[10] In this context, it does not seem

92   surprising that adults systematically pursuing vegetarian and vegan diets have a more

93   favourable profile of CVD risk factors[14,15] translating to lower prevalence of ischemic heart

94   disease (IHD; the predominant form of CVD in Western populations) risk[16,17] than otherwise

95   similar non-vegetarians, primarily attributed to their diet.[18] However, a note of caution is that

96   studies are inconsistent regarding whether the rate of mortality from IHD differs between

97   vegetarians/vegans and omnivores, with one study showing 26-34% reductions in risk for

98   different vegetarian diets[17], but another study reporting no difference [19]. Moreover, there is

99   currently no evidence that vegetarians/vegans have lower rates of cerebrovascular disease.

100   [17,20, 19]

101   Some of this inconsistency in the association of diet and mortality risk could potentially be

102   explained by differences in the uptake of treatment and other health services between

103   vegetarians and non-vegetarians; or differences in the duration of consuming the vegetarian

104   diet. Another possibility is that the cardioprotective effects of plant-based diets relating to

105   decreased IHD risk may be counter-balanced by a lack of beneficial effects on non-IHD CVD

106   risk. Further research is required to improve understanding of these scenarios.

107   While the overt manifestation of cardiovascular disease occurs primarily in adult life, the

108   origins of atherosclerosis start well before,[21] and the atherogenic process is influenced by

109   measurable risk factors. So far, research on childhood cardio-metabolic risk has placed

110   greatest emphasis on markers of growth and nutritional status, including birth weight,[22,23]

111   childhood body mass index (BMI)[24,25] and catch-up growth.[26] However, these childhood risk

112   factors are potentially influenced by dietary composition, and healthy childhood dietary

113   patterns have been found to be associated with lower adulthood CVD risk.[27] This might be

114   mediated via beneficial effects of prudent diets on the CVD risk factor profile in childhood

115   other than just BMI.

116   In this article we therefore review substantial evidence on (a) the association between meat-

117   free diets and CVD risk in adults, and (b) the developmental origins of atherosclerosis, and

118   (c) the tendency for childhood cardio-metabolic risk factors to track into adulthood. This

119   generates a new hypothesis that meat-free or plant-based diets in childhood, through their

120   effects on blood biochemistry and other cardiovascular risk factors, offer a novel opportunity

121   to promote a healthy childhood trajectory towards adult cardio-metabolic health.

122

123   **Plant based diets and adult CVD risk**

124   Diet represents a key modifiable direct risk factor for CVD, and it also impacts other

125   components of risk, including: obesity, unhealthy lipid profile, hypertension, raised blood

126   glucose, and even physical activity level. It is foods of plant origin that have the most

127   established protective effect on CVD.[10]

128   As previously noted, vegetarian diets may decrease the risk of IHD, which is likely to be at

129   least partly mediated via classical CVD risk factors. Descriptive analysis of cardiovascular

130   profile of vegetarians may thus help elucidate mechanisms through which plant-based diets

131   exert their cardioprotective effects.

132   First, vegetarians and vegans have lower levels of body fat, mainly characterised by BMI. A

133   recent systematic review incorporating meta-analysis of 71 cross-sectional studies examining

134   the effect of a vegetarian diet and 19 cross-sectional studies examining the effect of a vegan

135   diet showed that these diets are associated with 1.49 kg/m^2 (95% CI −1.72 - −1.25)

136   and 1.72 kg/m^2 (95% CI −2.21- −1.22) lower BMI, respectively.[20] These lower BMI values

137   are attributed to the lower energy density of diets high in fruits and vegetables, and the

138   satiating effect of increased fibre intakes.[28] The association of obesity with CVD risk is

139   mediated by various other risk factors.[22] And these, as well, show a better profile among

140   people following vegetarian diets.

141

142   Second, vegetarians, especially vegans, have lower levels of total and non-HDL cholesterol.

143   A recent systematic review with meta-analysis of observational studies showed estimates of

144   effect size ranging from 0.72 mmol/L(95% CI− 0.8 - −0.64) reductions in total cholesterol

145   and 0.55 mmol/L (95% CI −0.62 - −0.47) in LDL cholesterol (LDL-C) associated with

146   vegetarian diets compared to omnivore diets (based on 64 and 46 cross sectional studies

147   respectively) and 0.80 mmol/L (95% CI− 0.90 - −0.70) reductions in total cholesterol and

148   0.59 mmol/L (95% CI −0.77 -−0.40) in LDL-C associated with vegan diets (based on 19 and

149   13 cross-sectional studies respectively).[20] Both total and non-HDL cholesterol concentrations

150   tend to be highest in meat eaters and lowest in vegans, with vegetarians having intermediate

151   values.[30] In another systematic review and meta-analysis of 11 randomised clinical trials (7

152   included a vegan diet, 2 included a lacto-ovo vegetarian diet, 2 included a lacto vegetarian

153   diet), Wang et al.[14] showed that vegetarian diets were associated with significantly lower total

154   cholesterol, LDL-C and non-HDL with pooled estimated effects of -0.36 mmol/L (95%

155   confidence interval (95% CI- 0.55-−0.17), -0.34 mmol/L (95% CI −0.57-−0.11), and -0.30

156   mmol/L(95% CI −0.50-−0.10) respectively. A 1-mmol/L reduction in TC and LDL-C levels

157   results in a 26.6% to 29.5% decrease for any cardiovascular disease–related event.[31]

158   Therefore, the average reductions of TC and LDL-C concentrations following a vegetarian

159   diet would correspond to a decrease in cardiovascular disease risk of about 9.0% to 10.6%.[14]

160   Mechanistically, vegetarian diets may reduce blood cholesterol concentrations due to their

161   lower content of saturated, total fat and cholesterol,[32] and their higher intake of dietary fibre

162   and numerous phytochemicals, all of which have been linked to lower blood lipids.[33]

163   Third, adults on plant based diets have lower systolic (SBP) and diastolic blood pressures

164   (DBP), and lower risk of hypertension, compared to meat eaters. In the cross-sectional

165   analysis of a sub-set of 592 black women and men enrolled in the Adventist Health Study-2

166   (25% vegetarian and vegan; 75% non - vegetarian) the risk of hypertension varied among

167   dietary groups and was lowest for vegans and highest for omnivores. The relative risk (RR) in

168   comparison to omnivores was 0.37 (95% CI 0.19- 0.74) and 0.57 (95% CI 0.36-0.92) 0.53 for

169   vegans and vegetarians respectively in a model adjusted for, age, sex, physical activity.[34] In a

170   matched cohort study of 4109 Taiwanese non-smokers, where each vegetarian was matched

171   with five non-vegetarians by age, sex, and study site, vegetarians had 28% lower risk (RR

172   0.72; 95% CI 0.55-0.86) for hypertension adjusting for age, sex, C-reactive protein, waist

173   circumference, and fasting glucose.[35]

174   Similarly, a systematic review and meta-analysis of controlled clinical trials and

175   observational studies showed a reduction in mean SBP (−4.8 mm Hg; 95% CI−6.6 - −3.1)

176   and DBP (−2.2 mm Hg; ; 95% CI −3.5 -−1.0) after application of a vegetarian diet compared

177   with the consumption of omnivorous diets (7 controlled trials, including 311 participants;

178   mean age, 44.5 years) and lower mean SBP (-6.9 mm; CI, −9.1 - −4.7) and DBP (-4.7 mm

179   Hg; 95% CI, −6.3 -−3.1) associated with consumption of vegetarian compared with

180   omnivorous diets (32 observational studies; a total of 21,604 participants; mean age 46.6

181   years).[15]

182   Mechanistically, several dietary factors in plant-based diets, other than those affecting BMI,

183   may account for their effects on BP. Vegetarians have higher fibre intakes,[36] which have been

184   shown to lower blood pressure.[37] Other factors, including higher plant protein[38] and

185   potassium intake[39,40] and lower haem iron intake[41] may improve blood pressure regulation.

186   Potential mechanisms include baroreceptor sensitivity, direct vasodilatory effects, and

187   changes in catecholamine and renin–angiotensin–aldosterone metabolism,[42] along with

188   changes in blood viscosity.[38]

189

190   Every 10 mm Hg reduction in SBP significantly reduces the risk of major cardiovascular

191   disease events (RR 0.80, 95% CI 0.77–0.83), coronary heart disease (RR 0.83, 95% CI 0.78–

192   0.88), and stroke (RR 0.73, 95% CI 0.68–0.77).[44]

193   Fourth, plant-based diets are associated with lower blood glucose levels, insulin resistance

194   and diabetes risk.[45] In a systematic review and meta-analysis of observational studies,

195   including 27 studies with 2256 vegetarian and 2192 non-vegetarian participants, and 4 studies

196   of 83 vegans and 125 omnivores, plant-based diets were significantly associated with lower

197   blood glucose levels (vegetarians −5.08 mg/dL, 95% CI −5.98 - −4.19; vegans - 6.39 mg/dL,

198   95% CI −12.35 - −0.41).[20] Observational studies further show that the prevalence of type 2

199   diabetes is 1.6 to 2 times lower in vegetarians compared to omnivores, even after controlling

200   for body weight.[46, 47]

201

202   Likewise, clinical interventions in subjects with type 2 diabetes have demonstrated that

203   adopting a vegetarian diet leads to a greater reduction in fasting plasma glucose, HbA1c, and

204   hypoglycemic medication compared to a conventional hypocaloric diet.[47,48] These results

205   confirm substantial protective effects of the portfolio of foods found in plant-based diets, [49]

206   [50,51, 52] along with the avoidance of meat,[53] on glycaemic control and risk of diabetes.

207   Mechanistically, plant-based diets may confer protective effects on diabetes risk through

208   caloric restriction, reduced intake of saturated fatty acids, high intake of polyunsaturated and

209   monounsaturated fatty acids, low glycaemic index, increased intake of fibre, higher intake of

210   non-haem iron and reduction in iron stores, increased intake of antioxidants, vitamins and

211   micronutrients, high intake of vegetable instead of animal protein, and high intake of plant

212   sterols and prebiotics. All of these have been shown to have a positive effect on diabetes

213   prevention.[46]

214   Diabetes confers about a two-fold excess risk for CVD, independently from other

215   conventional risk factors. In people without diabetes, fasting blood glucose concentration is

216   modestly and non-linearly associated with risk of vascular disease.[54]

217   Finally, lower levels of C-reactive protein (CRP) have been reported in adult vegetarians

218   (0.77 mg/L; standard error (SE) 1.29) for vegetarians; (1.30 mg/L; (SE 1.38)) for matched

219   omnivores, P<0.01),[55] and a decrease in CRP was observed in adults adopting vegan diets (-

220   28.2%; (SE 10.8%), P = .02).[56] Some studies have shown that healthy adult lacto vegetarians

221   have significantly lower carotid intima media thickness (IMT)[57], and the advantage was

222   related to the duration of consuming the vegetarian diet[58], but one study showed no such

223   difference.[59]

224   Altogether, a lower prevalence of cardio-metabolic risk factors among adults following plant-

225   based diets is likely to be the primary reason why they have ~25% lower risk of developing

226   ischemic heart disease.[16,20] The overall pattern in which vegetarian or vegan diets affect IHD

227   risk factors and incidence is illustrated in Figure 1. The effects of meat-free diets on

228   cardiovascular risk factors are summarised in Table 1.

229   However, while the main burden of CVD morbidity and mortality occurs in adults, there is

230   compelling evidence that CVD risk is strongly shaped by experience at earlier ages.

231   **Atherosclerosis starts in childhood**

232   Atherosclerosis comprises arterial lesions that are a fundamental component of adult CVD.

233   These lesions develop over time, starting with the relatively harmless accumulation of lipid-

234   filled macrophages, called fatty streaks, and progressing to more advanced stages where the

235   streaks are raised and vulnerable to rupture, manifesting as fibrous and calcified plaques.[60]

236   Histological studies indicate that the clinically significant lesions develop from these initially

237   harmless changes in symptomatic individuals.[61]

238   It was early autopsy studies that first suggested that atherosclerosis begins early in life. Enos

239   et al.[62] showed gross evidence of coronary atherosclerosis among autopsies of 77.3% US

240   soldiers, average age 22 years, killed in the Korean war.[2]

241

242   Around the same time, Holman et al.[21] demonstrated the presence of fatty streaks in the

243   aortas of children as young as 3 years. Subsequently, McNamara et al[63] reported

244   atherosclerosis in 45% and severe coronary atherosclerosis in 5% of 105 autopsies of US

245   soldiers killed in Vietnam.

246   More recently, the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study

247   described the emergence of clinically significant atherosclerotic lesions in a large sample of

248   autopsied persons aged 15–34 years who died in accidents.[60] Other studies reported some

249   degree of fatty streaks in the aorta in all 12-15 year olds,[64] and fatty streaks in the coronary

250   arteries in~30% of children aged 8-11 years and 69% of 12-15 year olds.[61] The clinical

251   significance of these lesions depends on their anatomical location.

252   While epidemiological studies have not directly confirmed the link between the early

253   presence of aortic fatty streaks and the occurrence of clinically significant atherosclerotic

254   plaques in later life,[65,66] there is a relationship between the location of fatty streaks in the

255   coronary arteries in children and atherosclerotic lesions in the same site later in life.[67] In non-

256   black populations, the extent of involvement of coronary artery with fatty streaks in youth

257   predicts the extent of its involvement with raised lesions in older persons.[68] In an autopsy

258   study of coronary arteries of 565 subjects aged 0 to 29 years, the progressive transformation

259   of fatty streaks in children's coronary arteries to a well-advanced fibrous plaque in young

260   adulthood was observed.[69] In this study, by puberty a small 8%-10% percentage of children

11

261   had evidence of more advanced lesions and about 30% of the young adults in their twenties

262   had well-developed raised lesions with large extracellular lipid cores and thick fibromuscular

263   caps.[69]

264   Overall, the evidence indicates that atherosclerotic process starts in the early years, and this

265   emphasises the importance of understanding the factors contributing to variability between

266   individuals during childhood.

267   **Childhood antecedents of adult atherosclerosis and clinical CVD**

268   The only direct evidence linking cardio-metabolic risk factors other than BMI in youth [70]

269   with overt clinical disease in adulthood comes from genetic disorders related to high

270   cholesterol.

271   In homozygous familial hypercholesterolemia, a genetic disease whereby LDL cholesterol

272   clearance is impaired, LDL-C levels exceed 20.68 mmol/L already in infants, CVD events

273   begin in the first decade of life and life span is reduced[71]. In heterozygous

274   hypercholesterolemia, in which LDL-C levels usually exceed 5.17 mmol/L and total

275   cholesterol levels exceed 6.5 mmo/L beginning in infancy, 50% of men and 25% of women

276   experience clinical coronary events by the age of 50.[71]

277   Furthermore, in familial hypertriglyceridaemia, another genetic disorder resulting in excess

278   triglyceride levels, childhood triglycerides (TG) independently predict CVD in the 4th–

279   5th decade of life.[72]

280   The substantial genetic component of CVD risk can also be seen among children of patients

281   suffering from premature myocardial infarction (<55 years), who have higher levels of total

282   cholesterol, LDL-C, TG and lower levels of HDL cholesterol (HDL-C) than controls.[73]

283   Another piece of evidence linking childhood blood lipids with CVD risk in adulthood in the

284 context of genetic predisposition stems from Mendelian randomization studies. Meta-analysis

285 of such studies found a 54.5% (95% CI 48.8%-59.5%) reduction in the risk of IHD per each

286 mmol/l reduction in LDL-C (effect size 3-fold greater than that achieved via treatment with

287 statins in later life) due to genetic polymorphism, and thus relating to lifetime exposure. [74]

288 Most evidence suggesting that childhood cardio-metabolic physiology affects adult arterial

289 pathology is indirect, and comes from autopsy and imaging studies linking childhood risk

290 factors with atherosclerosis and its surrogate markers.

291 The extent to which the artery surface is involved in individual children with lesions varies,

292 however it is influenced by the same classical risk factors that predict adult coronary heart

293 disease. [61,75]

294 The Bogalusa Heart Study has demonstrated a strong association of BMI, SBP, DBP and

295 serum concentrations of total cholesterol, TG, LDL-C, and HDL-C with vascular lesions in

296 children and young adults on autopsy. [76]

297 The PDAY autopsy study showed strong relationships between atherosclerotic severity and

298 extent with age, non–HDL cholesterol, HDL-C, hypertension (determined by renal artery

299 thickness), tobacco use (thiocyanate concentration), diabetes mellitus (glycohemoglobin), and

300 (in men) obesity. It also showed that a 30 mg/dL incremental increase in non-HDL

301 cholesterol was equivalent to 2 years of 'vascular aging'.[77] The severity and extent of the

302 lesions were positively associated with age, and increased in association with the number of

303 risk factors. At the same time, an absence of risk factors was associated with a virtual absence

304 of advanced atherosclerotic lesions, even in the oldest subjects in the study.

305 Analyses from four longitudinal cohorts (Cardiovascular Risk in Young Finns Study,

306 Childhood Determinants of Adult Health study, Bogalusa Heart Study, and Muscatine Study)

307 showed that risk factors measured at age 9 years or after (total cholesterol, TG, blood

308 pressure, and BMI) were predictive of elevated carotid IMT in adulthood,[78] recognized as a

309 predictive measure of clinical coronary events in middle-aged and elderly populations.[79]

310 Similarly, SBP, DBP, total cholesterol , LDL-C, HDL- C and smoking status were linked to

311 IMT of the femoral artery, a surrogate measure of coronary and peripheral atherosclerosis, in

312 asymptomatic young individuals in the Bogalusa Heart Study.[80]

313 Additionally, in the Cardiovascular Risk in Young Finns Study, childhood LDL-C (≥80th

314 percentile), elevated blood pressure, skinfold thickness, low HDL-C (≤20th percentile), and

315 smoking were inversely associated with artery elasticity in adulthood,[81] a marker of

316 pathophysiological changes in the arteries relevant to the development of atherosclerosis later

317 in life.[82] Increased body size, increased blood pressure and decreased HDL-C were associated

318 with coronary artery calcification in young adults in the Muscatine Study.[83]

319 Other studies have examined the relationship of isolated childhood risk factors to various

320 measures of atherosclerosis and CVD risk. Dietary fat quality reflected in the serum

321 cholesterol ester fraction in childhood was associated with carotid IMT in adult women.[84]

322 Children with hypercholesterolemia and diabetes showed increased IMTs compared with

323 healthy controls[85] and cumulative exposure to hyperlipidaemia in young adulthood increased

324 subsequent risk of coronary heart disease in a dose-dependent fashion.[86] Other, non diet-

325 related risk factors like smoking[87] and exercise[88]in childhood were also associated with adult

326 atherosclerosis in a pattern similar to that in adulthood.

327 Collectively, all of these studies indicate that modifiable phenotypic traits in childhood,

328 including diet and body fatness, are associated with the early emergence of atherosclerotic

329 progression to calcified plaque, manifesting as overt cardiovascular disease in adult life.

330 Children with fewer cardio-metabolic risk factors show lower prevalence of atherosclerotic

14

331   risk in later life. Dietary-influenced risk factors in childhood and their relation to

332   atherosclerosis are summarised in Table 2.

333

334   **Tracking of childhood CVD risk factors and their determinants into adulthood**

335   Cardio-metabolic risk factors in childhood deserve attention not only because of their

336   association with atherosclerosis in adulthood, but also because there is evidence that they

337   themselves track (i.e. persist) into adult life, therefore generating a cumulative impact on the

338   process of disease.

339   Evidence for tracking is strongest for obesity, with childhood BMI levels predictive of adult

340   obesity.[89] A recent systematic review of 13 prospective or retrospective longitudinal studies

341   published after 2001 showed that the risk of an overweight child becoming an overweight

342   adult is at least twice as high compared with normal - weight children and it is even higher

343   for obese children.[90] This could be due both to the direct tracking of body composition, and

344   also due to the tracking of obesity-related behaviours – such as physical inactivity and

345   unhealthy diets- between childhood and adulthood.[91]

346   Correlation coefficients for cholesterol tracking are in the range of 0.4 and have been

347   reported consistently in numerous studies examining children as young as 5 to 10 years of

348   age and their lipid levels 20 - 30 years later.[71] In the Muscatine Study, 75% of children aged

349   5-10 years who had total cholesterol concentrations greater than the 90th percentile at

350   baseline had total cholesterol concentrations of >200 mg/dL in their early 20s.[92,93] In the

351   Bogalusa Heart Study, approximately 50% of those children who had total cholesterol levels

352   or LDL-C levels above the 75th percentile at baseline remained elevated 12 years later.[94] In

353   the same study, adverse glucose levels in childhood not only persisted into adulthood but also

354   predicted adult pre-diabetes and type 2 diabetes.[95]

355   In a retrospective cohort study of 1058 normoglycaemic, 37 pre-diabetic, and 25 type 2

356   diabetic adults aged 19–39 years followed on average for 17 years since childhood, at least

357   50% of the individuals who ranked in the top childhood quintile for glucose, insulin, and

358   HOMA insulin resistance maintained their high rank by being above the 60th percentile in

359   adulthood.[95]

360   Elevated blood pressure in youth predicts adult hypertension, and a systematic review and

361   meta- analysis of 50 cohort studies reported degree of tracking with correlation coefficient at

362   0.38 for SBP and 0.28 for DBP.[96]

363   Significant tracking of CRP levels was observed between childhood and adulthood in a

364   cohort of 1617 subjects, aged 3 to 18 years at baseline and re-examined at 24 to 39 years.

365   The age- and sex-specific correlations were the highest in the group aged 18 years at baseline

366   ($r=0.47$ in females, $r=0.32$ in males).[97]

367   Of particular relevance to this review, diet itself, one of the strongest correlates of

368   cardiometabolic risk, also tracks from childhood into adulthood. The Cardiovascular Risk in

369   Young Finns Study, a prospective cohort study with 21-year follow-up, reported some level

370   of tracking of dietary patterns. [98] Similarly, a review of studies published between 2003 and

371   2013 reported moderate level of tracking for a range of eating behaviours (e.g. food

372   preferences; dietary variety; dietary intake; eating habits) measured before 10 years of age

373   and reassessed in adulthood.[99]

374

375   **The significance of primordial prevention**

16

376

377   As discussed at the outset of this review, the considerable gains made in reducing CVD

378   mortality rates since the 1970-ties through risk factor reductions and better treatment of the

379   disease are increasingly challenged by adverse trends in obesity and diabetes.[100,101]

380   Better treatment strategies are not expected to offset these adverse trends, [102,7] and would

381   increase exponentially the medical costs given the ageing of most populations. Moreover,

382   they only reduce but do not eliminate the risk of CVD[103,104].

383

384   Therefore risk factor reduction strategies are critical for reducing the CVD burden. Numerous

385   modelling studies have estimated that population-wide risk factor reductions can bring

386   substantial decreases of CVD burden[8,105,106,107] even taking into account current trends of

387   obesity and diabetes. It has also been shown that mortality trends respond very rapidly to

388   changes in risk factors at the population level.[108]

389   Given compelling evidence that the atherosclerotic process starts in childhood, and is linked

390   to well-defined, modifiable risk factors that track into adulthood, there is increasing

391   recognition that primordial prevention, i.e. avoiding the development of risk factors before

392   the disease onset, should be embraced as a major component of global CVD prevention

393   policies.[109] This is an approach through which favorable patters for all lifestyle and all major

394   lifestyle-related risk factors can be promoted from conception throughout childhood. Those

395   patterns can then potentially be maintained into adulthood.[110]

396   The concept of primordial prevention is strongly backed by data. Two prospective studies

397   from the late 1960s and 1970s - the Chicago Heart Association Detection Project in Industry

398   Study[111] (n=8,816) and the Multiple Risk Factor Intervention Trial Study[112] (n = 12,866) -

399 showed that favorable levels of all readily-measured major CVD risk factors in young

400 adulthood (TC <5.17 mmol/L; SBP ≤ 120, DBP ≤ 80 and BMI < 25.0 kg/m^2) lead to

401 substantially reduced CVD mortality rates (76-89% for men and 60-67% lower in women)

402 and sizable increases in life expectancy (8-12 years greater).

403 So far, CVD prevention strategies targeting early life have primarily been focused on tackling

404 childhood obesity, though success rates are poor.[113] Interest has also focused on factors like

405 birth weight[23] and early catch-up growth,[26] though some of these traits are difficult to target

406 through interventions, due to the need to change maternal physiology. We know, however,

407 from the Cardiovascular Risk in Young Finns Study, Childhood Determinants of Adult

408 Health study, Bogalusa Heart Study, and Muscatine Study, that other classical CVD risk

409 factors relate to adult atherosclerosis independently from BMI,[78] and would therefore benefit

410 from additional interventions. For example, recent evidence from the US suggests that up to

411 1/3 of pre-pubertal children with normal weight have abnormal lipid levels[114] and that the

412 prevalence of hypertension in the paediatric population has been increasing.[115]

413 Therefore interventions effectively targeting all classical risk factors in young people could

414 potentially play a key role in preventive strategies. We therefore now link the two

415 components of our review – that adults consuming plant-based diets have lower CVD risk,

416 and that cardio-metabolic risk tracks from childhood into adulthood - by proposing a new

417 testable hypothesis: namely that plant-based diet in childhood could promote cardio-

418 metabolic health in adults, and thereby reduce CVD and promote longevity and health.

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

420 Diet in children appears to be one of the strongest determinants of the CVD risk factors.[116]

421 Additionally, childhood diets show some degree of tracking into adulthood, [98,99] associate

18

422   with adulthood cardiovascular risk factors and vascular markers of subclinical atherosclerosis

423   and CVD risk.[27]

424   The few available studies in this area suggest that healthy childhood dietary patterns are

425   associated with lower adulthood CVD risk.[27,117] Intakes particularly of plant foods

426   (vegetables, fruits and fibre) and polyunsaturated fatty acids have shown protective

427   effects.[27,117]

428   Vegan and vegetarian children have lower rates of overweight and obesity.[28] Preliminary

429   evidence suggests that they have lower cholesterol levels[118,114] and higher antioxidant status

430   in the blood.[120] They consume more fruits and vegetables than their omnivore

431   counterparts.[121,122] Moreover, a recent trail showed that an intervention with low-fat vegan

432   diet was more effective at reducing CVD risk factors in obese and hypercholesterolaemic

433   children aged 9 to 18 years old than with the American Heart Associated recommended diet.

434   Children assigned to the vegan intervention had more significant reductions in CVD risk

435   factors from baseline: BMI Z-score (−0.14), systolic SBP (−6.43 mm Hg), total cholesterol

436   (−22.5 mg/dL), LDL-C (−13.14 mg/dL), high sensitivity CRP (−2.09 mg/L), insulin

437   (−5.42uU/ml), myeloperoxidase (−75.34 pmol/L), mid-arm circumference (−2.02 cm),

438   weight (−3.05 kg); whereas the significant reductions in the AHA group were noted only for

439   the last 3 risk factors (69.23 pmol/L, /−1.55 cm, −1.14 kg respectively) and waist

440   circumference (−2.96 cm).[123]

441   Therefore vegetarian and vegan children might have a better CVD risk profile than omnivore

442   children, and if the diet and risk profile tracks into adulthood, plant based diets in paediatric

443   populations, through their effects on blood biochemistry, other cardiovascular risk factors and

444   establishing healthy eating patterns, could offer an effective strategy of CVD primordial

445   prevention. This would present a novel opportunity to promote a healthy childhood trajectory

446   towards cardiovascular health (see Figure 2).

447   At the same time, data on the safety of vegetarian diets in childhood is sparse, and suggests

448   increased risk of nutrient deficiencies especially in vegan children, including some that can

449   differentially affect CVD risk like vitamin B12, vitamin D, Omega 3 essential fatty acids and

450   iron.[121,124] Therefore two issues are of importance. First, further research is required to

451   comprehensively assess the safety, along with the CVD-protective potential, of vegetarian

452   and vegan diets in childhood. Second, preventive strategies should potentially consider not

453   only promoting vegatarian diets per se, but also increasing the percentage of plant foods

454   within omnivore diets in children.

455   **Conclusion**

456   The population - wide reduction of CVD risk factors seems currently to be the only feasible

457   strategy to combat the CVD epidemic. More attention should be given to paediatric

458   populations in this context to take advantage of primordial prevention. Atherosclerosis starts

459   in early life and progresses in relation to the same classical risk factors in children that

460   influence the course of the disease in adults. Moreover, these risk factors along with dietary

461   habits track into adulthood. Children with fewer cardio-metabolic risk factors show lower

462   prevalence of atherosclerotic risk in later life. Plant - based diets have been shown to

463   substantially reduce CVD risk factors, morbidity and mortality in adults along with offering

464   planetary sustainability benefits. If applied in children, they could potentially offer cardio-

465   metabolic health benefits, via reduction of CVD risk from the early life, a strategy which has

466   been tested to bring the most favourable CVD mortality reductions and increases in life

467   expectancy. At the same time, little is known about the safety and potential cardio-metabolic

468   benefits of these diets applied from childhood and further research in this area is warranted.

469

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

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

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

477　　**incidence.**

478　　**Figure 2. Potential direct and indirect mechanisms through which plant-based diets in**

479　　**children could benefit cardio-metabolic health in adults**.

480　　**References:**

481　　1.　WHO | Global status report on noncommunicable diseases 2010. WHO.
482　　　　http://www.who.int/nmh/publications/ncd_report2010/en/. Accessed April 6, 2017.

483　　2.　WHO | Disability-adjusted life years (DALYs). WHO.
484　　　　http://www.who.int/gho/mortality_burden_disease/daly_rates/text/en/. Accessed April 6,
485　　　　2017.

486　　3.　Levi F, Chatenoud L, Bertuccio P, Lucchini F, Negri E, La Vecchia C. Mortality from
487　　　　cardiovascular and cerebrovascular diseases in Europe and other areas of the world: an
488　　　　update. *Eur J Cardiovasc Prev Rehabil*. 2009;16(3):333-350.
489　　　　doi:10.1097/HJR.0b013e328325d67d.

490　　4.　Allender S, Scarborough P, O'Flaherty M, Capewell S. Patterns of coronary heart disease
491　　　　mortality over the 20th century in England and Wales: Possible plateaus in the rate of decline.
492　　　　*BMC Public Health*. 2008;8:148. doi:10.1186/1471-2458-8-148.

493　　5.　Ford ES, Capewell S. Coronary heart disease mortality among young adults in the U.S. from
494　　　　1980 through 2002: concealed leveling of mortality rates. *J Am Coll Cardiol*.
495　　　　2007;50(22):2128-2132. doi:10.1016/j.jacc.2007.05.056.

496   6.   O'Flaherty M, Allender S, Taylor R, Stevenson C, Peeters A, Capewell S. The decline in
497   coronary heart disease mortality is slowing in young adults (Australia 1976-2006): a time
498   trend analysis. *Int J Cardiol*. 2012;158(2):193-198. doi:10.1016/j.ijcard.2011.01.016.

499   7.   Emberson J, Whincup P, Morris R, Walker M, Ebrahim S. Evaluating the impact of population
500   and high-risk strategies for the primary prevention of cardiovascular disease. *Eur Heart J*.
501   2004;25(6):484-491. doi:10.1016/j.ehj.2003.11.012.

502   8.   O'Flaherty M, Bandosz P, Critchley J, et al. Exploring potential mortality reductions in 9
503   European countries by improving diet and lifestyle: A modelling approach. *Int J Cardiol*.
504   2016;207:286-291. doi:10.1016/j.ijcard.2016.01.147.

505   9.   Childhood origins of arterial disease : Current Opinion in Pediatrics. LWW.
506   http://journals.lww.com/co-
507   pediatrics/Fulltext/2007/10000/Childhood_origins_of_arterial_disease.3.aspx. Accessed April
508   30, 2017.

509   10.   Mozaffarian D. Dietary and Policy Priorities for Cardiovascular Disease, Diabetes, and Obesity.
510   *Circulation*. 2016;133(2):187-225. doi:10.1161/CIRCULATIONAHA.115.018585.

511   11.   Sabaté J, Soret S. Sustainability of plant-based diets: back to the future. *Am J Clin Nutr*.
512   2014;100 Suppl 1:476S-82S. doi:10.3945/ajcn.113.071522.

513   12.   The Market for Vegetarian Foods. http://www.vrg.org/nutshell/market.htm#market.
514   Accessed April 11, 2017.

515   13.   BigHospitality.co.uk. Vegetarian and vegan trend soars as consumers reduce meat intake.
516   BigHospitality.co.uk. http://www.bighospitality.co.uk/Trends-Reports/Vegetarian-and-vegan-
517   trend-soars-as-consumers-reduce-meat-intake. Accessed April 11, 2017.

518   14.   Wang F, Zheng J, Yang B, Jiang J, Fu Y, Li D. Effects of Vegetarian Diets on Blood Lipids: A
519   Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J Am Heart Assoc*.
520   2015;4(10):e002408. doi:10.1161/JAHA.115.002408.

521   15.   Yokoyama Y, Nishimura K, Barnard ND, et al. Vegetarian diets and blood pressure: a meta-
522   analysis. *JAMA Intern Med*. 2014;174(4):577-587. doi:10.1001/jamainternmed.2013.14547.

523   16.   Crowe FL, Appleby PN, Travis RC, Key TJ. Risk of hospitalization or death from ischemic heart
524   disease among British vegetarians and nonvegetarians: results from the EPIC-Oxford cohort
525   study. *Am J Clin Nutr*. 2013;97(3):597-603. doi:10.3945/ajcn.112.044073.

526   17.   Key TJ, Fraser GE, Thorogood M, et al. Mortality in vegetarians and nonvegetarians: detailed
527   findings from a collaborative analysis of 5 prospective studies. *Am J Clin Nutr*. 1999;70(3
528   Suppl):516S-524S.

529   18.   Fraser GE. Vegetarian diets: what do we know of their effects on common chronic diseases?
530   *Am J Clin Nutr*. 2009;89(5):1607S-1612S. doi:10.3945/ajcn.2009.26736K.

531   19.   Appleby PN, Crowe FL, Bradbury KE, Travis RC, Key TJ. Mortality in vegetarians and
532   comparable nonvegetarians in the United Kingdom. *Am J Clin Nutr*. December
533   2015:ajcn119461. doi:10.3945/ajcn.115.119461.

534   20.   Dinu M, Abbate R, Gensini GF, Casini A, Sofi F. Vegetarian, vegan diets and multiple health
535   outcomes: a systematic review with meta-analysis of observational studies. *Crit Rev Food Sci*
536   *Nutr*. February 2016:0. doi:10.1080/10408398.2016.1138447.

537   21.   Holman RL, McGill HC, Strong JP, Geer JC. The Natural History of Atherosclerosis. *Am J Pathol*.
538   1958;34(2):209-235.

539   22.   Palatianou ME, Simos YV, Andronikou SK, Kiortsis DN. Long-term metabolic effects of high
540   birth weight: a critical review of the literature. *Horm Metab Res Horm Stoffwechselforschung*
541   *Horm Metab*. 2014;46(13):911-920. doi:10.1055/s-0034-1395561.

542   23.   Wang S-F, Shu L, Sheng J, et al. Birth weight and risk of coronary heart disease in adults: a
543   meta-analysis of prospective cohort studies. *J Dev Orig Health Dis*. 2014;5(6):408-419.
544   doi:10.1017/S2040174414000440.

545   24.   Lloyd LJ, Langley-Evans SC, McMullen S. Childhood obesity and adult cardiovascular disease
546   risk: a systematic review. *Int J Obes 2005*. 2010;34(1):18-28. doi:10.1038/ijo.2009.61.

547   25.   Park MH, Falconer C, Viner RM, Kinra S. The impact of childhood obesity on morbidity and
548   mortality in adulthood: a systematic review. *Obes Rev Off J Int Assoc Study Obes*.
549   2012;13(11):985-1000. doi:10.1111/j.1467-789X.2012.01015.x.

550   26.   Jain V, Singhal A. Catch up growth in low birth weight infants: striking a healthy balance. *Rev*
551   *Endocr Metab Disord*. 2012;13(2):141-147. doi:10.1007/s11154-012-9216-6.

552   27.   Kaikkonen JE, Mikkilä V, Raitakari OT. Role of Childhood Food Patterns on Adult
553   Cardiovascular Disease Risk. *Curr Atheroscler Rep*. 2014;16(10):443. doi:10.1007/s11883-014-
554   0443-z.

555   28.   Sabaté J, Wien M. Vegetarian diets and childhood obesity prevention. *Am J Clin Nutr*.
556   2010;91(5):1525S-1529S. doi:10.3945/ajcn.2010.28701F.

557   29.   Klein S, Burke LE, Bray GA, et al. Clinical implications of obesity with specific focus on
558   cardiovascular disease: a statement for professionals from the American Heart Association
559   Council on Nutrition, Physical Activity, and Metabolism: endorsed by the American College of
560   Cardiology Foundation. *Circulation*. 2004;110(18):2952-2967.
561   doi:10.1161/01.CIR.0000145546.97738.1E.

562   30.   Bradbury KE, Crowe FL, Appleby PN, Schmidt JA, Travis RC, Key TJ. Serum concentrations of
563   cholesterol, apolipoprotein A-I and apolipoprotein B in a total of 1694 meat-eaters, fish-
564   eaters, vegetarians and vegans. *Eur J Clin Nutr*. 2014;68(2):178-183.
565   doi:10.1038/ejcn.2013.248.

566   31.   Schwingshackl L, Hoffmann G. Comparison of effects of long-term low-fat vs high-fat diets on
567   blood lipid levels in overweight or obese patients: a systematic review and meta-analysis. *J*
568   *Acad Nutr Diet*. 2013;113(12):1640-1661. doi:10.1016/j.jand.2013.07.010.

569   32.   Li D. Chemistry behind Vegetarianism. *J Agric Food Chem*. 2011;59(3):777-784.
570   doi:10.1021/jf103846u.

571   33.   Craig WJ. Nutrition concerns and health effects of vegetarian diets. *Nutr Clin Pract Off Publ*
572   *Am Soc Parenter Enter Nutr*. 2010;25(6):613-620. doi:10.1177/0884533610385707.

573 34. Orlich MJ, Fraser GE. Vegetarian diets in the Adventist Health Study 2: a review of initial
574   published findings. *Am J Clin Nutr*. 2014;100 Suppl 1:353S-8S. doi:10.3945/ajcn.113.071233.

575 35. Chuang S-Y, Chiu THT, Lee C-Y, et al. Vegetarian diet reduces the risk of hypertension
576   independent of abdominal obesity and inflammation: a prospective study. *J Hypertens*.
577   2016;34(11):2164-2171. doi:10.1097/HJH.0000000000001068.

578 36. Sobiecki JG, Appleby PN, Bradbury KE, Key TJ. High compliance with dietary recommendations
579   in a cohort of meat eaters, fish eaters, vegetarians, and vegans: results from the European
580   Prospective Investigation into Cancer and Nutrition–Oxford study. *Nutr Res*. 2016;36(5):464-
581   477. doi:10.1016/j.nutres.2015.12.016.

582 37. Evans CEL, Greenwood DC, Threapleton DE, et al. Effects of dietary fibre type on blood
583   pressure: a systematic review and meta-analysis of randomized controlled trials of healthy
584   individuals. *J Hypertens*. 2015;33(5):897-911. doi:10.1097/HJH.0000000000000515.

585 38. He J, Gu D, Wu X, et al. Effect of soybean protein on blood pressure: a randomized, controlled
586   trial. *Ann Intern Med*. 2005;143(1):1-9.

587 39. Haddad EH, Tanzman JS. What do vegetarians in the United States eat? *Am J Clin Nutr*.
588   2003;78(3 Suppl):626S-632S.

589 40. Aburto NJ, Hanson S, Gutierrez H, Hooper L, Elliott P, Cappuccio FP. Effect of increased
590   potassium intake on cardiovascular risk factors and disease: systematic review and meta-
591   analyses. *BMJ*. 2013;346:f1378. doi:10.1136/bmj.f1378.

592 41. Galan P, Vergnaud A-C, Tzoulaki I, et al. Low total and nonheme iron intakes are associated
593   with a greater risk of hypertension. *J Nutr*. 2010;140(1):75-80. doi:10.3945/jn.109.114082.

594 42. Sciarrone SE, Strahan MT, Beilin LJ, Burke V, Rogers P, Rouse IL. Biochemical and
595   neurohormonal responses to the introduction of a lacto-ovovegetarian diet. *J Hypertens*.
596   1993;11(8):849-860.

597 43. Ernst E, Pietsch L, Matrai A, Eisenberg J. Blood rheology in vegetarians. *Br J Nutr*.
598   1986;56(3):555-560.

599 44. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular
600   disease and death: a systematic review and meta-analysis. *The Lancet*. 2016;387(10022):957-
601   967. doi:10.1016/S0140-6736(15)01225-8.

602 45. Tonstad S, Butler T, Yan R, Fraser GE. Type of Vegetarian Diet, Body Weight, and Prevalence
603   of Type 2 Diabetes. *Diabetes Care*. 2009;32(5):791-796. doi:10.2337/dc08-1886.

604 46. Kahleova H, Pelikanova T. Vegetarian Diets in the Prevention and Treatment of Type 2
605   Diabetes. *J Am Coll Nutr*. 2015;34(5):448-458. doi:10.1080/07315724.2014.976890.

606 47. Kahleova H, Matoulek M, Malinska H, et al. Vegetarian diet improves insulin resistance and
607   oxidative stress markers more than conventional diet in subjects with Type 2 diabetes. *Diabet
608   Med J Br Diabet Assoc*. 2011;28(5):549-559. doi:10.1111/j.1464-5491.2010.03209.x.

609 48. Barnard ND, Cohen J, Jenkins DJA, et al. A low-fat vegan diet improves glycemic control and
610   cardiovascular risk factors in a randomized clinical trial in individuals with type 2 diabetes.
611   *Diabetes Care*. 2006;29(8):1777-1783. doi:10.2337/dc06-0606.

612 49. Fung TT, Schulze M, Manson JE, Willett WC, Hu FB. Dietary patterns, meat intake, and the risk
613   of type 2 diabetes in women. *Arch Intern Med*. 2004;164(20):2235-2240.
614   doi:10.1001/archinte.164.20.2235.

615 50. Sievenpiper JL, Kendall CWC, Esfahani A, et al. Effect of non-oil-seed pulses on glycaemic
616   control: A systematic review and meta-analysis of randomised controlled experimental trials
617   in people with and without diabetes. *ResearchGate*. 2009;52(8):1479-1495.
618   doi:10.1007/s00125-009-1395-7.

619 51. Aune D, Norat T, Romundstad P, Vatten LJ. Whole grain and refined grain consumption and
620   the risk of type 2 diabetes: A systematic review and dose-response meta-analysis of cohort
621   studies. *ResearchGate*. 2013;28(11). doi:10.1007/s10654-013-9852-5.

622 52. Cooper AJ, Forouhi NG, Ye Z, et al. Fruit and vegetable intake and type 2 diabetes: EPIC-
623   InterAct prospective study and meta-analysis. *Eur J Clin Nutr*. 2012;66(10):1082-1092.
624   doi:10.1038/ejcn.2012.85.

625 53. Pan A, Sun Q, Bernstein AM, et al. Red meat consumption and risk of type 2 diabetes: 3
626   cohorts of US adults and an updated meta-analysis. *Am J Clin Nutr*. 2011;94(4):1088-1096.
627   doi:10.3945/ajcn.111.018978.

628 54. Collaboration TERF. Diabetes mellitus, fasting blood glucose concentration, and risk of
629   vascular disease: a collaborative meta-analysis of 102 prospective studies. *The Lancet*.
630   2010;375(9733):2215-2222. doi:10.1016/S0140-6736(10)60484-9.

631 55. Szeto YT, Kwok TCY, Benzie IFF. Effects of a long-term vegetarian diet on biomarkers of
632   antioxidant status and cardiovascular disease risk. *Nutr Burbank Los Angel Cty Calif*.
633   2004;20(10):863-866. doi:10.1016/j.nut.2004.06.006.

634 56. Dod HS, Bhardwaj R, Sajja V, et al. Effect of intensive lifestyle changes on endothelial function
635   and on inflammatory markers of atherosclerosis. *Am J Cardiol*. 2010;105(3):362-367.
636   doi:10.1016/j.amjcard.2009.09.038.

637 57. Acosta-Navarro J, Antoniazzi L, Oki AM, et al. Reduced subclinical carotid vascular disease and
638   arterial stiffness in vegetarian men: The CARVOS Study. *Int J Cardiol*. 2017;230:562-566.
639   doi:10.1016/j.ijcard.2016.12.058.

640 58. Yang S-Y, Zhang H-J, Sun S-Y, et al. Relationship of carotid intima-media thickness and
641   duration of vegetarian diet in Chinese male vegetarians. *Nutr Metab*. 2011;8(1):63.
642   doi:10.1186/1743-7075-8-63.

643 59. Su T-C, Jeng J-S, Wang J-D, et al. Homocysteine, circulating vascular cell adhesion molecule
644   and carotid atherosclerosis in postmenopausal vegetarian women and omnivores.
645   *Atherosclerosis*. 2006;184(2):356-362. doi:10.1016/j.atherosclerosis.2005.04.022.

646 60. McGill HC, McMahan CA, Herderick EE, et al. Origin of atherosclerosis in childhood and
647   adolescence. *Am J Clin Nutr*. 2000;72(5):1307s-1315s.

648 61. Stary HC. Lipid and macrophage accumulations in arteries of children and the development of
649   atherosclerosis. *Am J Clin Nutr*. 2000;72(5):1297s-1306s.

650   62.   Enos WF, Holmes RH, Beyer J. CORONARY DISEASE AMONG UNITED STATES SOLDIERS KILLED
651   IN ACTION IN KOREA: PRELIMINARY REPORT. *J Am Med Assoc*. 1953;152(12):1090-1093.
652   doi:10.1001/jama.1953.03690120006002.

653   63.   McNamara JJ, Molot MA, Stremple JF, Cutting RT. Coronary Artery Disease in Combat
654   Casualties in Vietnam. *JAMA*. 1971;216(7):1185-1187.
655   doi:10.1001/jama.1971.03180330061012.

656   64.   Stary HC YZ. The natural history of atherosclerosis in the aorta in the first forty years of life.
657   In: *Syndromes of Atherosclerosis: Correlations of Clinical Imaging and Pathology.* New York:
658   Futura Publishing; 1996:225–38.

659   65.   Stehbens WE. The epidemiological relationship of hypercholesterolemia, hypertension,
660   diabetes mellitus and obesity to coronary heart disease and atherogenesis. *J Clin Epidemiol*.
661   1990;43(8):733-741. doi:10.1016/0895-4356(90)90231-D.

662   66.   Newman TB, Garber AM, Holtzman NA, Hulley SB. Problems With the Report of the Expert
663   Panel on Blood Cholesterol Levels in Children and Adolescents. *Arch Pediatr Adolesc Med*.
664   1995;149(3):241-247. doi:10.1001/archpedi.1995.02170150021003.

665   67.   Montenegro MR, Eggen DA. Topography of atherosclerosis in the coronary arteries. *Lab
666   Investig J Tech Methods Pathol*. 1968;18(5):586-593.

667   68.   Smith EB. THE INFLUENCE OF AGE AND ATHEROSCLEROSIS ON THE CHEMISTRY OF AORTIC
668   INTIMA.2. COLLAGEN AND MUCOPOLYSACCHARIDES. *J Atheroscler Res*. 1965;5(2):241-248.

669   69.   Stary HC. Evolution and progression of atherosclerotic lesions in coronary arteries of children
670   and young adults. *Arterioscler Dallas Tex*. 1989;9(1 Suppl):I19-32.

671   70.   Twig G, Yaniv G, Levine H, et al. Body-Mass Index in 2.3 Million Adolescents and
672   Cardiovascular Death in Adulthood. *N Engl J Med*. 2016;374(25):2430-2440.
673   doi:10.1056/NEJMoa1503840.

674   71.   Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in
675   Children and Adolescents: Summary Report. *Pediatrics*. 2011;128(Suppl 5):S213-S256.
676   doi:10.1542/peds.2009-2107C.

677   72.   Morrison JA, Glueck CJ, Wang P. CHILDHOOD RISK FACTORS PREDICT CARDIOVASCULAR
678   DISEASE, IMPAIRED FASTING GLUCOSE PLUS TYPE 2 DIABETES MELLITUS, AND HIGH BLOOD
679   PRESSURE 26 YEARS LATER AT MEAN AGE 38: THE PRINCETON-LRC FOLLOW-UP STUDY.
680   *Metabolism*. 2012;61(4):531-541. doi:10.1016/j.metabol.2011.08.010.

681   73.   Kelishadi R, Zadegan NS, Naderi GA, Asgary S, Bashardoust N. Atherosclerosis risk factors in
682   children and adolescents with or without family history of premature coronary artery disease.
683   *Med Sci Monit Int Med J Exp Clin Res*. 2002;8(6):CR425-429.

684   74.   Ference BA, Yoo W, Alesh I, et al. Effect of long-term exposure to lower low-density
685   lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a
686   Mendelian randomization analysis. *J Am Coll Cardiol*. 2012;60(25):2631-2639.
687   doi:10.1016/j.jacc.2012.09.017.

688   75.   Newman WP, Freedman DS, Voors AW, et al. Relation of serum lipoprotein levels and systolic
689   blood pressure to early atherosclerosis. The Bogalusa Heart Study. *N Engl J Med*.
690   1986;314(3):138-144. doi:10.1056/NEJM198601163140302.

691   76.   Berenson GS, Srinivasan SR, Bao W, Newman WP, Tracy RE, Wattigney WA. Association
692   between Multiple Cardiovascular Risk Factors and Atherosclerosis in Children and Young
693   Adults. *N Engl J Med*. 1998;338(23):1650-1656. doi:10.1056/NEJM199806043382302.

694   77.   McMahan CA, Gidding SS, Malcom GT, Tracy RE, Strong JP, McGill HC. Pathobiological
695   Determinants of Atherosclerosis in Youth Risk Scores Are Associated With Early and Advanced
696   Atherosclerosis. *Pediatrics*. 2006;118(4):1447-1455. doi:10.1542/peds.2006-0970.

697   78.   Juonala M, Magnussen CG, Venn A, et al. Influence of age on associations between childhood
698   risk factors and carotid intima-media thickness in adulthood: the Cardiovascular Risk in Young
699   Finns Study, the Childhood Determinants of Adult Health Study, the Bogalusa Heart Study,
700   and the Muscatine Study for the International Childhood Cardiovascular Cohort (i3C)
701   Consortium. *Circulation*. 2010;122(24):2514-2520.
702   doi:10.1161/CIRCULATIONAHA.110.966465.

703   79.   Hodis HN, Mack WJ, LaBree L, et al. The role of carotid arterial intima-media thickness in
704   predicting clinical coronary events. *Ann Intern Med*. 1998;128(4):262-269.

705   80.   Paul TK, Srinivasan SR, Wei C, et al. Cardiovascular risk profile of asymptomatic healthy young
706   adults with increased femoral artery intima-media thickness: The Bogalusa Heart Study. *Am J
707   Med Sci*. 2005;330(3):105-110.

708   81.   Juonala M, Järvisalo MJ, Mäki-Torkko N, Kähönen M, Viikari JSA, Raitakari OT. Risk Factors
709   Identified in Childhood and Decreased Carotid Artery Elasticity in Adulthood. *Circulation*.
710   2005;112(10):1486-1493. doi:10.1161/CIRCULATIONAHA.104.502161.

711   82.   Oliver JJ, Webb DJ. Noninvasive Assessment of Arterial Stiffness and Risk of Atherosclerotic
712   Events. *Arterioscler Thromb Vasc Biol*. 2003;23(4):554-566.
713   doi:10.1161/01.ATV.0000060460.52916.D6.

714   83.   Mahoney LT, Burns TL, Stanford W, et al. Coronary risk factors measured in childhood and
715   young adult life are associated with coronary artery calcification in young adults: the
716   Muscatine Study. *J Am Coll Cardiol*. 1996;27(2):277-284.

717   84.   Kaikkonen JE, Jula A, Mikkilä V, et al. Childhood serum fatty acid quality is associated with
718   adult carotid artery intima media thickness in women but not in men. *J Nutr*.
719   2013;143(5):682-689. doi:10.3945/jn.112.172866.

720   85.   Järvisalo MJ, Jartti L, Näntö-Salonen K, et al. Increased Aortic Intima-Media Thickness.
721   *Circulation*. 2001;104(24):2943-2947. doi:10.1161/hc4901.100522.

722   86.   Navar-Boggan AM, Peterson ED, D'Agostino RB, Neely B, Sniderman AD, Pencina MJ.
723   Hyperlipidemia in Early Adulthood Increases Long-Term Risk of Coronary Heart Disease.
724   *Circulation*. January 2015:CIRCULATIONAHA.114.012477.
725   doi:10.1161/CIRCULATIONAHA.114.012477.

726   87.   Priest JR, Nead KT, Wehner MR, Cooke JP, Leeper NJ. Self-reported history of childhood
727   smoking is associated with an increased risk for peripheral arterial disease independent of
728   lifetime smoking burden. *PloS One*. 2014;9(2):e88972. doi:10.1371/journal.pone.0088972.

729   88.   Ried-Larsen M, Grøntved A, Kristensen PL, Froberg K, Andersen LB. Moderate-and-vigorous
730   physical activity from adolescence to adulthood and subclinical atherosclerosis in adulthood:
731   prospective observations from the European Youth Heart Study. *Br J Sports Med*.
732   2015;49(2):107-112. doi:10.1136/bjsports-2013-092409.

733   89.   Srinivasan SR, Bao W, Wattigney WA, Berenson GS. Adolescent overweight is associated with
734   adult overweight and related multiple cardiovascular risk factors: the Bogalusa Heart Study.
735   *Metabolism*. 1996;45(2):235-240.

736   90.   Singh AS, Mulder C, Twisk JWR, Van Mechelen W, Chinapaw MJM. Tracking of childhood
737   overweight into adulthood: a systematic review of the literature. *Obes Rev*. 2008;9(5):474-
738   488. doi:10.1111/j.1467-789X.2008.00475.x.

739   91.   Craigie AM, Lake AA, Kelly SA, Adamson AJ, Mathers JC. Tracking of obesity-related
740   behaviours from childhood to adulthood: A systematic review. *Maturitas*. 2011;70(3):266-
741   284. doi:10.1016/j.maturitas.2011.08.005.

742   92.   Lauer RM, Lee J, Clarke WR. Factors affecting the relationship between childhood and adult
743   cholesterol levels: the Muscatine Study. *Pediatrics*. 1988;82(3):309-318.

744   93.   Lauer RM, Clarke WR. Use of cholesterol measurements in childhood for the prediction of
745   adult hypercholesterolemia. The Muscatine Study. *JAMA*. 1990;264(23):3034-3038.

746   94.   Webber LS, Srinivasan SR, Wattigney WA, Berenson GS. Tracking of Serum Lipids and
747   Lipoproteins from Childhood to Adulthood The Bogalusa Heart Study. *Am J Epidemiol*.
748   1991;133(9):884-899.

749   95.   Nguyen QM, Srinivasan SR, Xu J-H, Chen W, Kieltyka L, Berenson GS. Utility of Childhood
750   Glucose Homeostasis Variables in Predicting Adult Diabetes and Related Cardiometabolic Risk
751   Factors. *Diabetes Care*. 2010;33(3):670-675. doi:10.2337/dc09-1635.

752   96.   Chen X, Wang Y. Tracking of blood pressure from childhood to adulthood: A systematic
753   review and meta-regression analysis. *Circulation*. 2008;117(25):3171-3180.
754   doi:10.1161/CIRCULATIONAHA.107.730366.

755   97.   Juonala M, Viikari JSA, Rönnemaa T, Taittonen L, Marniemi J, Raitakari OT. Childhood C-
756   Reactive Protein in Predicting CRP and Carotid Intima-Media Thickness in Adulthood.
757   *Arterioscler Thromb Vasc Biol*. 2006;26(8):1883-1888.
758   doi:10.1161/01.ATV.0000228818.11968.7a.

759   98.   Mikkilä V, Räsänen L, Raitakari OT, Pietinen P, Viikari J. Consistent dietary patterns identified
760   from childhood to adulthood: the cardiovascular risk in Young Finns Study. *Br J Nutr*.
761   2005;93(6):923-931.

762   99.   Nicklaus S, Remy E. Early Origins of Overeating: Tracking Between Early Food Habits and Later
763   Eating Patterns. *Curr Obes Rep*. 2013;2(2):179-184. doi:10.1007/s13679-013-0055-x.

764   100. DevelopingCountries I of M (US) C on P the GE of CDM the C in, Fuster V, Kelly BB.
765   *Epidemiology of Cardiovascular Disease*. National Academies Press (US); 2010.
766   https://www.ncbi.nlm.nih.gov/books/NBK45688/. Accessed April 8, 2017.

767   101.   Capewell S, Buchan I. Why have sustained increases in obesity and type 2 diabetes not offset
768   declines in cardiovascular mortality over recent decades in Western countries? *Nutr Metab*
769   *Cardiovasc Dis NMCD*. 2012;22(4):307-311. doi:10.1016/j.numecd.2012.01.005.

770   102.   Capewell S, Ford ES, Croft JB, Critchley JA, Greenlund KJ, Labarthe DR. Cardiovascular risk
771   factor trends and potential for reducing coronary heart disease mortality in the United States
772   of America. *Bull World Health Organ*. 2010;88(2):120-130. doi:10.2471/BLT.08.057885.

773   103.   Bibbins-Domingo K, Grossman DC, Curry SJ, et al. Statin Use for the Primary Prevention of
774   Cardiovascular Disease in Adults: US Preventive Services Task Force Recommendation
775   Statement. *JAMA*. 2016;316(19):1997-2007. doi:10.1001/jama.2016.15450.

776   104.   Gosmanova EO, Kovesdy CP. Adherence to antihypertensive medications: is prescribing the
777   right pill enough? *Nephrol Dial Transplant*. 2015;30(10):1649-1656. doi:10.1093/ndt/gfu330.

778   105.   Hughes J, Kabir Z, Bennett K, et al. Modelling Future Coronary Heart Disease Mortality to
779   2030 in the British Isles. *PLoS ONE*. 2015;10(9). doi:10.1371/journal.pone.0138044.

780   106.   Scholes S, Bajekal M, Norman P, et al. Quantifying policy options for reducing future coronary
781   heart disease mortality in England: a modelling study. *PloS One*. 2013;8(7):e69935.
782   doi:10.1371/journal.pone.0069935.

783   107.   Huffman MD, Lloyd-Jones DM, Ning H, et al. Quantifying Options for Reducing Coronary Heart
784   Disease Mortality By 2020. *Circulation*. 2013;127(25):2477-2484.
785   doi:10.1161/CIRCULATIONAHA.112.000769.

786   108.   Capewell S, O'Flaherty M. Rapid mortality falls after risk-factor changes in populations. *Lancet*
787   *Lond Engl*. 2011;378(9793):752-753. doi:10.1016/S0140-6736(10)62302-1.

788   109.   Tanrikulu MA, Agirbasli M, Berenson G. Primordial Prevention of Cardiometabolic Risk in
789   Childhood. *Adv Exp Med Biol*. November 2016. doi:10.1007/5584_2016_172.

790   110.   Lauer RM, Burns TL, Daniels SR. *Pediatric Prevention of Atherosclerotic Cardiovascular*
791   *Disease*. Oxford University Press; 2006.

792   111.   Stamler J, Dyer AR, Shekelle RB, Neaton J, Stamler R. Relationship of Baseline Major Risk
793   Factors to Coronary and All-Cause Mortality, and to Longevity: Findings from Long-Term
794   Follow-Up of Chicago Cohorts. *Cardiology*. 1993;82(2-3):191-222. doi:10.1159/000175868.

795   112.   Multiple risk factor intervention trial. Risk factor changes and mortality results. Multiple Risk
796   Factor Intervention Trial Research Group. *JAMA*. 1982;248(12):1465-1477.

797   113.   Colquitt JL, Loveman E, O'Malley C, et al. Diet, physical activity, and behavioural interventions
798   for the treatment of overweight or obesity in preschool children up to the age of 6 years. In:
799   *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 2016.
800   doi:10.1002/14651858.CD012105.

801   114.   Seery T, Moodie D, Cephus C, Sexson K. LIPID PROFILES PERFORMED AT THE TIME OF
802   ROUTINE PHYSICAL EXAMINATIONS IN 9-11 YEAR OLDS WITHIN TEXAS CHILDREN'S PEDIATRIC
803   ASSOCIATES PRIMARY CARE PEDIATRIC CLINICS. *J Am Coll Cardiol*. 2014;12
804   Supplement(63):A1461. doi:10.1016/S0735-1097(14)61461-3.

805   115.   Din-Dzietham R, Liu Y, Bielo M-V, Shamsa F. High blood pressure trends in children and
806   adolescents in national surveys, 1963 to 2002. *Circulation*. 2007;116(13):1488-1496.
807   doi:10.1161/CIRCULATIONAHA.106.683243.

808   116.   Laitinen TT, Pahkala K, Venn A, et al. Childhood lifestyle and clinical determinants of adult
809   ideal cardiovascular health. *Int J Cardiol*. 2013;169(2):126-132.
810   doi:10.1016/j.ijcard.2013.08.090.

811   117.   Dahm CC, Chomistek AK, Jakobsen MU, et al. Adolescent Diet Quality and Cardiovascular
812   Disease Risk Factors and Incident Cardiovascular Disease in Middle-Aged Women. *J Am Heart
813   Assoc*. 2016;5(12). doi:10.1161/JAHA.116.003583.

814   118.   Ruys J, Hickie JB. Serum cholesterol and triglyceride levels in Australian adolescent
815   vegetarians. *Br Med J*. 1976;2(6027):87.

816   119.   Yen C-E, Yen C-H, Huang M-C, Cheng C-H, Huang Y-C. Dietary intake and nutritional status of
817   vegetarian and omnivorous preschool children and their parents in Taiwan. *Nutr Res*.
818   2008;28(7):430-436. doi:10.1016/j.nutres.2008.03.012.

819   120.   Krajčovičová-Kudláčková M, Šimončič R, Béderová A, Grančičová E, Magálová T. Influence of
820   vegetarian and mixed nutrition on selected haematological and biochemical parameters in
821   children. *Food Nahr*. 1997;41(5):311-314. doi:10.1002/food.19970410513.

822   121.   Nathan I, Hackett AF, Kirby S. The dietary intake of a group of vegetarian children aged 7-11
823   years compared with matched omnivores. *Br J Nutr*. 1996;75(4):533-544.

824   122.   al-Dlaigan YH, Shaw L, Smith AJ. Vegetarian children and dental erosion. *Int J Paediatr Dent*.
825   2001;11(3):184-192.

826   123.   Macknin M, Kong T, Weier A, et al. Plant-Based No Added Fat or American Heart Association
827   Diets, Impact on Cardiovascular Risk in Obese Hypercholesterolemic Children and Their
828   Parents. *J Pediatr*. 2015;166(4):953-959.e3. doi:10.1016/j.jpeds.2014.12.058.

829   124.   Melina V, Craig W, Levin S. Position of the Academy of Nutrition and Dietetics: Vegetarian
830   Diets. *J Acad Nutr Diet*. 2016;116(12):1970-1980. doi:10.1016/j.jand.2016.09.025.

831   125.   Snowdon DA, Phillips RL. Does a vegetarian diet reduce the occurrence of diabetes? *Am J
832   Public Health*. 1985;75(5):507-512.

833   126.   Jenkins DJA, Kendall CWC, Marchie A, et al. Effects of a Dietary Portfolio of Cholesterol-
834   Lowering Foods vs Lovastatin on Serum Lipids and C-Reactive Protein. *JAMA*.
835   2003;290(4):502-510. doi:10.1001/jama.290.4.502.

836

837

838

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

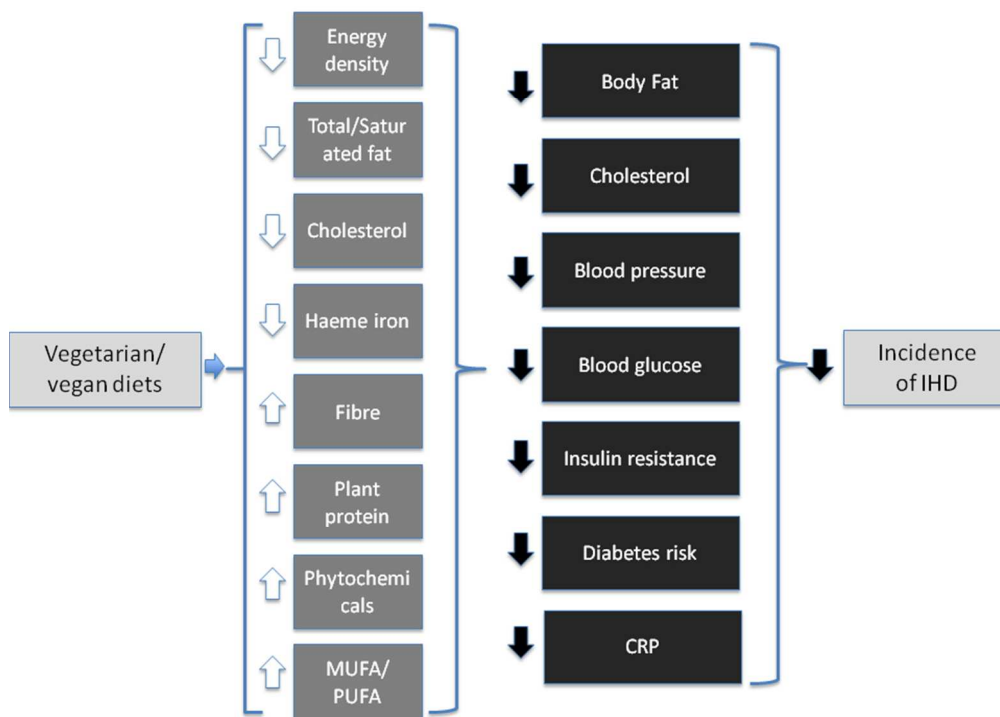| Study	Population	Findings	Locations of the lesions measured	Additional information	Reference
The Bogalusa Heart Study	Autopsies on 204 young persons 2 to 39 years	A strong association of BMI[1], SBP[2], DBP[3] and serum concentrations of total cholesterol, TG[4], LDL-C[5], and HDL-C[6] with vascular 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

35

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]

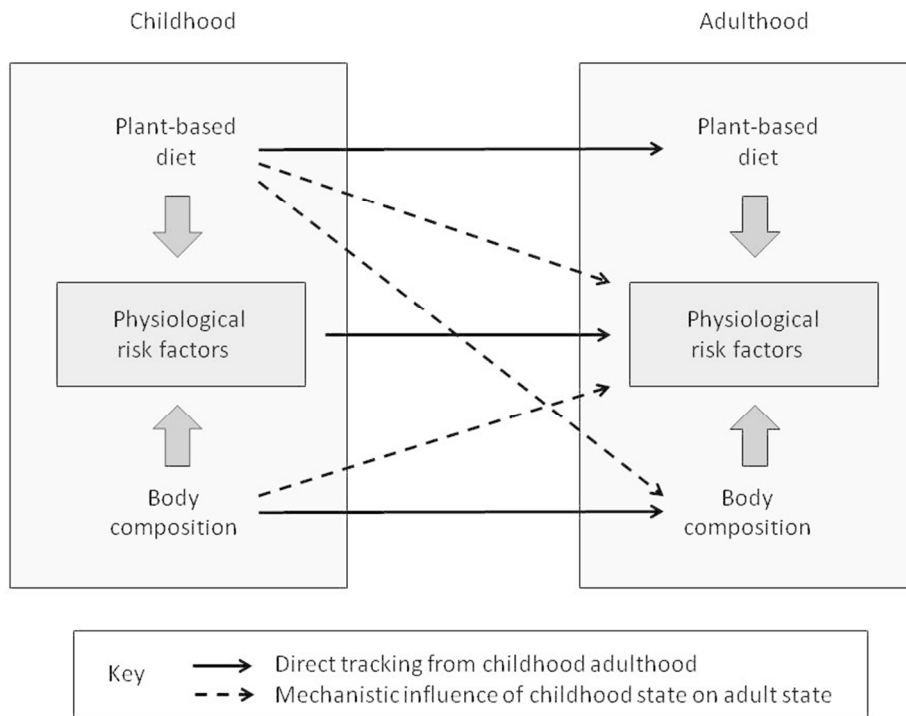|	and 33 years)				
Cross-sectional study	88 children (aged 11±2 years)	children with hypercholesterolemia and diabetes showed increased IMTs compared with healthy controls	Aortic and carotid IMT		Järvisalo et al. (2001)[85]

254x190mm (96 x 96 DPI)

254x190mm (96 x 96 DPI)