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Review

A scientific review of the reported effects of vegan nutrition on the occurrence and prevalence of cancer and cardiovascular disease

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That there exists an increased prevalence of non-communicable diseases is not readily disputed, though best practice for remedying these afflictions remains highly contentious. This paper investigates the influence of a wholly herbivorous (or vegan) diet on two leading non-communicable diseases (cancer and cardiovascular disease (CVD)). Relevant aspects considered are the biochemical effects of varying dietary concentrations of protein, calcium, essential fatty acids, cholesterol and cobalamin (B_{12}). Current literature and research investigating interactions between each focal compound and either cancer or CVD was assessed (noting where compounds influence both diseases simultaneously, the impact considered greatest in significance was chosen). Results are typically complex and indirect, with primary effects leading to secondary effects involving other compounds (including counterbalancing other focal compounds), and ancillary effects on comorbidity factors of the focal diseases. Outcomes included: weak risk reduction for colorectal and breast cancer due to a decreased propensity toward excessive dietary protein intake; possible risk reduction of prostate cancer from reduced calcium intake; cancer risk promotion due to disproportionate intakes of omega-3 relative to omega-6; CVD risk reduction from reduced cholesterol intake and insufficient evidence to consider B_{12} intake either promotive or predisposing for CVD. Caution is advised attributing dietary recommendations to these findings, as high levels of contention exist between authors due to disparate study results. Greater unanimity may be borne from future trials.

Key words: cancer, cardiovascular disease, non-communcable disease, diet, vegan, vegetarian, omnivorous, protein, essential fatty acids, calcium, cholesterol, B12.

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Introduction

Current interest in diets of hunter gatherers, both past[1–4] (Palaeolithic) and present[5] (e.g. the Papua New Guinean Samberigians and Kitavans and the Australian Aboriginal tribes) is due to hypothesis that their intake of wild meat, fish and shellfish, leafy vegetables, fruit, nuts, insects and larvae[2, 3] is causal of consistent findings of low relative risk (RR) for diseases such as obesity, hypertension, hyperinsulinaemia, ischaemic heart disease, stroke and malnutrition.[3] Outside the hunter-gatherer realms, significant dietary modifications from farming (meat and fish), refinement (grains, sugars, fats) and the inclusion of dairy, alcohol and salt are hypothesized to have produced ever-increasing occurrence of these maladies, thus affording them the labels 'diseases of civilization' or 'diseases of longevity'.[2]

At present, cardiovascular disease (CVD) and cancer are the most prevalent mortality causing non-communicable diseases globally.[6] Vast amounts of time, money and resources are utilized to identify risk reduction factors, many of which are fashioned after dietary aspects.

The modern diet consists of three main groups: omnivorous (consumption of all food groups); lacto-ovo-vegetarian or 'vegetarian' (consumption of all edible plant-derived material, eggs, dairy, honey; though no meat or fish) and vegan (sole consumption of edible plant-derived material). There exist variations to these (e.g. fructarian, pescatarian) as well as scope for dominance of particular food group or nutrient

depending on the desired outcome (e.g. high animal protein; low refined carbohydrate; low fat; high fibre, etc).

Nutritional research has invariably found vegans to consume less zinc, protein, calcium, fat (including saturated fat), cholesterol and B_{12} and more carbohydrate, fibre, vitamins A, C, B_6 (folate), B_9, potassium, magnesium, manganese, copper and iron (presumably plant-derived non-haeme iron, whose bioavailability is inferior to haeme iron)[7–9] relative to their omnivorous and vegetarian counterparts. One study reported vegans to show more diversity in their nutrient sources and to augment their B_{12}, calcium, zinc, selenium and vitamin D intake with supplements.[10]

Non-dietary related aspects were found to include higher socio-economic status, reduced alcohol and tobacco consumption and greater levels of education and dietary restraint (which reduced propensity toward obesity).[8, 11–13] While these factors may contribute to cancer and CVD risk reduction or promotion, only nutritional factors are investigated herein.

Cancer

Cancer encompasses a group of diseases related to malignant neoplasms. Known characteristics include: lack of apoptotic expulsion of mutant cells; prolific cell division with no inhibitor mechanisms; invasion of and nutrient diversion from 'normal' tissue cells; metastasis (blood and lymph) and/or tumour formation.[14] In 2007, 13% of global mortality (7.9 million people) was attributed to cancer.[15, 16] While recent reductions have occurred in affluent countries (presumed due to technological advances[16–20] and/or education[21, 22]), an aeging population may elevate mortality (~12 million by 2030).[15]

While cancers can arise from genetic predisposition, reduced immunity and adverse external environmental factors (pollution, toxins, etc.),[23, 24] most are considered preventable (e.g. ~1.5 million deaths linked to smoking).[16–20] Diet (including cooking methods and alcohol consumption, ingestion of carcinogenic-initiating or -promoting foodstuffs and exclusion of anti-carcinogenic foodstuffs) accounts for ~30% of cancers in developed countries.[15, 16, 20, 25–27]

While some propose the tumorigenic role of diet is more 'modifying' than 'instigating'[28]), the WHO's 'Global Burden of Disease' survey study[29] estimates (by way of extrapolating observational data) that increasing fruit and vegetable intake to a 600 g baseline could reduce the risk of oesophageal, stomach and lung cancer by 20%, 19% and 12%, respectively. Health authorities advocate diets limited in animal-based foods, charring cooking methods, dairy products, refined sugars, salt and hydrogenated and saturated fats, and rich in a selection of plant-based foods to protect against cancer.[23, 26, 27, 30]

This is not surprising the high quantity of non-nutritive phytochemicals (including carotenoids, polyphenols, flavenoids, isoflavones, catechins, phenolic compounds, indoles, tocotrienols and tocophenols) that plants contain possess well-documented antioxidant, antineoplastic, anti-inflammatory and/or anti-carcinogenic properties.[20, 28, 31–37] Elevated quantities of protective phytochemicals and fibre in vegan diets were confirmed by Dewell *et al.*,[38] though use of soy-protein supplements may have enhanced results. Steinmetz and Potter (1996)[36] conducted a journalistic review of 228 published research studies (22 of which were animal studies, whose results should be approached with caution) investigating the protective effects of vegetables and fruit (including tomatoes). They reported strong inverse correlations between high consumption and cancer (especially stomach, oesophageal, lung and bladder). Conversely, a significant number of the studies indicated positive correlations between citrus fruit and breast and colon cancers, and legumes and colon cancer.

Vegan diets, however, are not defined by what they incorporate, but rather what they omit. Whereby any diet can increase protective dietary components and limit detrimental ones, on a molecular level the difference between 'limiting' and 'removing' food groups is significant. Vegans omit meat, fish and dairy, lending conjecture toward protein, calcium and B[10] deficiencies and variations in essential fatty acid levels.[39, 40]

Protein

Vegan protein sources consist of a medley of legumes, grains and vegetables, contrasting with the more uniformed intake of predominantly animal-based products alongside grains in omnivorous and vegetarian diets.[10] Plant foods typically contain considerably less protein than animal products (e.g. tempeh/100 g/18 g; refried beans/1 cup(290 g)/16 g vs. flounder/3.5 oz(100 g)/30 g; chicken/3.5 oz(100 g)/31 g).[41] An exception is legumes, nuts and seeds, though these are generally eaten in relatively small amounts.

Thus, it is no surprise that on average vegans intake less protein. However, although Table 1 shows an ascending dietary protein intake (vegan → vegetarian → omnivorous), it also indicates most diets surpass the reference nutrient intake (RNI) requirements (~50 g/day or 10–15% of total energy intake (men 19–50 years = 55.5 g/day; women 19–50 years = 45.0 g/day; comprised 0.8 g/day/kilo body weight)). The only 'low' protein count study (found by Abdulla *et al.*[42]) ultimately concluded protein was not deficient due to above adequate essential amino acid levels.

Animal proteins contain a high biological value (BV). These biologically 'high-quality' proteins are considered 'complete' as they possess all essential amino acids in the required proportions.[43] An egg is the standard by which all other proteins are measured, and contains a BV rating of 100.[23] Plant products are typically incomplete (i.e. missing at least one amino acid) and are therefore considered 'low quality'.

Table 1. Pooled results of studies providing data of dietary protein intake in grams per day (g/day) and percentage of total daily energy (% of energy) for vegan, vegetarian and omnivorous diets for men, women and both sexes

Study	Vegan			Vegetarian			Omnivorous		
	Number/sex	g/day	%[a]	Number/sex	g/day	%[a]	Number/sex	g/day	%[a]
Abdulla *et al.*[42] (4-day study)	3/male	49 ± 8							
	3/female	37 ± 9							
	6/both		10 ± 1				35/both		12 ± 2
Rana and Sanders[157]	8/male		11.1 ± 0.73				8/male		13.3 ± 0.78
	10/female		12.1 ± 0.94*				10/female		14.9 ± 0.40
Key *et al.*[40]	18/both		11.5 ± 0.6				22/both		14.4 ± 0.6**
Draper *et al.*[9]	18/male	65 ± 27	11.7 ± 2.8	16/male	66 ± 21	12.0 ± 3.4	387/male	87	14.4
	20/female	47 ± 18	10.8 ± 2.3	36/female	56 ± 17	12.6 ± 3.0	377/female	66	15.5
Janelle and Barr[8]	8/both	51.9 ± 12.1	10.4 ± 1.6	15/both	57.1 ± 10.8	11.5 ± 2.1	22/both	77.1 ± 19.7	14.8 ± 2.3
Toohey *et al.*[126]	14/male	62.3 ± 8.5	12.0 ± 0.8	49/male	75.1 ± 4.7	12.1 ± 0.4			
	31/female	55.8 ± 3.7	11.3 ± 0.5	94/female	61.5 ± 2.9	11.7 ± 0.3			

[a]Percentage derived from total energy intake.
*$P < 0.01$; **$P < 0.001$.

While this may appear disadvantageous to vegans, a correlation is hypothesized between protein quality, insulin-like growth factor 1 (IGF-1) and increased incidence in prostate and breast cancer.[44, 45] IGF-1 (a somatomedin hormone) has a well-documented role in stimulation of prolific neoplastic cell growth.[46–48] One study reviewing correlations between varying cancers and IGF-1[49] found consistently high RR ascribed to colorectal cancer, premenopausal breast cancer and late stage colorectal cancer. The impact of IGF-1 down- and up-regulation of its agonists (six different IGF-1-binding proteins (IGFBPs)) has been investigated, predominantly covering protein 'quality',[45, 47, 50, 51] though also assessing fasting glucose levels[49] and citrus fruit consumption[52] (wherein high IGF-1/low IGFBP was found, corresponding with positive findings between citrus consumption and colon and breast cancers[36]).

Dietary amino acids were found to increase IGF-1 concentrations, thus offering an explanation for the possible correlation between high BV proteins and cancer.[51, 53–56] Muira *et al.*[51] investigated correlations between protein quality and hepatic IGF-1 mRNA content. Low-BV proteins were found to produce lower IGF-1 mRNA than high-BV proteins, concluding hepatic IGF-1 mRNA to be 'sensitively regulated by quantity and nutritional quality of dietary proteins'. This upholds Allen *et al.*'s[57] finding of significant trend ($P = 0.002$) for IGF-1 reduction from omnivorous, to vegetarian, to vegan (omnivorous ($n = 226$) = 20.3 nmol/l (95% CI: 19.5–21.1); vegetarian ($n = 237$) = 20.0 nmol/l (95% CI: 19.3–20.7); vegan ($n = 233$) 18.4 nmol/l (95% CI: 17.7–19.1) – ($P = <0.0001$)).

However, these findings are not consistent.[47, 50] Dewell *et al.*[50] investigated the contradictory role of soy proteins (a complete 'IGF-1 promoting' dietary protein combined with anti-proliferative and apoptotic capabilities of isoflavones). A weak rise in IGFBP-1 ($P < 0.01$) was correlated with vegetable protein, however protein (animal or soy) was not found to significantly alter IGF-1 levels.

A composition of research assessing possible dietary IGF-1 promoters and IGFBP inhibitors appear in Table 2 below. Fish and poultry were consistent IGF-1 promoters, while saturated fats (typically of animal origin) recurred as IGFBP inhibitors. Giovannucci *et al.*[54] noted the lack of correlation between red meat and IGF-1 promotion may be due to their study demographics (health-conscious people in a coastal locale).

Vegetable proteins include soy (legume) and quinoa (grain), both of which are considered 'complete',[58, 59] lending credence to their being IGF-1 promoters.[60] While increased milk consumption was repeatedly found to have strong positive correlation with increased IGF-1 levels, the null effect of other dairy products on IGF-1 levels leads to speculation that processing methods may destroy hormones linked to IGF-1 production.[55] The down-regulation of IGF-1 associated with tomato consumption and up-regulation of IGFBP-3 from lycopene corresponds to previous findings in prostate cancer risk reduction.[55, 56] McCarty[45] recorded the ability of low-BV proteins in vegan diets to increase glucagon production (thereby promoting the IGF-1 inhibiting cAMP and up-regulating IGFBP's) and to reduce IGF-1 bioavailability. However, in more recent papers[61, 62] McCarty[61, 63] regulates the vegan diet to a baseline and suggests the benefits conferred by IGF-1 down-regulation are surpassed by the ability of fish oil to both up-regulate apoptosis in lymphocytes and inhibit vascular endothelial growth (conceivably leading to tumourous growths). McCarty[62] also views IGF-1 reduction

Table 2. Pooled results of studies providing data of impacts (positive, negative or null) of ingestion of varying foods, food groups or nutrients on plasma IGF-1 and IGFBP concentrations

Study	IGF-1			IGFBP-3	
	Positive correlation	Negative correlation	No correlation	Positive correlation	Negative correlation
Dewell *et al.*[50]				Vegetable proteins (weak)	
Gunnell *et al.*[47] (case-controlled study; $n = 344$)	Polyunsaturated fat ($P = 0.017$); calcium ($P = 0.035$); milk ($P = 0.004$)			Polyunsaturated fats ($P = 0.05$); tomatoes and cooked tomato products	
Giovannucci *et al.*[54] (prospective study; $n = 51\,529$)	Animal proteins ($P \leq 0.0001$): Fish; Poultry; Milk; Vegetable proteins ($P \leq 0.0001$)		Red meat		
Holmes *et al.*[55, 56] (cross-sectional study; $n = 1037$)	Protein (0.002); animal protein ($P = 0.002$); fish ($P = 0.008$); omega3 ($P = 0.07$); calcium ($P = 0.009$); milk ($P = 0.01$); dairy ($P = 0.02$); energy ($P = 0.006$); cereal ($P = 0.0002$); grain ($P = 0.0002$); vitamin D ($P = 0.006$); dietary Vit D ($P = 0.006$)	Vegetable fat ($P = 0.04$)	Carbohydrates; vegetable protein; cheese; ice cream; poultry; red meat	Lycopene ($P = 0.003$); cereal; fish ($P = 0.004$); alcohol ($P = 0.02$); ice cream (0.02); omega3 ($P = 0.03$); energy ($P = 0.02$)	Total fat ($P = 0.006$); saturated fat ($P = 0.005$); mono. fat ($P = 0.03$); animal fat ($P = 0.02$); red meat ($P = 0.04$); ice cream ($P = 0.02$)
Kaklamani *et al.*[158] (cross- sectional study; $n = 115$)	Red meat; fat; oil	Energy from carbohydrates (especially bread)			

as a double-edged sword due to the effectiveness of IGF-1 in CVD risk reduction.

The most convincing argument is that IGF-1 is significantly linked to colorectal and breast cancer and that increased consumption of milk (most significantly), calcium and protein (to a lesser extent) have been found to factor in the up-regulation of IGF-1, suggesting protein should not be consumed in excess.

Essential fatty acids

Essential fatty acids ('EFAs') are fatty acids unable to be endogenously synthesized by mammals, yet which play pivotal roles in growth and development, and assistant with both the central nervous and immune systems. EFAs consist of two polyunsaturated fatty acids ('PUFAs'), being omega 3 ('n-3' or '$\omega - 3$') and omega 6 ('n6'; '$\omega - 6$'), both of which undergo chains of synthesis to increasingly biologically active states.

The n-3 parent state (alpha-linolenic acid; α-LNA; 18:3n-3) is converted to both eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3) (most biologically active). While α-LNA can be found in green plant matter, EPA and DHA are prevalent in fatty fish oil.[64] n-6 converts from linoleic acid (LA; 18:2n-6) (found in oils of seeds and grains) to γ-linolenic (GLA; 18:3n-6), dihomo γ-linolenic (DGLA; 20:3n-6) and arachiconic acid (AA; 20:4, $\omega - 6$). While the human genome is thought to have remained constant for the past 40 000 years, the n-6:n-3 consumption ratio has deviated significantly from the estimated 1:1–2:1 of the Palaeolithic hunter gather, to 15:1–17:1 currently estimated in Westernized countries.[65, 66]

n-3 and n-6 both produce eicosanoids (20-carbon signalling molecules),[67] though they have contradictory purposes. n-3-derived eicosanoids are anti-inflammatory, whreas n-6 eicosanoids (once desaturated and elongated from LA to AA) are inflammatory.[67, 68] Inflammation has a role in cancer formation[69] and AA-derived eicosanoids have been positively linked to cancer.[70, 71] Conversely, n-3-derived eicosanoids have been associated with tumorigenesis prevention due to their anti-inflammatory effects[67, 70, 72, 73] and their ability to inhibit biosynthesis of AA-derived eicosanoids.[70, 71, 74] This suppression arises from a relationship between n-3 and n-6, whereby they compete to be substrates for enzymatic activity, thus being natural agonists.[68, 71, 75, 76] n-3 holds greater affinity for the desaturases and elongases than n-6, allowing its inhibitory role over AA-derived eicosanoid production.

Of the n-3 family, it is the biologically active EPA and DHA that possess greatest suppression ability.[70] α-LNA can be converted to EPA and DHA, though this is biologically inefficient with studies reporting (i) a 20% conversion from α-LNA 24-hours post-ingestion[71] and (ii) a <5–10% for EPA and 2–5% for DHA.[77] Comparatively, direct intake of EPA and DHA produces physiologically active n-3 at recommended levels.[78]

Dietary avoidance of fish oil and other animal-derived sources of n-3 (eg. eggs and dairy) combined with increased carbohydrate intake is presumed causal of high plasma n-6 relative to n-3.[42, 79] Rosell *et al.*'s[73] cross-sectional study concluded that while vegans endogenously produced EPA and DHA in stable quantities, plasma concentrations were significantly lower than in omnivores (53% and 59%, respectively ($P < 0.001$)).

However, increased carbohydrate- and grain-fed animal consumption can also lead to omnivores having a low n-3:n-6 ratio.[71, 77, 80] Rosell *et al.*[73] found plasma concentrations of AA in omnivores to be lower than vegans but higher than vegetarians. Bourre's review[78] reports 90% of women in a Canadian trial consumed less than the recommended intake of n-3, as did their Australian and Hungarian counterparts in similar studies. Where high seafood levels were consumed (eg French and Inuit women), n-3 levels were adequate. O'Keefe[4] concurs, noting both low and high carbohydrate diets have 'low' n-3, while a Mediterranean diet has 'high' n-3 intake. Thus, increased grain consumption alone may not be causal of low n-3 levels.

Several authors have reviewed research of the biological interactions occurring between n-3, n-6 and cancer. Though results conflicted between increased n-3 intake being beneficial and recommended[68, 71, 78, 81] and the increase having little or no significant difference against RR,[81, 82, 83] no tumorigenic effects from increasing n-3 consumption were reported. This would suggest it is safe to err on the side of caution.

While fish oils have higher n-3 content than plant-based EFA's (e.g. 20–25% more than canola or soybean oil), they also raise serum low-density-lipoprotein (LDL) cholesterol[27, 84] and are a source of contaminants such as mercury, dioxins and PCB.[64, 77, 84–86] Plant alternatives rich in α-LNA (such as perilla and linseed oils) have been found to reduce (especially breast) cancer risk.[71, 77, 78] Plant-derived n-3 was also found to have superior stability relative to animal-derived n-3.[87] However, inefficient synthesis to the biologically active form would necessitate consumption of large volumes of α-LNA. Finally, while Leitzmann *et al.* found EPA and DHA may reduce risk of prostate cancer, they found increased α-LNA may raise risk.

Sufficient research exists to advocate a lowered n-6:increased n-3 diet until such time conclusive evidence is found. The Mediterranean diet combination of low red-meat and high vegetable and fish intake purports to be ideal;[88] however, with careful planning a vegan diet could prove successful without ancillary detrimental effects of fatty fish.

Calcium

Exogenous calcium intake is necessary for normal function. Intake occurs primarily through milk and milk products and, to a lesser degree, in vegetable, seeds and legumes. Every diet suffers calcium loss. High-BV (animal) proteins in vegetarian and omnivore diets compromise calcium absorption efficacy due to increased sulphuric acid in urine,[89] while vegans are compromised by the meagre amounts of absorbable calcium held within plants.[90] The volume of bioavailable calcium found in animal products adequately compensates for protein-derived loss; however, the lack of bioavailable calcium in plants often leaves vegans falling short of their 800 mg RNI requirements.[90] Indeed, vegan calcium consumption was found by Janelle *et al.* to average 578 ± 184 mg/day, and by Abdulla *et al.* to be 725 ± 227 mg/day (male) and 527 ± 206 mg/day (female). How this impacts cancer risk is unclear. Authors fail to reach consensus, at times being diametrically opposed.

Arguably, the most convincing evidence of a relationship between cancer and calcium and/or dairy products is increased risk of prostate cancer.[91–93] Factors lending credence are: (i) high saturated fat content and (ii) suppression by calcium of calcitriol (1,25-dihydroxyvitamin D_3, $1,25(OH)_2D_3$), being the metabolically active form of Vitamin D.[62, 91, 94] Vitamin D inhibits cancer formation by inducing cell differentiation, apoptosis and cellular arrest. An 11-year large-scale trial ($n = 20\,885$ male) presented findings of high dairy consumption lowering calcitriol levels, leading to a 32% RR increase in prostate cancer (RR: 1.34; 95% CI: 1.08, 1.63).[91] Another 10-year study[94] ($n = 3612$ male) found a strong RR for both for dairy intake (RR: 2.2; 95% CI: 1.2–3.9; $P = 0.05$) and dietary calcium (RR: 2.2; 95% CI: 1.4, 3.5; $P = 0.0001$). A high positive correlation for low-fat milk relative to other dairy forms upholds the vitamin D theory, as processing procedures are thought to remove this vitamin.

Current breast cancer research vacillates between calcium consumption being protective and predisposing. Main factors for consideration are: (i) high saturated fat; (ii) increased IGF-1 and (iii) the presence of conjugated linoleic acid (CLA), which are possible colorectal carcinogenesis inhibitors.[95] However, a review of 36 studies assessing RR between calcium and/or dairy products and breast cancer concluded there was no solid foundation for a positive association.[96]

Many studies report an inverse association between calcium and colon cancer.[95, 97, 98] Hypotheses are:[7] binding of calcium to secondary bile and fatty acids in the colonic lumen, thus suppressing their ability for growth and decreasing colonic epithelial cell proliferation; and[1] the presence of CLA. However, a 20 study review found very

weak, non-significant associations between calcium intake and colorectal cancer,[99] and recommends further investigation be undertaken concerning benefits ascribed to Vitamin D.

The overall research linking calcium and cancer is conflicting, multifaceted, ambiguous and/or unfinished. Co-factors appear to play pivotal roles, especially that of vitamin D and its biologically active derivative, calcitriol. While the vegan diet benefits from the up-regulation of calcitriol (due to lowered calcitriol-inhibiting calcium levels),[62] said benefits can be obtained merely by ultraviolet light exposure (though it is noted excess exposure promotes epidermal cancer).

Cardiovascular disease

CVD is a term encompassing those diseases affecting the heart and the blood circulatory passages. With the exception of the bacterial-induced rheumatic heart disease and heritable malformations that lead to congenital heart disease, most CVDs result from venous or arterial blockages (thrombosis), which occur by the rupturing of built-up atherosclerotic plaque, and the subsequent death of tissue from blood (and therefore oxygen and nutrient) starvation.[100] The two most common CVDs are cerebrovascular and coronary heart disease; however, CVD can affect arms and legs (peripheral arterial) and lungs (pulmonary embolisms).[23, 101–103]

CVD is the leading cause of global mortality, transcending geographic, gender and socio-economic borders.[6] The ~17.5 million (or 30%) of global mortalities in 2005 attributed to CVD is estimated to rise to ~20 million by 2015.[101]

Dietary recommendations to reduce CVD risk are: decreased intakes of saturated and trans-fats, sodium, cholesterol and unfiltered boiled coffee (contains 'cafestol', a LDL raising terpenoid lipid); combined with increased intake of longer chain omega-3 fatty acids, fruit and vegetables.[27] The latter are rich sources of antioxidants (which reduce the oxidized cholesterol that forms the basis of atherosclerotic plaque), potassium (possible thrombotic inhibitor), and fibre (thought to lower homocysteine and blood pressure levels). The ability of fruit and vegetables to protect against CVD is well documented and widely supported,[104–109] with Takachi *et al.*[110] (>77 000 Japanese cohort) finding the association much greater for CVD than for cancer. Similarly, Lock *et al.*s[29] 'Global Burden of Disease' study estimated a fruit and vegetable intake of 600 g/day could reduce heart disease and stroke by 31% and 19%, respectively.

With the exception of increasing omega-3 intake and reducing cafestol, non-consumption of animal products would appear to conform to CVD-preventing dietary recommendations. However, a study by Hu and Willett[111] reveals a complex and multifaceted relationship between diet, CVD risk and other intermediary biological mechanisms (e.g. oxidative stress, systematic inflammation, insulin sensitivity).

Cholesterol

Seminal works in the mid-1800s established causal links between atherosclerosis and cholesterol.[108, 111–114] Cholesterol has two major origins: endogenously though (primarily hepatic and intestinal) biosynthesis; and exogenously through dietary intake (the latter is considered unnecessary, as biosynthetically produced cholesterol suffices). Lipoproteins effect transportation in the body. Chylomicrons carry exogenous cholesterol (~85% triglycerides) together with cholesterol from the small intestine to the bloodstream for distribution throughout body. Remnant cholesterol is liberated in the liver. Very-LDL (VLDL) (~50% triglycerides) uptake hepatic cholesterol (chylomicron remnants and biosynthetically produced), and transport and unload triglyceride cargo in the bloodstream, losing size and density. Residual VLDL components (~50% cholesterol) form LDL. Cells up-take LDLs through receptor-mediated endocytosis. Upon sufficient cellular cholesterol uptake, negative feedback reactions remove receptors for cellular internalization. Excess LDL-cholesterol is retained in the bloodstream. High-density lipoproteins (HDL), (small, dense, containing ~50% protein) 'mop-up' excess cholesterol in the bloodstream and transport it to the liver for recycling.[23, 115–117]

This self-regulating cycle of cholesterol and lipid manufacture, transport and deconstruction suffers interference. If cholesterol levels increase and HDL is not similarly increased, the equilibrium, as noted in the Friedewald[118] equation, is lost.

$$C_{LDL} = C_{plasma} - C_{HDL} - \frac{TG}{5},$$

where C is cholesterol and TG triglycerides. Excess LDL-cholesterol in the bloodstream is linked to atherosclerotic plaque formation (by damaging the inner vein lining; oxidizing; causing inflammation and inciting the macrophage 'foam' assembly which forms plaque).[100] Elevated serum LDL-cholesterol levels are hypothesized as one of the major risk factors of CVD.

Table 3 shows a consistent pattern of increase for total serum cholesterol (TSC) and LDL across the vegan–vegetarian–omnivore diet range. Sacks *et al.*[8] similarly found the LDL-cholesterol levels of lactovegetarians to be 24% higher than vegans. Vegan diets typically consist of substantially less saturated fatty acids (SFAs) (purported to hold greater association high LDL cholesterol relative to other fatty acids), and should theoretically contain no exogenous cholesterol as dietary cholesterol sources are solely animal-derived products (including embryonic casings such as roe and egg yolks, due to cholesterol being a precursor to sex hormones).[119] While most vegans were found to consume cholesterol (in unknown forms), studies have shown the

Table 3. Pooled results of studies providing data of plasma concentrations (mmol/l) for TSC, LDL, HDL and TGLY (triglycerides) for participants (male and female) across the vegan-vegetarian-omnivore diet range

Study	Lipid test	Vegan		Vegetarian		Omnivorous	
		Number/sex	mmol/l	Number/sex	mmol/l	Number/sex	mmol/l
Appleby *et al.*[120]	TSC**	114/both	4.29 ± 0.140	1550	4.88 ± 0.1	1198	5.31 ± 0.101
	LDL**		2.28 ± 0.126		2.74 ± 0.090		3.17 ± 0.091
	HDL*		1.49 ± 0.048		1.5 ± 0.035		1.49 ± 0.035
Sanders *et al.*[79]	TSC*	22/both	4.1 ± 0.17			22/both	6.1 ± 0.19
	TGLY*	21/both	0.95 ± 0.07			21/both	1.35 ± 0.14
Lockie *et al.*[127]	TSC	10/both	3.89 ± 0.78	9/both	4.27 ± 0.96	10/both	5.61 ± 1.96

*$P < 0.01$; **$P < 0.001$.

Table 4. Pooled results of studies providing data of cholesterol intake (mg/day) across the vegan-vegetarian-omnivore diet range

Study	Vegan		Vegetarian		Omnivorous	
	Number/sex	mg/day	Number/sex	mg/day	Number/sex	mg/day
Lockie *et al.*[127]	10/both	29.0 ± 15.5	9/both	295 ± 190.6	10/both	374.5 ± 258.8
Appleby *et al.*[120]	26/male*	7 ± 1	26/male	267 ± 6	26/male	306 ± 5
	26/female*	4 ± 0	26/female	201 ± 3	26/female	266 ± 4
Dewell *et al.*[a38]	37/both	10 ± 24			37/both	200 ± 139

*$P < 0.001$.
[a]An intervention study of 37 study participants—omnivorous at baseline ('omnivorous' figure), and results from 1-year vegan intervention diet ('vegan' figure).

expected significant reductions in daily cholesterol intake (Table 4), with Appleby *et al.*[120] reflecting a difference between 4 and 7 mg/day and 201–306 mg/day for vegans and non-vegans, respectively.

While these results promote a vegan diet, studies are increasingly linking increased carbohydrate consumption to depressed HDL levels[115, 121] (by inhibiting hepatic production of the primary protein constituent of HDL, apopolipoprotein A-1 (apoA-1)[122–124]) and vegans have been consistently found to consume more carbohydrates than vegetarians and omnivores.[8, 42, 120] However, where some studies found vegans to have depressed HDL levels,[125] others found little or no difference.[120, 126] Fibre and phytosterol in whole-grain carbohydrates have also been found to interrupt cholesterol absorption).[127–130]

An additional, long-standing argument exists about the role of diet in CVD. Mann *et al.*[131] studied the hearts and aortae of 50 Masai villagers living almost exclusively on a meat and milk diet. Contrary to expectations, little evidence of CVD was found. Atherosclerosis did exist, however tunica media (the elastic cell wall) was found to enlarge enough to accommodate the plaque. This study is included in a comprehensive review by Ravnskov,[132] who identifies a range of global observational and experimental studies on CVD and diet, spanning >40 years. Ravnskov pools data to make ethnic comparisons, which counter leading theories on SFAs detrimental relationship with CVD. This is an important issue, as it would serve to nullify the benefits conferred by a vegan diet with regard to SFA (and thus cholesterol) reduction. A meta-analysis (27 studies) conducted by Hooper *et al.*[133] found reduction in dietary fat and cholesterol had limited effect on total mortality, though reduced CVD *events* by 16% (CI: 0.84;0.72,0.99), with those subjects remaining in the trail >2 years producing more credible evidence.

What can largely be extrapolated is that sufficient evidence exists to link diet, cholesterol and CVD, however, there remain unknown factors (environmental as well as biochemical) that may, in and of themselves, be causal or supplemental to this link. Robust arguments as to the benefits of a vegan diet with regard to serum cholesterol and SFAs exist; however, recommendations as to best practices for reducing CVD with regard to cholesterol and SFAs and other fatty acids are continuously evolving[121] (including new research for HDLs themselves becoming CVD catalysts[134]). Outcomes from these studies would affect dietary recommendations.

B_{12} (cobalamin)

B_{12} is involved in erythrocyte formation, DNA cell division and nervous system maintenance. It is consistently low in vegan nutrient studies.[134–137] Janelle and Barr[8] found vegans to have 25% of the B_{12} RNI. Fig. 1 revealed a

decreasing trend of B_{12} (omnivore to vegan), though two studies found only marginal decreases.[7, 138] However, this is not restricted to vegans. A study on Seventh-day Adventist ministers[136] found B_{12} to be lacking not only by the vegan subjects (73%), but also by 40% of their vegetarian and omnivorous peers.

The high vegan deficiency is due to an inability for plants and animals to synthesize B_{12}. Most animals either intestinally harbour B_{12}-synthesizing bacteria,[139] or intake by ingestion of other animals (especially eggs and liver) or algae. Vegetarians and omnivores typically consume sufficient amounts. A study into the bioavailability of plant-derived B_{12} (nori and spirulina) was conducted by Dagnelie *et al.*,[135] however they failed to find sufficient evidence to advocate dietary algae benefits. Vegans were found to be heavily reliant on supplemental sources of B_{12} (inactive synthetic cyanocobalamin, which biosynthesizes to biologically active methylcobalamin and adenosylcobalamin).[7, 8, 10]

While B_{12} hypovitaminosis can be causal in megaloblastic anaemia (cell division inhibition) and nerve degeneration,[139, 140] focus here is on B_{12}'s role in reducing plasma homocysteine (tHcy). tHcy is a sulphur amino acid involved in methionine and cysteine metabolism.[141] High tHcy serum levels may promote arterial and venous endothelial dysfunction,[142] leading to atherosclerosis, arterial and venous thromboembolisms and various CVDs (especially cerebral and peripheral vascular disease).[138, 143–147] A meta-analytical review by Wald *et al.*[147] reported that elevated tHcy serum concentrations had causal effect on ischaemic heart disease, thromboembolisms and stroke. However

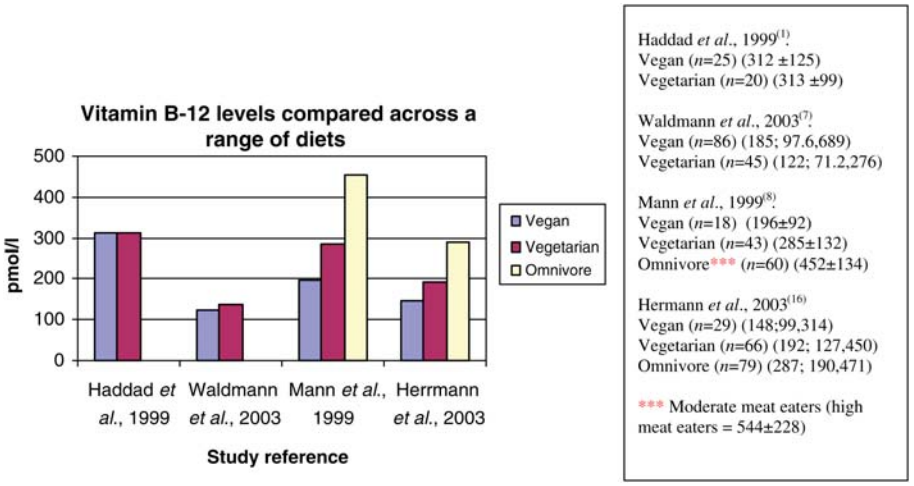

Figure 1. Pooled results of studies providing data of plasma B12 concentrations (mol/l) for trial participants (male and female) across the vegan-vegetarian-omnivore diet range.

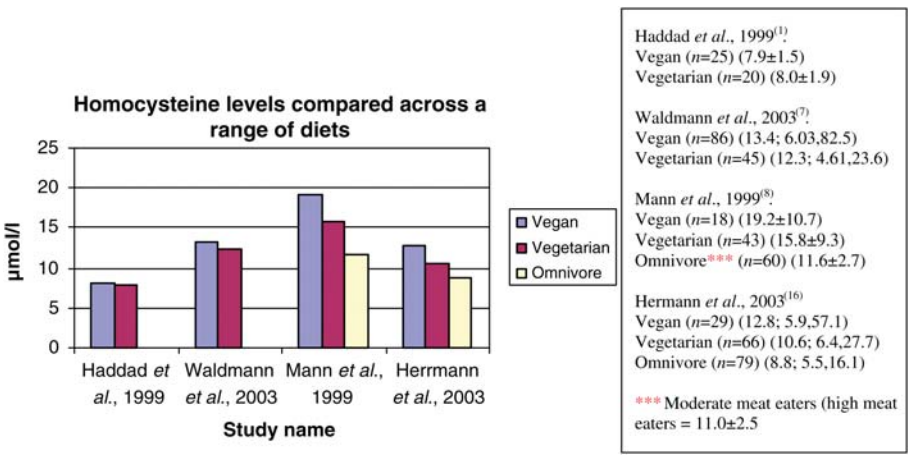

Figure 2. Pooled results of studies providing data of plasma homocysteine concentrations (µmol/l) for trial participants (male and female) across the vegan-vegetarian-omnivore diet range.

this is contentious, with most studies regarding elevated tHcy as being an 'important and independent' link.[146, 148]

B_{12}-dependent enzymes (methionine synthases) are catalysts for the remethylation of serum tHcy to methionine by way of transfer of the methyl group from 5-methyl-THF (5-methyltetrahydrofolate).[149] This leads to a reduction in tHcy serum concentration.[138, 143] This inverse is reflected in Fig. 2, whereby vegans show raised levels of tHcy in all but one study, being Haddad *et al.*[7, 138, 140, 150] Haddad *et al.*'s results may be ascribed to subjects being more prone to taking B_{12} supplements.

Many studies have examined how B_6 and folate (B_9) can lower tHcy levels.[27, 143, 144, 147, 148] This is relevant as folate and B_6 are primarily sourced through plant-based foods (oats, cornmeal, green vegetables, peas, chickpeas and brown rice).[151, 152] Indeed, vegans average substantially higher B_6 and folate intake, with serum concentrations greater than their counter-parts,[7, 140, 150] as can be seen at Table 5. Care should be exercised when considering these results, as USA and Canada (where these studies were conducted) have folate fortification standards in place, thus results may not be reflective of true global vegan folate levels.

For the purpose this study, it is important to ascertain whether the efficacy of folate and B_6 alleviates any CVD risk possibly incurred as a result of insufficient B_{12} levels. Table 6 provides a compilation of trials investigating interactions between folate, B_6, B_{12}, tHCY and CVD.

No large-scale studies established whether B-vitamins were CVD protective; however, Quinlivan *et al.*[153] and Waldmann *et al.*[154] support the hypothesis that increasing B_{12} lowers tHcy and subsequently, CVD risk. Loscalzo (in Brookes)[155] suggested that to acquaint tHcy and B vitamins may be exaggerated or 'oversimplifying a complicated metabolic network'. This could certainly be the case, as the NORVIT 2006[156] trial found CVD was *increased* by combined B-vitamin intake. With the data currently available, veganism would not be expected to bestow an increased risk of CVD.

Conclusion

Lands[67] says, 'Life and death are a summation of processes too complicated to be dependent solely on a single event…'. This is certainly applicable in this case. The vegan diet typically differs from vegetarian and/or omnivorous by: reduced protein, energy, saturated fat, cholesterol, calcium, B_{12}, phosphorous, zinc and sodium levels; and increased carbohydrate, fibre, saturated fat; vitamins A, C, B_6, B_9, magnesium and potassium levels. Whilst aspects of this diet in reducing risk of cancer and CVD may be obvious (e.g. increased phytochemicals), studies assessing the efficacy or detriment of some nutrients remain ambiguous and/or incomplete. There exist many intricacies, and few solid conclusions.

Table 5. Pooled results of studies providing data of folate intake (μm/day), folate serum levels (nm/l; ng/ml) and B6 daily intake (mg/day) across a vegan-vegetarian-omnivore dietary spread

B-Vitamin	Study	Number/sex	Vegan	Number/sex	Vegetarian	Number/sex	Omnivorous
Folate							
Nutrient intake	Janelle and Barr[8]	8/both	416 ± 142 μm	15/both	310 ± 83 μm	22/both	269 ± 77 μm
	Haddad *et al.*[7] (without supplement)	10/male	640 ± 250 μm			10/male	275 ± 175 μm
		15/female	435 ± 155 μm			10/female	240 ± 115 μm
Serum levels	Hermann *et al.*[140] (without supplement)	29/both	34.3 nmol/l (20.7, 72.7)	66/both	28.8 nmol/l (16.1, 77)	79/both	21.8 nmol/l (14.5, 51.5)
	Waldmann *et al.*[138]	86/both	33.6 nmol/l (19.4, 46.3)	45/both	35.1 nmol/l (18.9, 45.3)		
	Mann *et al.*[150]		7.8 ± 3.4 ng/ml		6.3 ± 2.4 ng/ml		5.6 ± 1.7 ng/ml
B6							
Nutrient intake	Janelle and Barr, 1995[8]	8/both	1.88 ± 0.63 mg	15/both	1.40 ± 1.04 mg	22/both	1.61 ± 0.45 mg
	Haddad *et al.*[7] (without supplement)	10/male	3.21 ± 1.33 mg			10/male	1.74 ± 0.48 mg
		15/female	2.17 ± 0.75 mg			10/female	1.68 ± 0.49 mg

Table 6. Pooled results of intervention trials investigating efficacy of B-vitamins (B6, B12, folate) in lowering tHCY and reducing risk of CVD

Study	Cohort size	Detail
Robinson *et al.*[159]	1550 men and women. 750 with vascular disease/800 control	Reduced levels of folate and B6 increase tHcy risk of atherosclerosis[a]
Billion *et al.*[160]	51 haemodialysis patients	Patients given folic acid (folate) supplements (2 months). tHcy decreased significantly from 38.1 $\pm$ 15 to 20.2 $\pm$ 7 μmol/l ($P < 0.001$); patients given daily B_{12} (added to folate supplements); impact of B12 considered negligible (19.8 $\pm$ 7 to 19.1 $\pm$ 5–20.3 $\pm$ 9, did not lower tHcy plasma levels)[a]
Quinlivan *et al.*[153]	53 patients with no predisposed illness	Initial folate treatment, followed by B12 supplementation inverse correlation between serum folate and tHcy diminished with folate intake; hypothesized greater CVD risk reduction from use of combined B12 and folate.[b]
Walmann *et al.*[154]	131 vegans	Correlating folate and B12 to tHcy levels; did not find an association between folate and tHcy concentration;[b] B12 and tHcy were found to inversely correlate ($P < 0.001$)[b]
Bonaa *et al.* (NORVIT Trial)[156]	3749 men and women with acute myocardial infarction	Given B6, folate and B12. Homocysteine lowered by 27% by folate and B12; folate and B12 small negate value on primary end point (myocardial infarction, stroke, coronary artery disease)—(RR: 1.08; 95% CI: 0.93–1.25);[b] increased trend of RR of primary end point when intake of B12, B6 and folate is combined (RR: 1.22, 95% CI: 1.00–1.50, $P = 0.05$)[a]
Brookes, 2006[155] (The Heart Outcomes Prevention Evaluation (HOPE) study)	Double-blind placebo trial of 5522 patients $\geq$55 years old with CVD or diabetes. 70% from Nth USA (folate supplementation) and 30% from EU and Sth USA (no mandatory fortification)	Given B6, folate and B12. Primary outcome events occurred in 18.8% and 19.8% of the intervention and control groups, respectively (RR: 0.95, 95% CI: 0.84–1.07; $P = 0.41$), although a 25% risk reduction occurred for stroke (considered an anomaly by authors), a 25% risk increase occurred for angina; combining folic acid, B6 and B12 did not reduce CVD in patients with vascular disease; not supported as a preventative treatment[a]
Van Oijen *et al.*[161]	229 patients from Coronary Care Unit	No statistical association between B12 and tHcy and the risk of ischaemic heart disease;[a] no association between serum B12 and serum B12 and serum tHcy considered independent factors[a]

[a]Supportive of vegan diet; [b]adverse to vegan diet.

High concentrations of animal-derived protein (high-BV) were found to stimulate the IGF-1 hormone, leading to significant correlations for colorectal and breast cancer. Vegans had lower IGF-1 concentrations due to lower intake of high-BV proteins.

Reduced calcium levels were weakly and inconclusively linked to increased risk for colon cancer and breast cancer, while more conclusively linked to a decreased risk for prostate cancer. Substantial discordance between authors was noted.

Biologically active forms of omega-3 (EPA and DHA) were consistently found to be beneficial in cancer risk reduction due to their anti-inflammatory nature and inhibition of the omega-6 fatty acid, arachiconic acid (pro-inflammatory; risk promoter). Vegans were found to consume reduced amounts of omega-3 in the biologically active forms and increased amounts of omega-6. Benefits of plant-derived omega-3 required further assessment.

Cholesterol was convincingly linked to increased risk of CVD, though the possibility of confounding environmental

factors warranted investigation, as did the detrimental influence of increased carbohydrate consumption on HDL depression.

Vegans were repeatedly found to fall below recommended B_{12} intake. Evidence strongly supports an inverse correlation between B_{12} and homocysteine (with raised concentrations of the latter being associated with increased CVD risk), though substantial trials reported no association between B vitamins and CVD. The amount of contradictory material warrants further monitoring, especially with regard to homocysteine interaction. There were no overarching findings with regard to cancer or CVD risk reduction or promotion from eliminating meat, fish or dairy from the diet. Though dietary intakes of protein, calcium, essential fatty acids, cholesterol and B_{12} varied between the diets, none of the effects were necessarily peculiar to any one type of diet. All aspects (beneficial or detrimental) were able to be incorporated into omnivorous, vegetarian and vegan diets (though bioavailability for some nutrients varied and supplements may be required).

Lands[67] goes on to say '. . . but there are situations in which a particular rate-limiting process can affect markedly the overall outcome.' Perhaps the effects of individual constituents of a particular diet remain largely academic, and it is the conscientiousness and/or ability of the individual to ensure correct intake of sufficient necessary and protective nutrients, while eschewing excess consumption of detrimental ones, that may afford them the greatest disease protection.

Author biography

Brighid has a BSc in Biodiversity and Conservation. Her interest in health and disease saw her take a post at the London School of Hygiene and Tropical Medicine on the EU FP7 funded 'MALACTRES' consortium, which is investigating multi-drug resistance in malaria.

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