IntechOpen

Vitamin B and Vitamin E

Pleiotropic and Nutritional Benefits

Edited by Juber Akhtar, Mohammad Ahmad, Mohammad Irfan Khan and Badruddeen

Vitamin B and Vitamin E - Pleiotropic and Nutritional Benefits

Edited by Juber Akhtar, Mohammad Ahmad, Mohammad Irfan Khan and Badruddeen

Published in London, United Kingdom

Vitamin B and Vitamin E - Pleiotropic and Nutritional Benefits
http://dx.doi.org/10.5772/intechopen.104353
Edited by Juber Akhtar, Mohammad Ahmad, Mohammad Irfan Khan and Badruddeen

Contributors
Hayder Lateef Al-msaid, Hydar Muhsin Khalfa, Hasan Hadi Ali, Lisa J. Hill, Adrian C. Williams, Christina Wood, Satrio Wibowo, Almira Pramadhani, Chen Yongjie, Ji Guangrong, Yu Naichun, Zhou Daguo, Li Zongguang, Gong Fengqing, Yi Weijiang, Chen Botao, Naresh Podila, Sathish Kumar Konidala, Jithendra Chimakurthy, Natesh Gunturu, Mithun Rudrapal, Srilatha Muddisetti, Suryaprabha Matangi, Yamarthi Venkateswara Rao

First published in London, United Kingdom, 2024 by IntechOpen
IntechOpen is the global imprint of INTECHOPEN LIMITED, registered in England and Wales, registration number: 11086078, 5 Princes Gate Court, London, SW7 2QJ, United Kingdom

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

Additional hard and PDF copies can be obtained from orders@intechopen.com

Vitamin B and Vitamin E - Pleiotropic and Nutritional Benefits
Edited by Juber Akhtar, Mohammad Ahmad, Mohammad Irfan Khan and Badruddeen
p. cm.
Print ISBN 978-1-83768-378-9
Online ISBN 978-1-83768-379-6
eBook (PDF) ISBN 978-1-83768-380-2

Meet the editors

Dr. Juber Akhtar has more than 16 years of research and teaching experience. He obtained his BPharm and MPharm from Jamia Hamdard, New Delhi, India, and Manipal University, Karnataka, India, respectively. He obtained his Ph.D. from Integral University, Lucknow, India. Dr. Akhtar is nominated as the head of the Faculty of Pharmacy, Integral University. He also served as chairman cum biological scientist for the Institutional Animal Ethics Committee (IAEC). He works at the Causality Assessment Committee (CAC) and is in charge of the Animal House facility at the Integral University. He has experience teaching abroad and was previously a professor at Buraydah College of Pharmacy and Dentistry, Kingdom of Saudi Arabia. Dr. Akhtar has more than 100 publications in reputed journals to his credit. He served as an academic book editor for international publishers and is an editorial board member for many esteemed journals. He has supervised a dozen Ph.D. and MPharm students in research projects. Dr. Akhtar's area of research interest is the development of nanoparticulate drug delivery systems.

Dr. Badruddeen obtained both a BPharm and MPharm from Hamdard University, Delhi, India. He obtained a Ph.D. in Pharmacology from Integral University, Lucknow, India, in 2014. He has expertise in cardiovascular, neurodegenerative, and endocrine diseases. He has experience in researching the safety, toxicity, and clinical efficacy of herbal and allopathic drugs. He has many original articles in reputed journals to his credit. Dr. Badruddeen is an academic book editor and an editorial board member for many esteemed journals. He has supervised a dozen research scholars and is a member of the Indian Science Congress Association, member secretary of the Institutional Animal Ethics Committee (IAEC), coordinator of the Adverse Drug Monitoring Center (AMC), chairman of the Causality Assessment Committee (CAC), and a member of the Animal House facility, Integral University.

Dr. Mohammad Irfan Khan obtained an MPharm from Hamdard University, Delhi, India. He also holds a Ph.D. in Phytochemistry. He has expertise in Ayurvedic medicine and nutraceuticals and has worked with some of the world's major pharmaceutical companies. He has more than 13 years' experience in research and formulation development of Ayurvedic, herbal, and nutraceutical products and successfully developed more than 100 formulations. He has more than fifty original papers in international journals to his credit. Dr. Khan has supervised many research scholars at post-graduate and Ph.D. levels.

Dr. Mohammad Ahmad holds a specialization in Pharmacology from Jamia Hamdard, New Delhi, India. He received his Ph.D. from Integral University, Lucknow, India. Presently, he is an Assistant Professor of Pharmacology, Faculty of Pharmacy, Integral University. He has been teaching PharmD, BPharm, and MPharm students and conducting research in the field of diabetes and cancer. From 2011 to 2014, he worked as a research assistant on a project sponsored by the Council for Science and Technology, Uttar Pradesh, India. He has published more than twenty original articles in reputed journals. He is a member of the British Society of Nanomedicine, Indian Science Congress Association, and International NanoScience Community, Budapest, Hungry. He is also a social nominee of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). Dr. Ahmad is actively involved in research and his areas of interest include pharmacology and drug and pharmaceutical regulatory affairs. He is also engaged in research pertaining to diabetes mellitus, oral delivery of anticancer agents, and chemoprevention using natural bioactive compounds.

Contents

Preface

This book, *Vitamin B and Vitamin E – Pleiotropic and Nutritional Benefits*, is an insightful exploration of a group of essential vitamins that hold the key to optimal human health and vitality. It is a comprehensive overview of the multifaceted world of vitamin B, a critical water-soluble vitamin, and vitamin E, an oil-soluble vitamin, both of which play integral roles in bodily functions and overall well-being. Understanding the importance of these vitamins is paramount in a world where lifestyle choices and dietary habits often fall short of meeting our nutritional needs. The vitamin B complex encompasses a spectrum of vitamins, each with unique properties and contributions to health ranging from energy metabolism to neurological health and from cell division to the synthesis of red blood cells.

This book is organized into three sections. Chapters discuss cellular metabolic reactions in which B vitamins act as cofactors, how B vitamins are supplied primarily through dietary intake, gut health and gut microbiota, vitamin B and its association with the disease pellagra, and the medicinal significance and complications associated with vitamin E deficiency.

The book is designed for a diverse readership, including scholars and researchers in the field of nutrition and health care as well as students and individuals interested in optimizing their wellbeing. Our hope is that the content herein will serve as a valuable resource, empowering readers with knowledge that can positively influence their dietary choices and lifestyle decisions.

We extend our sincere gratitude to the authors and contributors who have shared their expertise and insights, making this book possible. We also express our heartfelt appreciation to our readers for embarking on this educational journey with us.

May this book inspire curiosity, spark intellectual discourse, and pave the way for a healthier, well-nourished world.

Sincerely,

Dr. Juber Akhtar
Professor,
Faculty of Pharmacy,
Integral University,
Lucknow, India

Badruddeen, Mohammad Irfan Khan and Mohammad Ahmad
Integral University,
Lucknow, India

Section 1

Role of Vitamin B in Body Health and Gut Flora

Chapter 1

Vitamin B Complex and Body Weakness

Hayder Lateef Al-msaid, Hydar Muhsin Khalfa and Hasan Hadi Ali

Abstract

B vitamins are crucial for metabolism. They are chemically unique vitamins with a variety of uses that are often present in the same meals. The vitamin B often operates in concert to provide the body with a multitude of health advantages. The metabolism has been demonstrated to be supported and speeded up by vitamin B. Maintain toned muscles and healthy skin. Boost immune and nervous system performance. Improved red blood cell development and division help to avoid anemia. Together, these factors also assist in battling the signs and causes of stress, depression, and cardiovascular disease. Water-soluble and found throughout the body, all vitamin B. Any excess that is expelled in the urine daily replenishes them, and a vitamin B shortage may result in a wide range of health issues.

Keywords: vitamin B, increasing vitamin B, decreasing vitamin B, vitamin B and body activities, body weakness

1. Introduction

Eight water-soluble vitamins known as B vitamins are crucial for maintaining healthy cell metabolism. In the past, the B vitamins were considered to be a single vitamin known simply as the B vitamin (most people thought it was somewhat similar to vitamin C or vitamin D) [1]. They are chemically separate vitamins that are often present in the same foods and serve a variety of purposes, according to research. Vitamin B complexes are dietary supplements that include all eight B vitamins [2].

The exact name of each vitamin indicates which B vitamin supplements are being taken individually (e.g., B1, B2, and B3), The B vitamins often operate in concert to provide the body with a multitude of health advantages [3]. The metabolism has been demonstrated to be supported and speeded up by B vitamins. Maintain toned muscles and healthy skin, and boost immune and nervous system performance. Improved red blood cell production helps to avoid anemia. Together, these factors also serve to battle the signs and causes of stress, depression, and cardiovascular disease [4].

Water soluble and found throughout the body, all B vitamins. Any extra excreted in the urine is daily replaced with them. A large number of different health issues

may be brought on by vitamin B deficiency [5]. Important new research in this field is presented in this book.

Contrary to popular belief, oral vitamin B12, 1 mg daily, is used to treat the majority of vitamin B12 deficient patients worldwide.

There are at least six distinct ways that vitamin B3 (niacin) insufficiency may manifest, although they all overlap. The intake may be inadequate even when the food provides an adequate amount of niacin and there are no issues with absorption or storage [6]. This is because certain people may need unusually high levels of vitamin B-3, which a conventional diet cannot provide, due to hereditary factors. Up to one-third of genetic mutations cause the matching enzyme to have a decreased affinity for its own enzyme, which lowers the pace of the reaction [7].

Therefore, extremely large dosages of the matching enzyme may be employed to cure the roughly 50 hereditary illnesses of humans caused by these faulty enzymes. Vitamin B3 serves as a cofactor in many of the enzymes that are implicated in various hereditary diseases. These include increased risks for cancer and alcoholism brought on by poor aldehyde dehydrogenase binding, phenylketonuria II, and hyperphagia brought on by inadequate dihydropteridine reductase binding [8].

The HM74A and HM74B subtypes of niacin-responsive receptors were only recently identified. Niacin stimulates prostaglandin production *via* the high-affinity receptor HM74A. The HM74A protein is dramatically reduced in areas of the brain of schizophrenia patients, indicating a niacin-related deficiency that results in significantly increased vitamin B3 needs [9].

Niacin deficiency is most often brought on by diets with little to no vitamin B3 in them. For instance, pellagra is often detected in people who have consumed a lot of maize, a grain for which niacin is difficult to come by patients who have issues with absorption and storage are also at risk for vitamin B3 insufficiency. The body's supply of this vitamin and certain antibiotics will be depleted by excessive eating of foods like sweets and carbs [10].

Niacin deficiency is often caused by addiction and may be remedied by taking large amounts of this vitamin. Niacin, for example, is needed as a cofactor for aldehyde dehydrogenase, one of the key enzymes involved, making vitamin B3 essential for the breakdown of alcohol. Niacin and nicotine have chemical similarities; hence, nicotine may occupy receptor sites. High dosages of vitamin B3 have undoubtedly assisted some individuals in kicking their nicotine addiction [11].

The excessive oxidative stress that results in unusually high metabolic demand for this vitamin may also lead to a niacin deficit. It seems that diseases like Parkinson's, amyotrophic lateral sclerosis, and multiple sclerosis are caused by an excessive amount of dopamine being broken down, which produces neurotoxins like dopachrome [12].

This process may be speed up by vitamin B3, although the body often has low levels of the vitamin. Similar to this, individuals with schizophrenia create excessive amounts of adrenaline, as well as its hazardous metabolites, adrenochrome, and other chromium indoles. They, therefore, have niacin depletion, which is now recognized as the disease's diagnostic sign [13]. With aging, the body's capacity to absorb nutrients often decreases. As a consequence, niacin deficiency, among other vitamin inadequacies, is most prevalent among the elderly. These deficiency-related conditions react to high-dose niacin, including lipid imbalances, cardiovascular diseases, stroke, and arthritis. The recommended daily therapeutic intervention varies from 10 mg in newly diagnosed instances of pellagra from 6 to 10 grams for cholesterol normalization, cardiovascular disease, and stroke, according to the literature and Dr. Abram Hoover's experience with more than 5000 patients [14].

2. Health and folic acid

There is no evidence that folic acid is also important for the development of the central nervous system. Folic acid has long been recognized to cause a kind of anemia known as megaloblastica, but there is no evidence that it may cause problems early in pregnancy and at the time of conception [15].

The neural tube develops with birth abnormalities as a result. Inadequate amounts of folic acid have recently been linked to increased blood levels of the amino acid homocysteine (Hcy). Hcy is a well-known risk factor for conditions affecting the neurological and cardiovascular systems, as well as for dementia, Alzheimer's disease, osteoporotic fractures, and problems during pregnancy [16].

Folic acid has also been linked to reducing the risk of a variety of cancers. Recent epidemiological studies, for instance, show a negative correlation between folate status and the frequency of colorectal adenomas and carcinomas, indicating that lowering this risk may require maintaining appropriate folate levels [17].

On the other side, a number of studies indicate that excessive intakes, often linked to folic acid supplements, may raise the risk of breast cancer in postmenopausal women, particularly in those who consume moderate amounts of alcohol. Additionally, there is a chance that extensive folic acid fortification may conceal a vitamin B12 shortage, which might result in neurological impairment. Similar to folic acid insufficiency, vitamin B12 deficiency results in anemia and irreparable harm to the central and peripheral neurological systems [18].

However, over many generations, folate fortification may also have an impact on genetic selection for potentially deleterious genotypes and epileptic seizure management. There is a lot of interest in learning if dietary supplements and food products include folic acid, which is increasingly being considered on a global scale as an essential functional food element [19].

Folic acid fortification may be beneficial or damaging to health. Crohn's disease (CD), which may affect any portion of the gastrointestinal system, and ulcerative colitis (UC), which can affect the colon, are the two primary manifestations of inflammatory bowel disease (IBD), which is a chronic relapsing–relapsing inflammatory disorder of uncertain cause. The cornerstone of therapy for the majority of IBD patients is medical care with aminosalicylates (5-ASA), steroids, and immunosuppressive or immunosuppressive drugs. Surgery is only performed on people who have serious illnesses that are resistant to medical treatment or who have problems [20].

In the development, management, and therapy of IBD, nutrition is crucial. Inflammatory bowel disease patients often experience malnutrition, particularly those with Crohn's disease (CD). Patients with inflammatory bowel illness have been reported to have a variety of vitamin and mineral deficiencies. Despite their pathogenic significance in clinical symptoms and the many consequences associated with IBD, nutritional disorders are often disregarded in the care of patients. There are several factors that contribute to malnutrition in IBD, including inadequate oral nutritional intake, malabsorption, and nutrient loss [21], excessive nutritional needs, iatrogenic justification for surgery or treatment. Members of the "B vitamin complex" include thiamine (vitamin B1), riboflavin (vitamin B2), niacin, pyridoxine (vitamin B6), pantothenic acid, biotin, folic acid (vitamin B9), and vitamin B12. These are substances that dissolve in water and are crucial for the metabolic functions of living cells [22].

They function as coenzymes or as prosthetic groups attached to enzymes. When one of these vitamins is improperly ingested, the utilization of the other vitamins may

be compromised. Folic acid and vitamin B12 deficiencies are often reported in IBD patients, and they are also linked to the anemia, thrombosis, and carcinogenesis that are associated with the disease [23].

Patients with IBD have also been shown to have low blood concentrations of other "vitamin B complex" members because of their deficiencies. By changing branched-chain carbonic acids into straight-chain branched carbonic acids, adenosylcobalamin-dependent CoA-carbonyl mutations accelerate the 1,2-rearrangement of carbonyl groups. Only two mutants of this enzyme family are now known, isobutyryl-CoA and methylmalonyl-CoA (MCM, EC 5.4.99.2). Both of these mutants have undergone substantial research [24].

All of the substances are significant water and soil contaminants; therefore, the novel cobalamin and CoA-carbonyl mutations play a hitherto unrecognized function in both natural and induced bioremediation processes. Consequently, the pathways that have not yet been connected to CoA-carbonyl mutation action. Additionally, it is probable that the enzyme structure and the fold that were used to predict the development of substrate specificity are related. Finally, the potential biological and kinetic effects of using a cobalamin-dependent enzyme to bend the routes are explored [25].

The water-soluble, catalytically active form of vitamin B6 is called pyridoxal 5′-phosphate (PLP), and it functions as a cofactor for several crucial human enzymes. Unique to a range of reactions to amino acids are PLP-dependent enzymes. They have the capacity to catalyze (transport, decarboxylation, or substitution/deletion). Various reactions happen without an enzyme. However, the protein portion simultaneously directs the enzyme's catalytic power toward a particular process. This specificity is not absolute, however. Physiologically significant side reactions that most PLP enzymes catalyze may also provide fascinating stereochemical and mechanical details about the structure of the enzyme's active site [1].

Dental spirochetes include cytolysin, a PLP-dependent C-S lyase whose most significant interaction is the removal of, from L-cysteine to create pyruvate, ammonia, and H2S. The latter is most likely in charge of the catalytic enzyme's hemolytic and hemeoxide-related action. One of the best examples of PLP-dependent enzymes' very versatile catalysts is cystalysin. In reality, it has only recently been shown that cetalicin is present [26].

Additionally, it may catalyze the transition between L- and D-alanine with turn numbers estimated in minutes, as well as the cracking of both isoforms of alanine, desulfurization of sulfuric acid L-cysteine, and decarboxylation of L-aspartate and oxalacetate. The cofactor binding mode, substrate specificity, formation of intermediate reactions typical of most PLP enzymes, and involvement of some active site residues in primary and secondary catalytic reactions are just a few of the intriguing characteristics of cystalysin that have been revealed through extensive biochemical investigations [27].

3. High homocysteine levels

Plasma from patients with renal failure, hypothyroidism, and methyltetrahydrofolate reductase polymorphism as well as those with homocystinuria, a hereditary disorder with a recessive pattern, was examined. The most crucial cerebral impairment, osteoporosis, lens shift, and arterial and venous thrombosis are among clinical symptoms of elevated plasma homocysteine levels. About 50% of deaths in patients with chronic renal failure are caused by cardiovascular illnesses, which are the main

source of morbidity and mortality in the general population. Hyperhomocysteinemia is decreased by vitamin B6, vitamin B12, and folic acid. Transformation of sulfur and the remethylation process [28].

Although vitamin B medications often fail to correct plasma homocysteine levels, their long-term benefits are helpful in lowering the life-threatening vascular dangers that patients with homocystinuria face.

Patients with chronic renal failure, particularly those with stage V chronic kidney disease, are found to have hyperhomocysteinemia. The outcomes of observational clinical investigations on the consequences of increased plasma homocysteine levels on cardiovascular disease in hemodialysis patients have varied. In fact, several studies have shown a relationship between hypohomocysteinemia and cardiovascular disease fatalities in addition to hyperhomocysteinemia. The strong correlation between homocysteine and inflammatory indicators of malnutrition may be the cause of these contradicting observations [29].

Malnutrition-atherosclerotic syndrome is a serious clinical disease that often affects dialysis patients, interfering with homocysteine levels. My colleagues and I recently noticed in a clinical study that dialysis patients who were receiving vitamin B treatment and had high protein catabolism and low homocysteine levels outlived the other three groupings by a substantial margin. Recent prospective clinical trials that looked at the effects of moderate hyperhomocysteinemia patients receiving vitamin B treatment to decrease homocysteine on cardiovascular events revealed no therapeutic benefits. Because some of the patients had normal homocysteine levels, the follow-up period may have been too little, and confounding variables were not taken into consideration, these findings may be deceptive [30].

The study discusses the interesting mystique surrounding homocysteine and highlights the most relevant information about the impact of vitamin B therapy on cardiovascular events.

4. Vitamin B12

Two important enzyme pathways the conversion of homocysteine to methionine and the conversion of methylmalonyl coenzyme A to succinyl coenzyme are affected physiologically by it. Elevated blood homocysteine and methylmalonic acid result from disruption of any of these processes brought on by vitamin B12 deficiency. When folic acid levels are low, homocysteine levels also increase. It has been proposed that serum homocysteine rather than serum vitamin B12 analysis is more sensitive to intracellular functional vitamin B12 insufficiency. As a result, in the so-called one-carbon cycle, homocysteine, vitamin B12, and folic acid are strongly tied to one another [31]. The suggested mechanism is connected to methylation processes involving the nervous system's metabolism of homocysteine. The coenzyme that is required for its effective functioning is vitamin B12 methionine can only be produced when 5-methyletrahydrofolate donates its methyl group to tetrahydrofolate. On the other side, folate stimulates the remethylation of homocysteine, a cytotoxic molecule that contains sulfur, making it a cofactor in one-carbon metabolism [32].

Amino acids have the ability to cause DNA strand breaks, oxidative damage, and cell death. What or what appears to be consistent with the widespread belief that vitamin B12 and folic acid, either directly through the maintenance of two functions, DNA synthesis and methylation reactions, or indirectly, as a result of their deficiency, which results in methylation reactions mediated by SAM that are inhibited by its

product SAH, and from through the related toxic effects of homocysteine causing direct damage to the vascular endothelium and inhibition of N-methyl-D [33].

This vitamin functions in a rising number of organs and bodily systems, the list of which is constantly expanding. The peripheral and central neurological systems, bone marrow, skin, mucous membranes, bones, and blood vessels are all impacted, in addition to children's typical growth. In addition to a sophisticated chemical structure, vitamin B12 (cobalamin) also includes the trace element cobalt, which is vital for human health. Vitamin B12 has significant immunological and neurotrophic effects in addition to playing a significant role in DNA synthesis. The human body's many systems must remain in balance. Even under the worst illness stressors, the individual is the ideal illustration of a system that always strives to attain optimum control. Consider that everything is standard and replaceable (as needed) if vitamin B12 is one of these things, why is it important, it is conceivable that therapy with vitamin B12 may rectify abnormalities brought on by other physiologically active chemicals even when the blood cobalamin level is normal [34]. This has been shown to be effective in treating recurrent aphthous stomatitis with vitamin B12 (regardless of blood level!) in the authors' research. This phenomenon is referred to as the "master switch" effect. Deficiency in vitamin B12 is a widespread issue that affects the entire population. Clinically significant is the early identification of vitamin B12 insufficiency, and there is evidence that deficiency occurs more often than anticipated. Patients who are unable to absorb vitamin B12 from food and people with dietary habits that exclude animal foods are both at risk for vitamin B12 insufficiency [35]. In addition, owing to the association between meat, cholesterol, and cardiovascular disease, there is a widespread inclination to steer clear of foods rich in vitamin B12, such as beef. Additionally, there is a propensity toward vegetarianism due to ideological reasons, particularly among the younger population. Two key causes of the low consumption of animal products, particularly red meat, are changes in lifestyle among population groups with high socioeconomic status and the prevalence of poverty. As a result, the amount of vitamin B12 in the general population is declining, which has an impact on the pathology caused by vitamin B12 deficiencies (e.g., neurological and hematological disorders). If more studies corroborate the link between homocysteine and vitamin B12, the authors may also report an increase in cardiovascular disease. Instead of these changes, major health issues should be avoided [36].

5. Vitamin B6

This vitamin is made up of a number of pyridoxal-containing substances, including pyridoxol, pyridoxamine, pyridoxaldehyde, and its derivatives. Structure the pyridoxine transporter at the sinusoidal pole has a determining hepatocyte absorption of pyridoxal, the catalytically active form of vitamin B6. Because pyridoxal may be transported to cells by an organ transport system when pyridoxine transporters in hepatocytes can specifically detect and bind to the structure. Thus, pyridoxine may be used as a liver-targeting group and added to big molecules and low molecular weight drugs to be used as contrast in MRI agents and anticancer comparisons [37]. The study of medication transport to the liver advances. The insertion of pyridoxine into these compounds has been shown to boost their liver absorption, and the molecules that include pyridoxine groups have liver-targeting characteristics.

6. Conclusions

B vitamins are crucial for metabolism. They are chemically unique vitamins with a variety of uses that are often present in the same meals.

The B vitamins often operate in concert to provide the body with a multitude of health advantages. The metabolism has been demonstrated to be supported and speeded up by vitamin B. Maintain toned muscles and healthy skin. Boost immune and nervous system performance. Improved red blood cell development and division help to avoid anemia. Together, these factors also assist to battle the signs and causes of stress, depression, and cardiovascular disease.

Water soluble and found throughout the body, all B vitamins. Any excess that is expelled in the urine daily replenishes them, and a vitamin B shortage may result in a wide range of health issues.

Author details

Hayder Lateef Al-msaid*, Hydar Muhsin Khalfa and Hasan Hadi Ali
Department of Biology, Kufa University, Najaf, Iraq

*Address all correspondence to: haiderl.ligan@uokufa.edu.iq

IntechOpen

References

[1] Hrubša M, Siatka T, Nejmanová I, Vopršalová M, Kujovská Krčmová L, Matoušová K, et al. Biological properties of vitamins of the B-complex, part 1: Vitamins B1, B2, B3, and B5. Nutrients. 2022a;**14**(3):484

[2] Vidović B, Đuričić B, Odalović M, Milošević Georgiev A, Tadić I. Dietary supplements use among Serbian undergraduate students of different academic fields. International Journal of Environmental Research and Public Health. 2022;**19**(17):11036

[3] Peterson CT, Perez Santiago J, Iablokov SN, Chopra D, Rodionov DA, Peterson SN. Short-chain fatty acids modulate healthy gut microbiota composition and functional potential. Current Microbiology. 2022;**79**(5):128

[4] Sarojnalini C, Hei A. Fish as an important functional food for quality life. U: Functional Foods, (Lagouri, V, Ured). 2019;**2019**:77-97

[5] Fratoni V, Brandi ML. B vitamins, homocysteine and bone health. Nutrients. 2015;**7**(4):2176-2192

[6] Hanna M, Jaqua E, Nguyen V, Clay JB. B vitamins: Functions and uses in medicine. The Permanente Journal. 2022;**26**:89-97

[7] Bellows L, Moore R, Anderson J, Young L. Water-soluble vitamins: B-complex and vitamin C. Food and nutrition Series Health. 2012;**9**:312

[8] Huang Y, Shan Y, Zhang W, Lee AM, Li F, Stranger BE, et al. Deciphering genetic causes for sex differences in human health through drug metabolism and transporter genes. Nature Communications. 2023;**14**(1):1-15

[9] Miller CL, Dulay JR. The high-affinity niacin receptor HM74A is decreased in the anterior cingulate cortex of individuals with schizophrenia. Brain Research Bulletin. 2008;**77**(1):33-41

[10] Gries CL, Scott ML. The pathology of thiamin, riboflavin, pantothenic acid and niacin deficiencies in the chick. The Journal of Nutrition. 1972;**102**(10):1269-1285

[11] Johnson S. The multifaceted and widespread pathology of magnesium deficiency. Medical Hypotheses. 2001;**56**(2):163-170

[12] Sauve AA. NAD+ and vitamin B3: From metabolism to therapies. Journal of Pharmacology and Experimental Therapeutics. 2008;**324**(3):883-893

[13] Foster HD. What Really Causes Schizophrenia. Canada: Trafford Publishing; 2003

[14] Nordell AD, McKenna M, Borges ÁH, Duprez D, Neuhaus J, Neaton JD, et al. Severity of cardiovascular disease outcomes among patients with HIV is related to markers of inflammation and coagulation. Journal of the American Heart Association. 2014;**3**(3):e000844

[15] Reynolds E. Vitamin B12, folic acid, and the nervous system. The Lancet Neurology. 2006;**5**(11):949-960

[16] Reynolds EH. The neurology of folic acid deficiency. Handbook of Clinical Neurology. 2014;**120**:927-943

[17] Ruiz RB, Hernández PS. Diet and cancer: Risk factors and epidemiological evidence. Maturitas. 2014;**77**(3):202-208

[18] Green R, Kara N, Cocks H. Vitamin B12 deficiency: An unusual cause of vocal

fold palsy. The Journal of Laryngology & Otology. 2011;**125**(12):1309-1311

[19] Heasman M, Mellentin J. The Functional Foods Revolution: Healthy People, Healthy Profits? UK: Earthscan; 2001

[20] Bressler B, Marshall JK, Bernstein CN, Bitton A, Jones J, Leontiadis GI, et al. Clinical practice guidelines for the medical management of nonhospitalized ulcerative colitis: The Toronto consensus. Gastroenterology. 2015;**148**(5):1035-1058

[21] Balestrieri P, Ribolsi M, Guarino MPL, Emerenziani S, Altomare A, Cicala M. Nutritional aspects in inflammatory bowel diseases. Nutrients. 2020;**12**(2):372

[22] Lykstad J, Sharma S. Biochemistry, Water Soluble Vitamins. USA. 2019

[23] Gold SL, Manning L, Kohler D, Ungaro R, Sands B, Raman M. Micronutrients and their role in inflammatory bowel disease: Function, assessment, supplementation, and impact on clinical outcomes including muscle health. Inflammatory Bowel Diseases. 2022;**1**:1-257

[24] Erbach J, Bonn F, Diesner M, Arnold A, Stein J, Schröder O, et al. Relevance of biotin deficiency in patients with inflammatory bowel disease and utility of serum 3 hydroxyisovaleryl carnitine as a practical everyday marker. Journal of Clinical Medicine. 2022;**11**(4):1118

[25] Stogios PJ, Bordeleau E, Xu Z, Skarina T, Evdokimova E, Chou S, et al. Structural and molecular rationale for the diversification of resistance mediated by the Antibiotic_NAT family. Communications Biology. 2022;**5**(1):263

[26] Gupta S. Recent reports on pyridoxal derived Schiff base complexes. Reviews in Inorganic Chemistry. 2022;**42**(2):161-177

[27] Mukherjee S, Banerjee O, Singh S. The role of B vitamins in protecting mitochondrial function. In: Molecular Nutrition and Mitochondria. USA: Academic Press; 2023. pp. 167-193

[28] Ibodov B, Shamsieva U, Akramova D. Hyperhomocysteinemia is a prior Diator of congenital anomalies. Eurasian Medical Research Periodical. 2023;**16**:15-20

[29] Fujita M, Wander K, Tran T, Brindle E. Characterizing the extent human milk folate is buffered against maternal malnutrition and infection in drought-stricken northern Kenya. American Journal of Biological Anthropology. 2022;**179**(2):171-183

[30] Percival R. The Meat Paradox:'Brilliantly Provocative, Original, electrifying'Bee Wilson. Hachette UK: Financial Times; 2022

[31] Malalasekara L, Escalante-Semerena JC. A method for the isolation of α-ribazole from vitamin B12, and its enzymatic conversion to α-ribazole 5′-phosphate. In: Methods in Enzymology. Vol. 668. USA: Academic Press; 2022. pp. 125-136

[32] McCabe CF, LaBarre JL, Domino SE, Treadwell MC, Baylin A, Burant CF, et al. Maternal and neonatal one-carbon metabolites and the epigenome-wide infant response. The Journal of Nutritional Biochemistry. 2022;**101**:108938

[33] Pandya M, Shah S, Dhanalakshmi M, Juneja T, Patel A, Gadnayak A, et al. Unravelling Vitamin B12 as a potential inhibitor against SARS-CoV-2: A computational approach. Informatics in Medicine. 2022;**30**:100951

[34] Jomova K, Makova M, Alomar SY, Alwasel SH, Nepovimova E, Kuca K, et al. Essential metals in health and disease. Chemico-Biological Interactions. 2022;**2022**:110173

[35] Cicero AF, Minervino A. Combined action of SAMe, folate, and Vitamin B12 in the treatment of mood disorders: A review. European Review for Medical and Pharmacological Sciences. 2022;**26**(7):2443-2459

[36] Liu Y, Geng T, Wan Z, Lu Q, Zhang X, Qiu Z, et al. Associations of serum folate and vitamin B12 levels with cardiovascular disease mortality among patients with type 2 diabetes. JAMA Network Open. 2022;**5**(1):e2146124-e2146124

[37] Gai Y, Li Y, Wu S, Xu L, Lu Y, Lan X, et al. Preparation and In vitro evaluation of a gadolinium-containing Vitamin E TPGS micelle as a potential contrast agent for MR imaging. Pharmaceutics. 2023;**15**(2):401

Chapter 2

Vitamin B, Role of Gut Microbiota and Gut Health

Satrio Wibowo and Almira Pramadhani

Abstract

The human gastrointestinal system is constantly exposed to pathogenic microorganisms and beneficial compounds, such as food components and commensal bacteria. Vitamin B are a class of water-soluble organic compounds obtained through diet, supplementation, and gut microbiota synthesis. B vitamins are absorbed for host metabolism in the small intestine, whereas microbes produce and absorb B vitamins in the large intestine. The authors have accumulated evidence from various studies that each B vitamin plays an essential role in gastrointestinal health and has a reciprocal relationship with the gut microbiota. Previous studies have also proven that microbial imbalance in the gut lead to competition for the utilization of B vitamins between the host and microbes, affecting the gut microbial composition, gut health, and host metabolism. This review aims to explain further the types of B vitamins in human digestion, the mechanism of B vitamin synthesis, and the role of B vitamins in the composition of the gut microbiota and the health of the gastrointestinal tract. Thus, it can help practitioners to consider administering B vitamins to maintain the patient's gut health.

Keywords: B vitamins, microbiota, intestine, biosynthesis, gut health

1. Introduction

The human gastrointestinal system is continuously exposed to toxic compounds, such as pathogenic microorganisms, and beneficial compounds, such as food components and commensal bacteria. Therefore, the immunity of the gastrointestinal system must be balanced between an active and suppressive immune response. Vitamins are micronutrients essential for normal human metabolism because they have various physiological effects, one of which is immunity. So, vitamin deficiency causes an increased risk of infectious diseases, allergies, and inflammation that can damage the gastrointestinal system. Over the past decade, a large number of studies have investigated the role of vitamins in various gastrointestinal diseases, including their potential in the prevention or treatment of various malignancies, inflammatory diseases, and hepatobiliary disorders [1, 2].

One of the vitamins that have a role in the gastrointestinal system is vitamin B, a group of water-soluble organic compounds with various functional roles, including cofactors in many enzymatic reactions, cellular energy-producing reactions, neurotransmitter synthesis, cell signaling, nucleic acid biosynthesis, and immune

function. The intestine is an important organ, especially for storing and absorbing food. The gut also has the densest microbiota in the body, consisting primarily of four major phyla, that is, Bacteroidetes, Firmicutes, Proteobacteria, and Actinobacteria. The microbiota will maintain a symbiotic relationship with the host and protect against harmful pathogens. Some gut microbiota also produces limited amounts of B vitamins, and some require B vitamins for growth. Much evidence has shown that a healthy gut is associated with a healthy microbiota ecology, and B vitamins play an essential role in modifying the gut microbiota [3].

Although B vitamins from food are mainly absorbed in the small intestine, excess B vitamins cannot be absorbed in the small intestine and are transferred to the more distal intestine. Thus, the biosynthesis of B vitamins is mostly supplied by the distal gut microbiota. B vitamins in the distal intestine are dominant in performing important physiological functions in the body, including acting as nutrients for the host and microbiota, regulating immune cell activity, mediating drug efficacy, suppressing colonization of pathogenic bacteria, and modulating colitis. Therefore, the deficiency of B vitamins will certainly damage normal cell metabolism and trigger the development of several pathogenic microorganisms in the intestines [3, 4].

2. Types of B Vitamins in human digestion

Vitamins are essential micronutrients that all living cells need to carry out biochemical reactions. Vitamins are classified into fat-soluble and water-soluble. The fat-soluble vitamins are vitamins A, D, E, and K, while the water-soluble vitamins include vitamin C, biotin (vitamin H or B7), and a series of B vitamins—thiamin (B1); riboflavin (B2); niacin (B3); pantothenic acid (B5); pyridoxine, pyridoxal, pyridoxamine (B6); folic acid (B9), and cobalamin (B12) [5]. Fat-soluble vitamins act as essential elements of cell membranes, and the excess is stored by cells. Water-soluble vitamins function as coenzymes for specific chemical biochemical reactions, and the excess is excreted in the urine [6].

2.1 Vitamin B1

Vitamin B1 (thiamin) is a cofactor for several enzymes, including pyruvate dehydrogenase and a-ketoglutarate dehydrogenase, which are involved in the tricarboxylic acid (TCA) cycle. The thiamin molecule consists of a pyrimidine ring (4-amino-2-methylpyrimidine) and a thiazolium (4-methyl-5-(2-hydroxyethyl)-thiazolium), linked by a methylene bridge between the C3 carbon atom of the pyrimidine ring and the N3 nitrogen atom of the thiazolium ring. Vitamin B1 is found in high concentrations as thiamin pyrophosphate (TPP) [2, 7]. Thiamine strengthens the immune system, degrades glucose, helps nerve communication, and maintains processes in cells and tissues [8].

The intestinal epithelium absorbs free thiamine through thiamine transporters, that is, THTR-1 and THTR-2, which are transported to the blood for distribution throughout the body. Free thiamine is converted back to TPP and used for energy metabolism in the TCA cycle. The mechanism of thiamine absorption from food and microbiota is relatively similar. However, TPP produced by the gut microbiota is not converted to free thiamin because alkaline phosphatase is not secreted in the large intestine. Thus, TPP from the microbiota is absorbed directly by the large intestine.

The TPP transporter is widely expressed in the apical membrane of the colon. Absorbed TPP enters the mitochondria via MTPP-1 and is used as a cofactor for ATP formation. This suggests that TPP microbiota is vital for energy generation in the large intestine, by a mechanism that differs between vitamin B1 from the diet and from the microbiota [2].

2.2 Vitamin B2

Vitamin B2 (riboflavin) and its active forms (flavin adenine dinucleotide FAD] and flavin mononucleotide FMN]) are cofactors for enzymatic reactions in the TCA cycle and electron transport mediators of fatty acid oxidation (β-oxidation). Riboflavin is also involved in the metabolism of folate, vitamin B12, and vitamin B6, so it helps maintain the integrity of the mucosa, skin, eyes, and nervous system. Riboflavin is essential in the early development of the brain and postnatal gastrointestinal tract, as it can modulate some metabolic activities such as DNA repair, iron absorption and distribution, inflammation, and immune responses [2, 9].

The process of riboflavin absorption in the small intestine and colon is specific and mediated by the transporters RFVT-1, RFVT-2, and RFVT-3. All three are products of the SLC52A1, SLC52A2, and SLC52A3 genes expressed in the human gut, respectively, with RFVT-3 expression being the dominant one [9]. Exogenous vitamin B2 in the form of FAD or FMN is converted into free riboflavin by FAD pyrophosphatase and FMN phosphatase in the small intestine [2].

2.3 Vitamin B3

Niacin and niacinamide, known as nicotinic acid (NA) and nicotinamide (Nam), are different forms of vitamin B3. Vitamin B3 is a biosynthetic precursor for nicotinamide adenine dinucleotide (NAD+) and nicotinamide adenine dinucleotide phosphate (NADP+), which are coenzymes in respiratory oxidation processes, the Krebs cycle, the formation and inhibition of reactive oxygen species (ROS), post-translational protein and regulatory protein modification, and the formation of a second messenger. Vitamin B3 also functions for DNA proliferation. Thus, vitamin B3 is the center of homeostasis and cellular growth [2, 8, 10].

In contrast to other B vitamins, vitamin B3 can be produced by mammals via the endogenous enzymatic pathway from tryptophan and stored in the liver. However, vitamin B3 must also be obtained from food [2]. Vitamin B3 deficiency is endemic in some areas of the world where malnutrition is common. In more developed countries, vitamin B3 deficiency is caused by poor food choices, adverse drug reactions, alcoholism, and infectious or autoimmune diseases [6, 10].

2.4 Vitamin B5

Vitamin B5 (pantothenic acid) is a coenzyme A (CoA) precursor, an important cofactor for the TCA cycle and fatty acid oxidation. CoA has a role in various human biochemical reactions, such as cell growth, intermediate metabolism, and neurotransmitter synthesis. The structure of CoA functions as an activating carbonyl group and as an acyl group carrier to help facilitate these reactions. Like vitamins B1 and B2, vitamin B5 is also involved in controlling host immunity through energy production by immune cells [2, 11].

From dietary sources, vitamin B5 is found in high concentrations as CoA or phosphopantethein. CoA and phosphopantetheine are then converted to free pantothenic acid by endogenous enzymes such as phosphatase and pantetheinase in the small intestine. Whereas, from the microbiota, Vitamin B5 is produced in the form of free pantothenic acid, which is directly absorbed in the large intestine, converted to CoA, and distributed in the same way as vitamin B5 from food [2].

2.5 Vitamin B6

Vitamin B6 has the basic structure of 2-methylpyridine, 3-hydroxypyridine, and 5-hydroxymethyl pyridine. Vitamin B6 consists of various forms, that is, pyridoxal (aldehyde, eCHO), pyridoxine (alcohol, eCH2OH), and pyridoxamine (amine, eCH2NH2). These forms of vitamin B6 are precursors of the coenzymes pyridoxal phosphate (PLP) and pyridoxamine phosphate (PMP), which are involved in various cellular metabolic processes, including amino acid, lipid, and carbohydrate metabolism. Vitamin B6 also plays a role in nucleotide synthesis, neurotransmitter metabolism, and heme synthesis. So, this vitamin affects almost all aspects of metabolic function and cellular homeostasis. Vitamin B6 deficiency causes inflammation such as allergies and rheumatoid arthritis, as well as nerve dysfunction [2, 12].

Dietary vitamin B6 is available in the form of PLP or PMP, which is then converted into free vitamin B6 by the endogenous enzyme pyridoxal phosphatase and subsequently absorbed by the small intestine. Absorption of B6 from food sources occurs primarily in the small intestine jejunum, with the absorption rate varying according to the B6 species present. Meanwhile, microbial-synthesized vitamin B6 in the form of PLP is converted into free vitamin B6 in the large intestine, then absorbed through passive transport, transported to the blood, and distributed throughout the body [2, 12, 13].

2.6 Vitamin B7

Biotin (vitamin B7 or vitamin H) is a B-complex vitamin that acts as an essential coenzyme for five carboxylases: pyruvate carboxylase, 3-methylcrotonyl-CoA carboxylase (MCC), propionyl-CoA carboxylase (PCC), and acetyl-CoA carboxylase 1 and 2. This carboxylase helps several chemical processes in cells, including gluconeogenesis, amino acid metabolism, and fatty acid synthesis. Acetyl-CoA carboxylase 1 is found in the cytoplasm and catalyzes the binding of bicarbonate to acetyl-CoA during the synthesis of fatty acids, while another carboxylase is found in mitochondria. PCC catalyzes a critical step in the metabolism of propionyl-CoA, which is derived from the catabolism of odd-chain fatty acids and several other nutrients. Meanwhile, MCC catalyzes the metabolism of the amino acid leucine. Pyruvate carboxylase catalyzes the conversion of pyruvate into oxaloacetate, which is a key step in gluconeogenesis [14, 15].

The enzyme holocarboxylase synthetase (HLCS) catalyzes the binding of biotin to all five carboxylases, thus playing an essential role in biotin-dependent metabolic pathways. In addition, HLCS also functions in gene regulation at the chromatin level. Meanwhile, the biotinidase enzyme in the small intestine catalyzes the release of biotin from the breakdown product of carboxylase, thus playing an important role in biotin recycling. Free biotin is then absorbed via the biotin transporter SMVT [2, 15].

2.7 Vitamin B9

Vitamin B9 (folate), in its active form as tetrahydrofolate, is a cofactor in several metabolic reactions, including the synthesis of DNA and amino acids. A folic acid is a synthetic form of folate found in supplements. Bacteria use folate to synthesize the nucleic acids that make up their DNA. In an animal model of endometrial carcinoma study, folate was found to be the most important B-complex vitamin for nucleic acid synthesis, amino acid conversion, and antioxidant properties for eliminating free radicals [16]. In addition to DNA synthesis, folate also functions as a cofactor in homocysteine methylation and reduces the risk of *neural tube defects* [8]. Folate supplementation studies have also demonstrated a role in preventing other diseases, such as neurological disorders and cognitive and psychiatric disorders, and protection against degeneration in ulcerative colitis [17].

Vitamin B9 in food is available in monoglutamate and polyglutamate folate. In the intestinal epithelium, the folate transporter PCFT deconjugates polyglutamate folate to monoglutamate folate, which is then absorbed in the small intestine. Before being transported to the blood, monoglutamate is converted to tetrahydrofolate (THF), an active form and cofactor. Intestinal bacteria produce vitamin B9 as THF from GTP, erythrose 4-phosphate, and phosphoenolpyruvate. Bacterial THF is absorbed directly in the large intestine via PCFT and circulated throughout the body by the blood [2]. Folic acid is converted by the body into DHFR (DiHydro-Folate Reductase), which commensal and pathogenic bacteria can use to form nucleic acids, thus being the basis of their survival and reproduction cycles [2, 17].

2.8 Vitamin B12

Vitamin B12 (cobalamin) is composed of a corrin ring, with a cobalt center, and has upper and lower ligands as coordinates. The active forms of this vitamin are methylcobalamin and adenosylcobalamin, which catalyze the synthesis of methionine. Food vitamin B12 is decomposed from protein into free vitamin B12 by pepsin in the stomach. Free vitamin B12 is then absorbed by small intestinal epithelial cells via intrinsic factor (IF), a gastric glycoprotein. In epithelial cells, the IF-vitamin B12 complex is decomposed into free vitamin B12 by lysosomes and then released into the blood, becoming an active form and distributed throughout the body. Cobalamin and cobamide contain cobalt, but cobamide has a lesser ligand consisting of 5, 6-dimethylbgensiidazole (DMB). Mechanically, the lower DMB ligand is essential for binding Vitamin B12 to intrinsic factor (IF); then, it can be recognized by cubilin and megalin, which facilitate endocytosis in intestinal epithelial cells. Bacterial Vitamin B12 is synthesized from precorrin-2 to produce adenosylcobalamin, which is absorbed directly by the large intestine and distributed throughout the body [2, 18].

Vitamin B12 functions for nucleotide synthesis, branched-chain amino acid regulation, long-chain fatty acid metabolism, and cellular development. Vitamin B12 is also a vital cofactor in cytoplasmic methionine synthase and in mitochondrial methylmalonyl-CoA mutase, leading to homocysteine methylation to methionine and the conversion of methylmalonyl-CoA to succinyl-CoA. Furthermore, Vitamin B12 is a cofactor that other gut microbiota use to regulate the breakdown of short-chain fatty acids such as butyrate, propionate, and acetic acid. Vitamin B12 has also been shown to maintain healthy nerve cells and help red blood cell synthesis. This vitamin plays a role to immune homeostasis, utilization of microbial metabolites, and cellular metabolism, making it an essential factor in immunity against pathogens [2].

3. Synthesis of Vitamin B and role of microbiota

Humans cannot synthesize vitamins except for vitamin D. So, other vitamins must be obtained exogenously from food or the gut microbiota. Commensal bacteria found in the gut, such as Lactobacillus and Bifidobacterium, can synthesize de novo vitamins in the human body. Members of the gut microbiota can synthesize vitamin K and most of the water-soluble B vitamins, such as vitamins B12, B9, B6, B2, and B1 [6]. Each of the B vitamins has a different synthesis mechanism, and the microbiota synthesize most.

3.1 Vitamin B1

Various gut microbiota, mainly in the large intestine, produce vitamin B1 as free thiamin and TPP. *Bacteroides fragilis* and *Prevotella copri* (phylum Bacteroidetes); *Clostridium difficile*, some *Lactobacillus spp*., *Ruminococcus lactaris* (Firmicutes); *Bifidobacterium sp.* (Actinobacteria); and *Fusobacterium varium* are microbiota that can produce vitamin B1 through thiazole and pyrimidine synthesis pathways [2]. It is estimated that synthesizing thiamin by gut microbes supplies about 2.3% of the daily requirement of human vitamin B1. The enzymes involved in the thiamin biosynthetic pathway are dominantly found in enterotype 2, which is one of the gut microbiota clusters rich in *Prevotella sp.* [4]. In the intestine, there is *Faecalibacterium spp.* (Firmicutes), which lacks the vitamin B1 synthesis pathway and requires vitamin B1 for growth. Therefore, these bacteria must obtain vitamin B1 from other bacteria or from the host's diet via thiamin transporters in the mucosa. This indicates that there is competition for vitamin B1 requirements between the host and specific microbiota [5].

3.2 Vitamin B2

Not much different from vitamin B1, the synthesis of vitamin B2 is also widely played by the microbiota. Riboflavin from food, plus riboflavin produced by commensal bacteria, causes excess riboflavin in the distal intestine. In addition to the common lactic acid bacteria producing riboflavin in the gut, genomic analysis of 256 species of human gut microbiota has found 56% of the microbiota possess a cluster of genes for de novo riboflavin biosynthesis [4]. *B. fragilis, P. copri, C. difficile, Lactobacillus plantarum, Lactobacillus fermentum,* and *R. lactaris* have important factors for the synthesis of vitamin B2, so these bacteria are important sources of vitamin B2. *Bacillus subtilis* and *Escherichia coli* can also carry out riboflavin biosynthesis. Riboflavin biosynthesis requires guanosine 5′-triphosphate (GTP) and ribulose 5-phosphate as precursors. The first step of the branch of the GTP-dependent biosynthetic pathway is encoded by ribA, which catalyzes the 3,4-dihydroxy-2-butanone 4-phosphate configuration of ribulose 5-phosphate [5]. In clinical trials, it was found that daily consumption of 200 g of yogurt for 2 weeks can contribute to total vitamin B2 in the body, which is reflected in an increase in plasma-free riboflavin levels. This clinical trial also showed that most of the Lactobacilli strains consume riboflavin, thereby reducing its bioavailability in fermented products. Tempe, a traditional Indonesian fermented soybean meal, has been shown to increase the concentration of B vitamins such as riboflavin due to its microbial biosynthesis. The last article also reported that bacterial isolation from tempeh, which was shown to belong to Streptococcus and Enterococcus, significantly increased the concentration of riboflavin in this fermented product [19].

3.3 Vitamin B3

Unlike other B vitamins, vitamin B3 can be synthesized by the body from the amino acid tryptophan through endogenous enzymatic pathways and then stored in the liver. Niacin is a group of nicotinamide and nicotinic acid. These two metabolites are precursors for nicotinamide adenine dinucleotide (NAD), so nicotinamide and nicotinic acid can also be produced by recycling NAD in cells. An organism is considered a niacin producer when it contains the de novo synthesis pathway of NAD. These organisms include *B. fragilis, P. copri, R. lactaris, C. difficile, Bifidobacterium infantis, Helicobacter pylori,* and *F. varium* [2, 20]. Colonocytes have mechanisms that mediate niacin uptake transporters. Supplementation of microcapsules containing niacin will release its contents in the ileocolonic area, which increases the serum niacin concentration according to the dose consumed. Intake of 900 to 3000 mg niacin microcapsules will significantly increase the Bacteroidetes population [4].

3.4 Vitamin B5

For the synthesis of vitamin B5, bacteria synthesize from 2-dihydropantoate and beta alanine via the de novo synthesis pathway. Bacteria that have a biosynthetic pathway for vitamin B5 include *B. fragilis*, *P. copri*, some *Ruminococcus spp.*, *Salmonella enterica*, and *H. pylori*. Some bacteria synthesize free pantothenic acid, which is directly absorbed in the large intestine to be converted into Co, and distributed in the same way as vitamin B5 from food. Various bacteria, including *E. coli*, *Salmonella typhimurium*, and *Corynebacterium glutamicum*, can synthesize vitamin B5. Some of these bacteria use aspartate and intermediate metabolites of valine biosynthesis to produce vitamin B5. In contrast, most of the *Fusobacterium spp.*, *Bifidobacterium spp*., some strains of *C. difficile*, *Faecalibacterium spp*., and *Lactobacillus spp.* do not have this pathway, and some express pantothenic acid transporters to utilize vitamin B5 as an energy source. This indicates that these bacteria compete with the host for vitamin B5 [2, 3, 6, 21].

3.5 Vitamin B6

There are various forms of vitamin B6 in the body, that is, pyridoxine, pyridoxal, and pyridoxamine. Vitamin B6 in food is converted into free vitamin B6 by endogenous enzymes, such as pyridoxal phosphatase, before being absorbed by the small intestine. Microbiota with a biosynthetic pathway for vitamin B6 includes *B. fragilis*, *P. copri*, *Bifidobacterium longum*, *Collinsella aerofaciens*, and *H. pylori*. In contrast, most of the Firmicutes genera (*Veillonella, Ruminococcus, Faecalibacterium,* and *Lactobacillus spp.*) lack the vitamin B6 biosynthetic pathway [2].

3.6 Vitamin B7

As much as 40% of the human gut microbiota can synthesize de novo vitamin B7. The microbiota produce this vitamin as free biotin, which is synthesized from malonyl CoA or pimellate via pimeloyl CoA. Microbiota with a biosynthetic pathway for vitamin B7 include *B. fragilis, P. copri*, *F. varium,* and *Campylobacter coli*. The production of vitamin B7 affects others microbiota; for example, *B. longum*, which produces pimelate, a precursor of vitamin B7 that certainly increases the production of vitamin B7 by other gut microbiota. Biotin absorption in the small and large intestines occurs via a transporter-mediated process encoded by the SLC5A6 gene. Lipopolysaccharides

inhibit colonic biotin uptake by impairing the expression of these membrane transporters. Biotin utilization also occurs between the host and bacteria, like *Lactobacillus murinus*, which consumes and reduces the biotin available in the intestine [2, 4].

3.7 Vitamin B9

The gut microbiota synthesizes vitamin B9 as tetrahydrofolate (THF) from GTP, erythrose 4-phosphate, and phosphoenolpyruvate. Dihydropteroate synthase catalyzes Folate biosynthesis, which reduces dihydrofolate to tetrahydrofolate [5]. THF is then directly absorbed in the large intestine and distributed throughout the body. Microbiota such as *B. fragilis*, *P. copri*, *C. difficile*, *L. plantarum*, *Lactobacillus reuteri*, *Lactobacillus delbrueckii ssp. bulgaricus,* and *Streptococcus thermophilus* and several species of *Bifidobacterium spp*., *F. varium*, and *S. enterica* have folate biosynthetic pathways. It shows that almost all species in all phyla of microbiota produce folate. However, the ability of some of these bacteria to produce and utilize folate varies widely due to strain-dependent properties. Some Bifidobacteria do not produce folate when this vitamin is present, whereas others produce it regardless of vitamin concentration. Microorganisms are also able to increase folate content in a wide variety of foods [2, 19].

3.8 Vitamin B12

Vitamin B12 is a vitamin that contains cobalt, with the active forms being methylcobalamin and adenosylcobalamin. Dietary vitamin B12 forms a complex with dietary protein, further decomposed into free vitamin B12 by pepsin in the stomach. Free vitamin B12 is then absorbed by small intestinal epithelial cells via a gastric glycoprotein, intrinsic factor (IF). In epithelial cells, the IF-vitamin B12 complex is decomposed into free vitamin B12 by lysosomes and then released into the blood, which is further converted into the active form and distributed throughout the body [2].

Vitamin B12 is produced by aerobic and anaerobic pathways, with 30 different enzymes required for its biosynthesis. Several genes express enzymes essential for de novo vitamin B12 biosynthesis [18]. Bacterial vitamin B12 is synthesized from precorrin2 to produce adenosylcobalamin, which is then absorbed directly by the large intestine and distributed throughout the body. Microbiota with a biosynthetic pathway for vitamin B12 include *B. fragilis*, *P. copri*, *C. difficile, Faecalibacterium prausnitzii*, *R. lactaris*, *Bifidobacterium animalis, B. infantis*, *B. longum*, and *F. varium*. In addition to the microbiota, *L. plantarum* and *Lactobacillus coryniformis* also produce vitamin B12 from fermented foods, and *B. animalis* synthesizes vitamin B12 during milk fermentation [2, 21].

4. Sources of B Vitamins from the diet

Sources of B vitamins can be obtained apart from the biosynthetic mechanism, that is, exogenously from food. Vitamin B1 is found in high concentrations as thiamin pyrophosphate (TPP) in meat, especially pork and chicken; egg; cereals and rice; as well as nuts. The *World Health Organization* (WHO) / *Food and Agriculture Organization* (FAO) recommends a daily intake of 1.1–1.2 mg of vitamin B1 for adults [2].

Vitamin B2 is found in many animal sources, such as poultry, fish, liver, and eggs. Dairy products and cheese can also be sources of riboflavin, which makes a significant

contribution to children and adults. Vegetable sources such as cereals, grain products, and bread can be a source of riboflavin-rich foods in some developing countries. Leafy greens, such as broccoli, mustard, and turnips, are also good sources of riboflavin. Natural grain products tend to be relatively low in riboflavin, but when intake is increased, these foods increase the bioavailability of riboflavin. WHO/FAO recommends a daily intake of 1.0–1.3 mg of vitamin B2 for adults [2, 15].

Animal foods such as fish and meat contain vitamin B3 as nicotinamide, and plant foods such as nuts and mushrooms contain vitamin B3 as nicotinic acid. WHO/FAO recommends a daily intake of 11–12 mg of vitamin B3 for adults. Vitamin B5 is high in concentrations of CoA or phosphopantetheine in the liver, eggs, milk, chicken, beef, salmon, cereals, grains, and fermented soybeans. WHO/FAO recommends a daily intake of 5 mg of vitamin B5 for adults [1, 2, 11].

Vitamin B6 is abundant in salmon, chicken, tofu, sweet potatoes, potatoes, bananas, and avocados. Vitamin B6 found in food is in the form of PLP or PMP. WHO/FAO recommends a daily intake of 1.3–1.7 mg of vitamin B6 for adults. Vitamin B7 is abundant in foods such as egg yolks, heart, cereals such as oats, nuts, vegetables such as spinach and mushrooms, rice, and vegetable oil. Dairy and breast milk products also contain biotin. Raw egg whites contain large amounts of avidin, which binds tightly to vitamin B7 and prevents its absorption in the intestines. WHO/FAO recommends a daily intake of vitamin B7 of 30 g for adults [1, 2, 14].

Foods such as beef liver, spinach, and asparagus are high in vitamin B9. Legumes, red meat, and liver also contain high levels of folate. However, up to 70% of folate is lost during cooking due to thermal degradation or dissolution in the cooking water. WHO/FAO recommends a daily intake of 400 g of vitamin B9 for adults. Most humans get vitamin B12 from food, especially from animal protein and fermented foods. Vitamin B12 is found in beef liver, bivalves, salmon, chicken, eggs, beans, and spinach. WHO/FAO recommends a daily intake of 2.4 g of vitamin B12 for adults [2, 18, 22].

From the explanation of the acquisition of vitamins from these foods, malnutrition will significantly inhibit normal metabolism in infants and the elderly. In the case of dietary supplements, vitamin-containing probiotic products are generally produced as freeze-dried powders and formulated as capsules, powders, and tablets [23]. Parameters influencing the manufacture of this dietary supplement include viable cell count and water activity. For the application of probiotics as food and drink, the product is prepared in the form of vegetative cells and added to food products [24]. Probiotic products require special care for the profile of a product, mitigation of health risks due to pathogens, and maintenance of aseptic conditions [25].

5. Role of B Vitamins in gut microbiota

B vitamins are biosynthetic precursors of essential cofactors in various metabolic pathways and play an important role in immunity. In addition to being needed by the host, B vitamins are also needed by some intestinal microbiota for metabolism. Thus, in addition to producing B vitamins, the gut microbiota also consumes B vitamins for primary enzymatic reactions. The gut microbiota is one of the densest microbial communities in the human body. This microbial community consists primarily of four main phyla, that is, Bacteroidetes, Firmicutes, Proteobacteria, and Actinobacteria. In the large intestine, the microbiota are grouped into 2, namely, B-vitamin-producing bacteria and auxotrophic bacteria. The survival of bacteria of auxotrophic species is highly dependent on B vitamins. Although most B vitamins are absorbed in the small

intestine, B vitamins are produced and absorbed by bacteria mainly through the large intestine. Many B-vitamin transporters are expressed in the large intestine. As a result, there is competition between the host and bacteria. So that the host experiencing dysbiosis—the gut microbiota is unbalanced, and significantly affects the metabolism of B vitamins in the gut [13].

5.1 Vitamin B1

Thiamine produced in the gut microbiota has a specific role in the composition or function of the gut microbiome. Thiamin is required by certain gut bacteria, *Bacteroides thetaiotaomicron* and *Faecalibacterium spp.*, which have potential consequences on the host thiamine. Thiamine biosynthesis and its transport system are essential for the growth of B. thetaiotaomicron. Although *Faecalibacterium spp.* has a vitamin B1 synthesis pathway, this species requires more vitamin B1 for growth than production. Therefore, these bacteria must obtain vitamin B1 from other bacteria or host food via transporters, such as *B. thetaoimicron* [2, 4]. Intestinal dysbiosis may lead to a predominance of thiamin-only-consuming bacteria, which may contribute to decreased thiamin availability to the host. *E. coli* in the human fecal microbiota was found to be negatively correlated with fecal thiamin [26].

5.2 Vitamin B2

Riboflavin is vital in the growth of bacteria that are very sensitive to oxygen as an electron transfer agent. Examples of bacteria that are sensitive to oxygen are *F. prausnitzii* and Roseburia. *F. prausnitzii* is a major butyrate producer in the human microbiota and has anti-inflammatory properties and gut-protective functions. Vitamin B2 is also an essential precursor to flavin mononucleotide and flavin adenine dinucleotide (FAD), coenzymes of glutathione reductase that protect cells from reactive oxygen species (ROS). Thus, vitamin B2 can act as an indirect antioxidant and modifies the gut microbiota condition through ROS reduction. This condition is also proven to reduce the population of *E. coli*. Previous studies showed that supplementation of dietary riboflavin for 14 days increased *F. prausnitzii* and Roseburia and concomitantly reduced *E. coli*. Phylum Actinobacteria and Firmicutes express riboflavin transporters and enzymes required to form FAD and FMN from free riboflavin [2, 4, 27]. Vitamin B2 also directly affects the fecal microbiome, namely, the genera Alistipes and Clostridium. However, this increase occurred only with high doses of riboflavin supplied directly to the large intestine and may not apply to intakes from foods or dietary supplements that are absorbed mostly in the small intestine [27].

5.3 Vitamin B3

Vitamin B3 is the only B vitamin that humans can synthesize. It is a precursor to nicotinamide adenine dinucleotide (NAD), a coenzyme in cellular oxidation–reduction reactions with a central role in aerobic respiration. Niacin acts as an agonist for the cell surface receptor niacin receptor 1, which pairs with G-proteins. Niacin also has strong antioxidant and anti-inflammatory properties and can function as a modulator of gut protection and prevent bacterial endotoxin production. Thus, niacin deficiency causes intestinal inflammation and diarrhea, which has a direct impact on the gut microbiota population. Vitamin B3 deficiency impacts the diversity and low number of Bacteroidetes, especially in obese individuals. Supplementation with tryptophan

and niacin has been shown to restore the composition of the gut microbiota through the angiotensin I (peptidyl-dipeptidase A)-converting enzyme. Furthermore, intake of niacin microcapsules (900 to 3000 mg) significantly increased the Bacteroidetes population. These results suggest that niacin has a beneficial effect on gut microbial composition in humans [2–4].

5.4 Vitamin B5

Lactobacillus spp., *Streptococcus spp.*, and *Enterococcus spp*. are members of the phylum Firmicutes that do not produce pantothenate but require pantothenic acid for their growth. This indicates that there is a symbiosis in the distal intestine between pantothenic acid-eating bacteria and pantothenic acid-producing bacteria. A study has demonstrated the uptake of pantothenic acid and biotin by the sodium-dependent multivitamin transporter (SMVT, SLC5A6) across the intestinal loop. Mostly Fusobacterium and *Bifidobacterium spp*., some strains of *C. difficile*, and *Faecalibacterium spp*., lack the vitamin B5 synthesis pathway but express the pantothenic acid transporter to utilize vitamin B5 as an energy producer [2, 4].

5.5 Vitamin B6

Vitamin B6 can play an essential role in shaping microbiota composition and metabolic capacity. In bacteria such as *E. coli*, vitamin B6 is synthesized in the PLP form from various precursors, including, deoxyxylulose 5-phosphate, 4-phosphohydroxy-L-threonine, glyceraldehyde-3-phosphate, and D-ribulose 5-phosphate. PLP produced by commensal bacteria works with ribonucleotide metabolism to facilitate the effects of 5-fluorouracil, a drug used to treat colorectal cancer. Vitamin B6 deficiency results in a marked decrease in intestinal arginine biosynthesis, and disruption of this metabolic pathway leads to the selective growth of certain gut bacteria, namely, the Bacteroidaceae family, and an increase in Lachnospiraceae. An increase in vitamin B6-producing bacteria such as *Bacteroides acidifaciens* has been shown to weaken the colonization of S. typhimurium and promote recovery from intestinal inflammation [4, 28].

5.6 Vitamin B7

Free biotin can affect the composition of the gut microbiota because it is required for the growth and survival of some microbiota. *Prevotella spp.*, *Bifidobacterium spp.*, Clostridium, Ruminococcus, Faecalibacterium, and *Lactobacillus sp.* do not have the vitamin B7 synthesis pathway because it lacks the essential biotin biosynthetic gene. However, they express a free biotin transporter, indicating a need for biotin. These results indicate that these bacteria also utilize biotin from food and bacteria to compete with the host. Therefore, it is necessary to control diseases related to some of these microbes. Another study showed that enzymes in the biotin biosynthetic pathway were overexpressed in the Bacteroides enterotype. Biotin uptake in the small and large intestines occurs via a carrier-mediated process involving the SMVT system encoded by the SLC5A6 gene [2, 4]. SMVT dysfunction reduces biotin in the intestine, causing dysbiosis, and induces Nox and ROS, which cause damage to enterocyte apoptosis. This mechanism causes the intestinal villi to shrink and increases intestinal permeability, inflammation, and dysplasia, all of which induce dysbiosis [29].

5.7 Vitamin B9

Folate is essential for several metabolic processes, including carbon transfer, thymidylate synthesis, purine synthesis, and the synthesis of several amino acids. Once absorbed, folate also participates in nucleotide synthesis, DNA repair, and methylation [30]. This function applies to both the host and the microbiota that require folate. The biosynthesis and expression of folate transporters in the gut microbiota are influenced by gut microbes, such as Bifidobacteria. In commensal bacteria, a vitamin B9 metabolite, 6-formylpterin (6-FP), is produced by the photodegradation of folic acid. This metabolite cannot activate MAIT cells (mucosal-associated invariant T), suppressing excessive MAIT cell responses and preventing excessive allergic and inflammatory responses [4].

5.8 Vitamin B12

Microorganisms use various forms of cyanocobalamin in many reactions, including methionine synthesis, carbon skeleton mutation, elimination reactions, amino mutations, and acetate and methane synthesis [31]. As many as 83% of the microbiota (260/313 species) encode cobalamin-dependent enzymes. Most of these species also lack the genes needed to synthesize cobalamin. In another report, 75.9% of bacteria utilized cobalamin, and only half possessed the cobalamin biosynthetic pathway. An example is *B. thetaiotaomicron*, which does not encode the cobalamin biosynthetic pathway gene but has three homologous cobalamin transporters. This statement indicates that this microbiota depend on the cobalamin absorption mechanism to maintain survival. Supplementation of 3.94 g/ml cyanocobalamin was shown to increase fecal cobalamin, with a lower Bacteroides population condition. Cobalamin and its derivatives also determine pathogenicity in the host gut. The bacterial transcription factor EutR requires ethanol amine, cobalamin precursors, and cobalamin-derived adenosylcobalamin for transcription of virulence factors required for host infection and spread of *enterohemorrhagic E. coli* (EHEC) serotypes O157:H7 and Salmonella [4].

6. The role of B Vitamins on human digestive health

The B vitamins in our body have several crucial physiological functions. The functional roles of these micronutrients are diverse, ranging from cellular energy-producing reactions such as the mitochondrial citric acid cycle to respiratory oxidation, immunity, neurotransmitter synthesis, cell signaling, and nucleic acid biosynthesis. Thus, a deficiency of B vitamins will impair normal cell metabolism and trigger the development of several chronic diseases in humans [4, 32]. Apart from being essential for the human body, B vitamins are also crucial in shaping the diversity and richness of the gut microbiota. A wealth of evidence has shown that a healthy gut lies in a healthy microbial ecology [3, 4].

6.1 Vitamin B1

Thiamin is a precursor of thiamin pyrophosphate, which is essential for carbohydrate metabolism and nerve function. Energy metabolism, particularly the balance between glycolysis and the citric acid cycle, is related to the functional control of immune cells, which is referred to as immunometabolism. Immunometabolism

by vitamin B1 is vital for glycolysis-dependent digestive cells, especially Peyer's patch. In the gut, nave immunoglobulin (Ig)M+ B cells differentiate into IgA+ B cells in the Peyer patch, and then, IgA+ B cells differentiate into IgA-producing plasma cells in the lamina propria. The naive B cells in Peyer's patch prefer to use the vitamin B1-dependent citric acid cycle to generate ATP. However, once B cells differentiate into IgA-producing plasma cells, they switch to using glycolysis to generate ATP [2, 3].

Consistent with the importance of vitamin B1 in generating energy in the gut, mice fed a vitamin B1-deficient diet showed impaired maintenance of naive B cells in Peyer's patches. In addition to reducing the number of naive B cells in Peyer's patch, thiamin deficiency also reduces the size of B cell follicles, evidenced by the reduction of naive B cells in female Balb/c experimental animals. The researchers also showed that feeding the mice a vitamin B1-deficient diet caused the vitamin B1 deficiency to last for only a week. Vitamin B1 deficiency that affects the host immune response through the regulation of differentiation and proliferation of these immune cells ultimately affects the gut microbiota [2, 3].

6.2 Vitamin B2

Riboflavin is required for the development of the gastrointestinal tract after birth and is linked to crypt hypertrophy, crypt bifurcation dysfunction, and a loss of proliferative potential in intestinal cells. These changes are visible during the postnatal and post-weaning stages. These changes were irreversible, even after the experimental administration of riboflavin in vivo and in vitro. Riboflavin deficiency has been shown to reduce the number of villi but, on the other hand, can increase the length of the villi. Reduction of riboflavin in humans has also been associated with shortened duodenal crypts and reduced cell division. In vitro studies using Caco-2, HCT116, and HT29 cells demonstrated a potential mechanism for the riboflavin deficiency phenotype, which led to the result that riboflavin inhibited cell growth by reducing cellular ATP generation and increasing oxidative stress. This impairs mitosis and accumulates aneuploidy cells. These changes in gut morphology may also be associated with an adaptive response to stress-induced deficiency [4].

Riboflavin is also essential for methylation reactions, nucleotide synthesis, and DNA stability and repair. A cohort study in the Netherlands on a diet in cancer suggested that riboflavin was likely to be associated with a reduced risk of proximal colon cancer among women (RR = 0.61; P-trend = 0.07). This finding is reinforced by results from the Women's Health Initiative cohort observational study, which showed that higher total riboflavin intake was associated with a reduced risk of colorectal cancer (HR = 0.81; 95% CI: 0.66–0.99) [1].

6.3 Vitamin B3

Human and mouse colonic epithelial cells possess efficient and specific mechanisms for vitamin B3 absorption. This vitamin plays an essential role in reducing inflammation, so a deficiency will lead to inflammatory bowel diseases such as ulcerative colitis. Vitamin B3 controls inflammation by inhibiting vascular permeability in intestinal tissue by activating PGD2/DP1 signaling in endothelial cells. This vitamin also modulates the inflammatory response by increasing the rate of ATP generation in Caco-2 cells. In addition, vitamin B3 is involved in various cellular oxidation–reduction metabolic reactions and rapamycin signaling pathways, thereby suppressing colon inflammation [3, 32].

Vitamin B3 synthesized by the gut microbiota contributes to local colonocyte nutrition and maintains intestinal stem cell morphology. Vitamin B3 is also known to protect colonic epithelial cells against dextran-sulfate-sodium (DSS)-induced apoptosis and promote cell proliferation in experimental animals. The mechanism of protection of the intestinal epithelium by vitamin B3 is by activating the prostanoid D 1 (DP1) receptor on macrophages and endothelial and colonic epithelial cells. One study found that retention of vitamin B3-containing enemas effectively promoted mucosal healing in patients with ulcerative colitis, with possible mechanisms of downregulation of colonic inflammatory cytokines and suppression of pro-inflammatory gene expression [3, 4].

6.4 Vitamin B5/pantothenic acid

Vitamin B5, or pantothenic acid, is an essential coenzyme A (CoA) precursor and acts as a carrier protein. This vitamin is involved in various metabolic pathways, such as the citric acid cycle, cell growth, neurotransmitter synthesis, and fatty acid oxidation [4]. Dietary pantothenic acid supplementation also affects the gut microbial profile. Increased intake of pantothenic acid increased the relative numbers of Prevotella and Actinobacteria [3].

6.5 Vitamin B6/pyridoxine

Vitamin B6 functions primarily as a cofactor for the biosynthesis and catabolism of amino acids. In addition, this vitamin is also involved in fatty acid biosynthesis and neurotransmitter biosynthesis and as an antioxidant [3]. Relative pyridoxine deficiency is found in 10–25% of Inflammatory Bowel Disease (IBD) cases. Plasma levels of B6 are considered a risk factor for thrombosis in patients with IBD because they have an inverse relationship with homocysteine [1].

A cross-sectional study has shown an association between the severity of intestinal irritation and low dietary vitamin B6 intake. The mechanism of this phenomenon is that the lack of vitamin B6 affects the balance of anti-inflammatory and pro-inflammatory cytokines. Vitamin B6 deficiency also reduces microbial diversity and significantly alters gut metabolites such as short-chain fatty acids, which also play an essential role in triggering this irritation. In addition, studies of vitamin B6 deficiency in animals have shown a significant reduction in the number of mucus-secreting cells, an important factor in maintaining gut health. Vitamin B6 also decreases cell calcium transport but does not affect the basic morphology of enterocytes, such as cell viability, cell volume, membrane permeability, and protein content [4].

Vitamin B6 can influence colorectal carcinogenesis through its role in DNA synthesis and methylation. Animal studies have shown that this vitamin can inhibit angiogenesis, suppress nitric oxide, and reduce oxidative stress [1].

6.6 Vitamin B7/Biotin

Vitamin B7 acts as a coenzyme for several biochemical reactions, such as glycolysis, cell signaling, and epigenetic regulation. This vitamin also controls the expression of genes, including nuclear factor kappa B (NF-kB), through a histone-binding mechanism known as biotinylation. Therefore, this vitamin may also have an anti-inflammatory effect on the gastrointestinal mucosa [32].

6.7 Vitamin B9/Folate

Vitamin B9 is essential for the replication and regeneration of nucleic acids, affecting cells' survival rate. Folate is involved in synthesizing S-adenosylmethionine (SAM), which is required for cellular biosynthesis and DNA methylation. This vitamin is essential for replicating and recovering nucleic acids, influencing survival rates through cell proliferation and regeneration. In addition, folate regulates gene activity, regenerates the intestinal lining, reduces lymphocyte growth, and reduces NK cell cytotoxicity [3]. Thus, every living cell, including gastrointestinal cells, requires folate to carry out these various biochemical and biosynthetic processes [4].

Because of its essential role in producing methyl donors, folate deficiency significantly impairs DNA replication. Folate deficiency causes an increase in the crypt depth of the intestinal mucosa in the duodenum and jejunum, resulting in a decreased villi-to-crypt ratio. In experimental animals, induced methyl donor deficiency by feeding a folate-deficient diet accompanied by the antibiotic succinylsulfathiazole 1% has also increased crypt depth and altered gut cell differentiation. In this study, folate deficiency also caused megaloblastic changes in the epithelial cell nuclei and reduced crypt mitosis. These changes are seen more prominently in the ileum with elongation of the crypts, an increase in goblet cells, and a decrease in Paneth cells. Deficiencies of folate, riboflavin, vitamin B6, and vitamin B12 concomitantly alter Wnt signaling in the experimental colon and decrease apoptosis in epithelial cells. Unexpectedly, these changes are irreversible, even with an excess of folate [4].

Folate deficiency significantly alters intestinal cell morphology and is associated with increased intestinal carcinogenesis [3]. Two case–control studies demonstrated that folate supplementation and high red blood cell folate levels significantly reduced the risk of dysplasia and neoplasia in patients with ulcerative colitis. Folate supplementation, in combination with sulfasalazine administration, has a protective effect on the development of colorectal cancer in patients with chronic ulcerative colitis. The mechanism of folate protection against colorectal cancer is to prevent aberrations in DNA synthesis and aberrations in DNA methylation. However, it should be noted that folate deficiency can also occur due to IBD therapy, such as methotrexate and sulfasalazine. A recent meta-analysis of folate supplementation has found that folate plays a role in preventing pancreatic cancer. Individuals with a high dietary folate intake were 34% less likely to develop pancreatic cancer than individuals with a low folate intake [1].

6.8 Vitamin B12

Like folate, cobalamin is involved in the synthesis of methyl donors. These donors are essential for the nucleic acid synthesis and protein and lipid metabolism. Vitamin B12 also acts as a cofactor for methionine synthase in sulfur amino acid metabolism to recycle homocysteine into methionine. The effect of vitamin B12 deficiency on colonic morphology is similar to that of folate deficiency because of its association with several cellular metabolic reactions. Vitamin B12 deficiency protects against DSS-induced inflammation in C57BL/6 mice. Other studies have shown reduced cell differentiation and gut protective factors in vitamin B12-deficient mice. In addition, in patients with vitamin B12 deficiency, the villi become shorter with a reduced villi/crypt ratio. Deficiency or excess of vitamin B12 affects the growth of gut microbiota.

However, vitamin B12 deficiency did not relatively change the gut microbiota composition in healthy mice but did change it in DSS-induced colitis mice [4, 6, 32].

Vitamin B12, together with vitamins B9 and B6, influence the occurrence of colorectal carcinoma through its role in DNA synthesis and methylation. In addition, these three vitamins have been shown to inhibit angiogenesis, suppress nitric oxide, and reduce oxidative stress in animal models. However, an experimental study that administered a combination of folic acid (2.5 mg), vitamin B6 (50 mg), and vitamin B12 (1 mg) in 1470 subjects did not reduce the risk of colorectal carcinoma after a follow-up period of 9.3 years. Patients with celiac disease also have higher total plasma homocysteine levels than the general population, indicating lower serum levels of vitamins B6, B9, and B12 [1].

The liver is the physiological reservoir of cyanocobalamin in humans. Vitamin B12 deficiency is observed in several liver diseases such as hepatitis, cirrhosis, and hepatocellular carcinoma. Vitamin B12 inhibits HCV through the inhibition of ribosome entry sites. Vitamin B12 is also associated with aphthous stomatitis (**Figure 1**) [1].

7. Conclusion

B vitamins act as cofactors for several cellular metabolic reactions. In addition to vitamin B3, other B vitamins must be obtained through dietary intake, supplementation, and synthesis of the gut microbiota. The biosynthesis of B vitamins in the gut

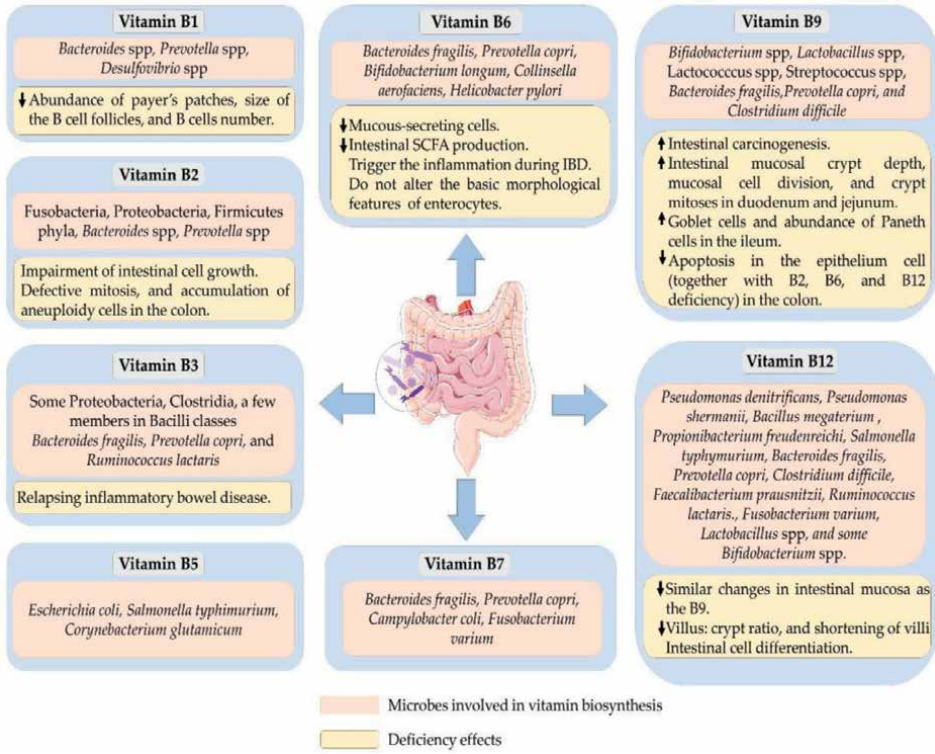

Figure 1.
Summary of the main gut bacteria synthesizing B vitamins and the effects of their deficiency on gut health [3].

is influenced by several factors, including exposure to antibiotics and free radicals, genetic makeup, dietary habits, and lifestyle. Competition between gut microbiota, pathogenic microbes, and the host leads to deficiency conditions, especially if exogenous intake is not optimal. A deficiency of B vitamins ultimately affects the gut microbial composition, gut health, and overall host metabolism.

Author details

Satrio Wibowo[1]* and Almira Pramadhani[2]

1 Department of Pediatrics, Faculty of Medicine, University of Brawijaya, Malang, Indonesia

2 University of Brawijaya, Malang, Indonesia

*Address all correspondence to: satrio_wibowo@ub.ac.id

References

[1] Masri OA, Chalhoub JM, Sharara AI. Role of vitamins in gastrointestinal diseases. World Journal of Gastroenterology. 2015;**21**(17):5191-5209. DOI: 10.3748/wjg.v21.i17.5191

[2] Yoshii K et al. Metabolism of dietary and microbial vitamin B family in the regulation of host immunity. Frontiers in Nutrition. 2019;**1**:48. DOI: 10.3389/fnut.2019.00048

[3] Hossain KS, Amarasena S, Mayengbam S. B vitamins and their roles in gut health. Microorganisms. 2022:**10**(6):1168. DOI: 10.3390/microorganisms10061168

[4] Uebanso T et al. Functional roles of B-vitamins in the gut and gut microbiome. Molecular Nutrition and Food Research. 2020;**64**(18):2000426. DOI: 10.1002/MNFR.202000426

[5] Gu Q, Li P. Biosynthesis of vitamins by probiotic bacteria. 2016. 10.5772/63117

[6] Jiang Q et al. Metagenomic insights into the microbe-mediated B and K2 vitamin biosynthesis in the gastrointestinal microbiome of ruminants. Microbiome. 2022;**10**(1):1-16. DOI: 10.1186/S40168-022-01298-9/FIGURES/5

[7] Tylicki A et al. Thiamine and selected thiamine antivitamins-biological activity and methods of synthesis. Bioscience Reports. 2018;**38**:20171148. DOI: 10.1042/BSR20171148

[8] Karunaratne DN et al. Nutrient delivery through nanoencapsulation. In: Nutrient Delivery. New York: Elsevier; 2017. pp. 653-680. DOI: 10.1016/b978-0-12-804304-2.00017-2

[9] Thakur K et al. Riboflavin and health: A review of recent human research. Critical Reviews in Food Science and Nutrition. 2017;**57**(17):3650-3660. DOI: 10.1080/10408398.2016.1145104

[10] Makarov M, Trammell SA, Migaud ME. The chemistry of the vitamin B3 metabolome. 2019. 10.1042/BST20180420

[11] Sanvictores T, Chauhan S. Vitamin B5 (pantothenic acid). In: Clinical Guide to Nutrition & Dietary Supplements in Disease Management. Florida: StatPearls Publishing; 2022. pp. 699-701. DOI: 10.1016/B978-0-443-07193-5.50106-0

[12] da Silva VR, Gregory JF. 'Vitamin B6. In: Present Knowledge in Nutrition. New York: Elsevier; 2020. pp. 225-237. DOI: 10.1016/B978-0-323-66162-1.00013-5

[13] Putnam EE, Goodman AL. B vitamin acquisition by gut commensal bacteria. 2020. 10.1371/journal.ppat.1008208

[14] Saleem F, Soos MP. Biotin deficiency. Journal of Nutrition Education. 2019;**13**(3):96. DOI: 10.1016/S0022-3182(81)80040-4

[15] Zempleni J, Kuroishi T. Biotin. Advances in Nutrition. 2012;**3**(2):213-214. DOI: 10.3945/AN.111.001305

[16] Dalto DB, Matte JJ. Pyridoxine (Vitamin B6) and the glutathione peroxidase system; a link between one-carbon metabolism and antioxidation. Nutrients. MDPI AG. 2017. DOI: 10.3390/nu9030189

[17] Scaglione F, Panzavolta G. Folate, folic acid and 5-methyltetrahydrofolate are not the same thing. 2013. 10.3109/00498254.2013.845705

[18] Roth W, Mohamadzadeh M. Vitamin B12 and gut-brain homeostasis in the pathophysiology of ischemic stroke. eBioMedicine. 2021;**73:**103676. DOI: 10.1016/J.EBIOM.2021.103676

[19] Leblanc JG et al. B-Group vitamin production by lactic acid bacteria-current knowledge and potential applications. 2011. DOI: 10.1111/j.1365-2672.2011.05157.x

[20] Dimitrov D et al. Systematic genome assessment of B-vitamin biosynthesis suggests co-operation among gut microbes. Frontiers in Genetics. 2015;**1**:148. DOI: 10.3389/fgene.2015.00148

[21] Indira M et al. Bioactive molecules of probiotic bacteria and their mechanism of action: A review. Biotech. 2019;**9**(8):1-11. DOI: 10.1007/s13205-019-1841-2

[22] Ami N et al. Folate and neural tube defects: The role of supplements and food fortification. Pediatrics & Child Health. 2016;**21**(3):145-149. DOI: 10.1093/PCH/21.3.145

[23] Fenster, K. et al. (2019) 'microorganisms The Production and Delivery of Probiotics: A Review of a Practical Approach'. 10.3390/microorganisms7030083.

[24] Mishra, S. et al. (2019) 'microorganisms Probiotics and Prebiotics for the Amelioration of Type 1 Diabetes: Present and Future Perspectives'. 10.3390/microorganisms7030067

[25] Khaneghah AM, Fakhri Y. Probiotics and Prebiotics as Functional Foods: State of Art. Agri Res & Tech: Open Access J. 2018;**13**(3):10.19080/ARTOAJ.2018.13.555884

[26] Barra NG et al. Micronutrients impact the gut microbiota and blood glucose. Journal of Endocrinology. BioScientifica Ltd. 2021:R1-R21. DOI: 10.1530/JOE-21-0081

[27] Pham VT et al. Vitamins, the gut microbiome and gastrointestinal health in humans. Nutrition Research. 2021;**95**:35-53. DOI: 10.1016/J.NUTRES.2021.09.001

[28] Mayengbam S, Chleilat F, Reimer RA. Vitamin B6 deficiency impairs gut microbiota and its metabolites in rats. 2020

[29] Neophytou C, Pitsouli C. Biotin controls intestinal stem cell mitosis and host-microbiome interactions. Cell Reports. 2022;**38**(10):110505. DOI: 10.1016/J.CELREP.2022.110505

[30] Mukhopadhyay B. et al. Microbial metabolic capacity for intestinal folate production and modulation of host folate receptors. 2019. 10.3389/fmicb.2019.02305

[31] Stabler SP. Vitamin B12. In: Present Knowledge in Nutrition. New York: Elsevier; 2020. pp. 257-271. DOI: 10.1016/B978-0-323-66162-1.00015-9

[32] Xu Y et al. Cobalamin (Vitamin B12) induced a shift in microbial composition and metabolic activity in an in vitro colon simulation. Frontiers in Microbiology. 2018;**9**(Nov):1-9. DOI: 10.3389/fmicb.2018.02780

Section 2

Vitamin B and Pellagra

Chapter 3

Pellagra: Down Not Out If Down and Out – Part 1

Adrian C. Williams, Christina Wood and Lisa J. Hill

Abstract

Pellagra is caused by a dietary deficiency of milk and meat leading to insufficient nicotinamide (vitamin B3), the precursor to nicotinamide adenine dinucleotide (NAD). "Pellagra sine pellagra" was well recognised and may be common as supplementation was never globally implemented and a screening test never developed. Meat and milk intake varies 30-fold globally so there are perhaps 2 billion at risk of deficiency. Such patients will have physical and cognitive stunting, poor conduct and be prone to acute and chronic infections, including TB, and premature ageing, including dementia. Resilience may be poor to NAD-consuming insults whether chemical, microbial or traumatic that conspires to cause brain injury but comes with the opportunity for pre-conception dietary corrections breaking cycles of deprivation and poor educational outcomes. Such individuals may otherwise be subject to discrimination as was the pellagra ridden "Butterfly" caste causing racial and ethnic tensions. Poor countries with many having to spend 50-80% of income on food and very little on animal produce cannot develop properly unlike wealthier meat rich empires, past and present. The many benefits of experiments with food programmes and basic income support are because, as Engels curves predict, more is spent on milk and meat enabling demographic, epidemiological, and economic transitions and modernity.

Keywords: NAD, pre-conception nutrition, addiction, opiates, cycles of deprivation, empires, meat transitions, demographic transitions, epidemiological transitions, TB, poverty traps, metabolic syndrome, class ceilings

1. Introduction

Cycles of life, right from lifes origin to humankind, depend upon nuclear fusion reactions and low entropy photon- energy from the sun. Photosynthesis splits water in to the oxygen that we breathe and hydrogen that combined with CO2 forms the carbohydrates that we eat and is carried by NAD to mitochondria forming proton-motive forces during oxidative phosphorylation producing usable energy as ATP and reduced nicotinamide adenine dinucleotide phosphate (NADPH) for growth [1–3]. Increasing use of oxygen and NAD supplies allowed animal evolution from the Cambrian (when animals started eating animals) to mammals (increasing milk supplies) and man [4].

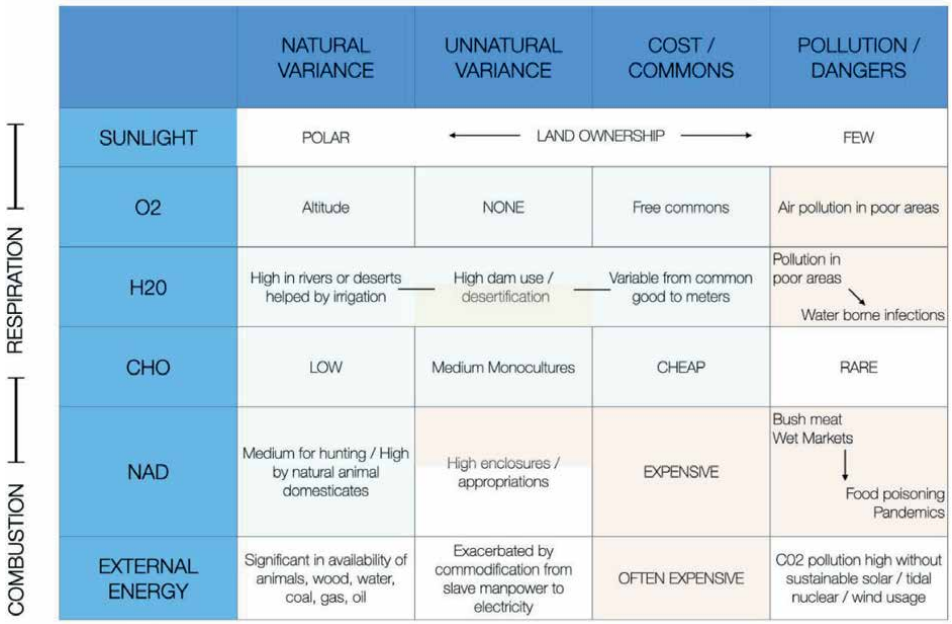

Figure 1.
Basic elements of the energy cycle had a natural variance based on geography. Human history often exagerated these variances first by making hunting meat easier in some geographies and quite dangerous for the hunters even as they shared in an equitable way as social insurance - and then with the advent of agriculture natural domesticates varied by continent and meat became expensive everywhere often shutting out the poor. Meat was more available in the middle-east and Europe and less available in the Americas and Africa - that also had to contend with many carnivorous competitors and more parasitic disease in the tsetse belt.

High meat intake and sharing by hunters was a major feature of our evolution, early economics and relationships with animals and each other in our "social leap [5–11]. Combined with selected plants, some psychedelic, and use of fire (cooking releases nicotinamide from meat and from (maize) plants if cooked carefully and learnt culturally) - meat was an important factor in how our brains expanded and our minds changed [12–14]. Oxygen is freely available, water less so and NAD supplies needed for energy and as metabolic master molecules are much harder to obtain. This difficulty has worsened while we "niche constructed" agriculture as sources became expensive creating self-reinforcing transgenerational "poverty traps" that are hard to escape from and contrast with rich others as "meat elites" that "hit the jackpot": more recently we moved away from mixed farming and agroecology to industrial farming with damaging effects on carbon, nitrogen and phosphorus cycles and made inequalities of meat consumption worse in places (**Figures 1–3**) [15–22].

2. Engel's curves and social metabolisms

As Cicero said (43 CE) in his essay De Natura Deorum *"we create, as it were, a second world within the world of nature"* but our conscious keystone species currently has this world divided geographically effecting a NAD and proton-related lottery of our life chances and (brain) health – as well as contributing to climate change endangering biodiversity from many mammalian and other extinctions [23–25]. Life is energetically expensive and constantly needs to overcome the second law of

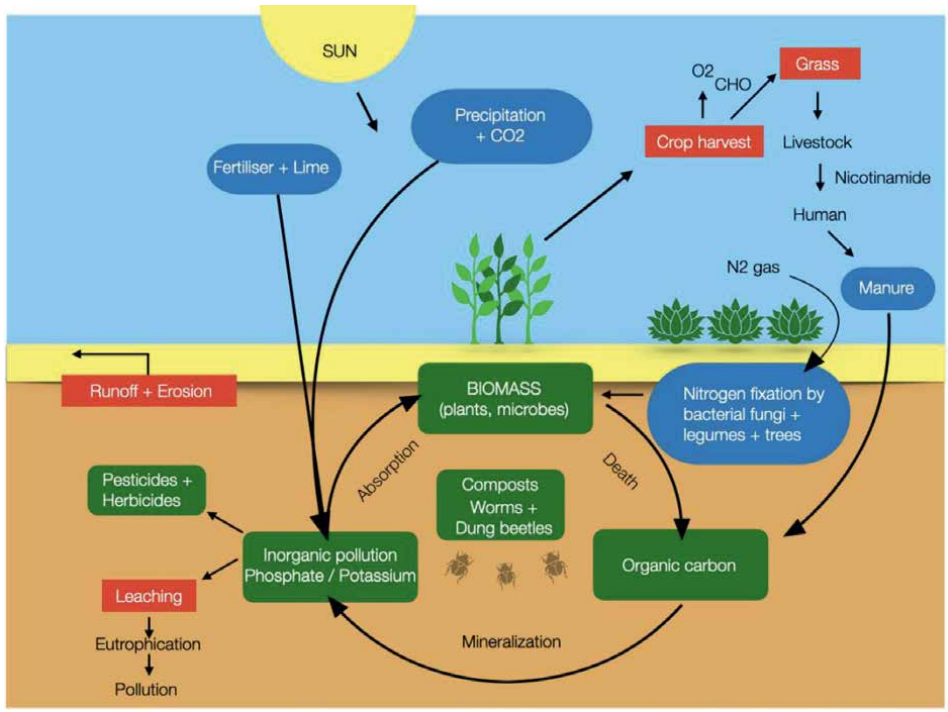

Figure 2.
Many natural cycles such as the nitrogen and carbon cycle were enhanced by good farming techniques but later these got disrupted in the short-term quest for high yields. For instance animal (and often human) manure is usually no longer returned directly to the soil – The classic metabolic rift. Use of natural gas to make ammonia-based fertiliser damages the carbon and nitrogen cycle with methane leaks and CO2 and N20 emissions compounded by eutrophic effects on biodiversity compared with natural nitrogen fixation by clover and legumes. This creates a second metabolic rift as artificial fertilisers mean that animals and plants need not be grown together. Ruminants contribute to CH4 emissions and new pastureland usually requires deforestation. On the other hand perennial grasses are often on land that cannot be used for crops and if well-managed, often with silviculture, can act as a carbon sink, as can the oceans at the same time as supplying sources of nicotinamide.

thermodynamics (as Schrodinger pointed out in "*What is Life*" in 1943) and combat increasing entropy but preferably not, as is happening, at other people's expense [26–31]. This ties in with concepts of a social metabolism and free energy that interacts with internal homeostatic mechanisms (Claude Bernard's 1850 *"milieu interieur"* that can easily be overwhelmed both for the individual, as our discussion of pellagra will demonstrate, and for the anthroposphere [26, 32–34].

Much has been said on the damage done to health and happiness from relative inequality and the spectre of "status anxiety" but absolute disposable income in relation to the cost of a balanced diet may be the more important foundation: Engel's curves predict that once calorie intake is satisfied from starches and sugars families spend more on fresh vegetables and meat (**Figure 4**) [35]. This rise up the food chain that improves both health - and wealth is not a zero-sum game as it is the basis for expansion of markets for actual luxuries and modernisation [36–42]. Low incomes makes this impossible and is exacerbated by relative prices of healthy versus unhealthy foods often being worse with added "poverty premiums" in poor countries and neighbourhoods and the distraction of technological luxuries in a post-industrial world - let alone increasing costs for energy or rent leading to "slow micronutrient starvation" and metabolic risk [43–47]. The true cost (hours of work needed)

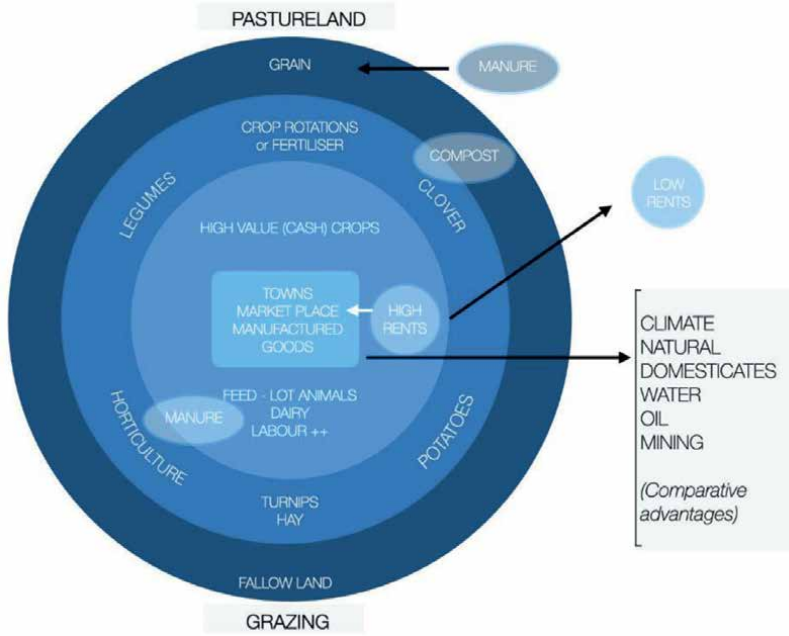

Figure 3.
Many cultures closely integrated a balance between cereals vegetables and animal products. Mixed farming is shown but trading relationships between pastoralists and agriculturalists were common. Where a balance was difficult behaviours included warfare to obtain land or cattle or slaves for farm labour or captives to cannibalise. Hunting was maintained for longer if domesticates were inadequate or sometimes if climate change meant that it had to be re-introduced. Class fights over pastureland with attempts to enclose it and severe punishment for poaching was common. Mixed farming leading to reasonable diets for all through frequent feast days was easier when transport constraints contained food products locally. Industrialisation and urban rural splits developed and even if there were some benefits to the development of water and railway networks to supplies this usually favoured the rich core, with more meat/milk or out of season or tropical foods, not the periphery or third world where the export of cash crops farmed on plantations often destroyed local mixed farming. Distance created space for complexity in supply chains with monopolies and corporate and financial middle-men and though lowering prices non-accountable costs to health and well-being and the climate with environmental degradation and labour exploitation rose. Many pellagra outbreaks were linked to market failures such as that of cash crops such as cotton.

to pay for a breakfast of bacon and eggs has fallen by over 90% over a hundred years for workers but this advantage has not been shared with all within or across countries [48, 49].

In part 1 we talk about pellagra largely in the context of economic class; in part 2 we talk about the development of high meat, and therefore nicotinamide, divergences and convergences between countries and continents. As Charles Dickens said (1859) in another crucial and informative era "*it was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness…*" – we argue it is time to correct a basic and foolish inequality from which many other inequalities derive but we need to review nutritional science and the importance of NAD and the history of pellagra first [50–58].

3. Nutritional science: 19th and 20thC history and public health

Following on from Hippocrates and dietary and exercise regimens and the importance of diet for human progress and "perfectibility" Condorcet, Godwin and

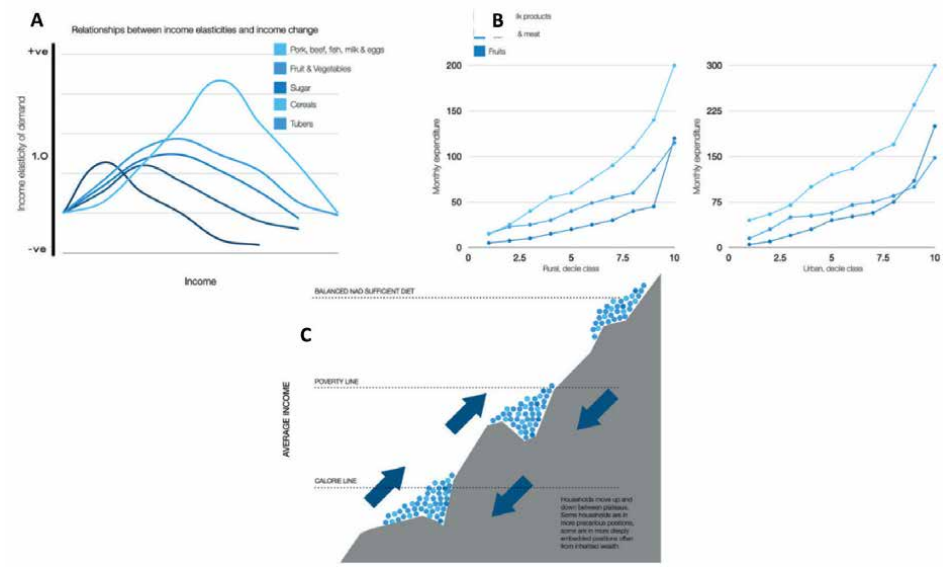

Figure 4.
A) Engel's curves illustrate how the poor will favour cheap starches and cereals for their calories and only when their income rises and a lower proportion of income is spent on food will they eat much meat or vegetables that are more expensive and involve more waste. Income has to pay for other necessities such as rent and (from wood or charcoal to electricity) heat for warmth and cooking as defined first by Maslow's hierarchy of needs. Increasing (technological) "Veblen" luxuries may compete with a healthy diet as do excessively cheap calories from sugars and oils in ultra-processed foods. B) Engel's curves also often differ between rural and urban populations and as we will see later between rich and poor countries. Rich countries are more likely to have subsidised meat and fortified with vitamins, including vitamin B3, cereals. C) an optimal nicotinamide rich, but not too rich, (around 10–15 mg/day) will be well above the poverty line but by no means unachievable if it was made a priority.

Frank (who in 1970 commented "*starvation and sickness are pictured on the face of the entire working class. You recognise it at first sight*") took a more optimistic stance than Malthus. Magendie ("pas d'azote"), Mulder, von Liebig (who developed meat extracts), von Voit, Chittenden ("Nutrition of Man" 1907) and Atwater began to understand the difference between nitrogenous protein and non-nitrogenous calorific fuels and made specific arguments for greater rationality over food choices, including meat. Physicians, such as See (1887) made dietary and sanitary recommendations that included milk to strengthen resistance and reduce exposure to (infectious) disease and infant diarrhoea as did early public health officers such as Newman (who wrote on the importance of nutrition in his book "the building of a Nations health" (1939) and Newsholme. All was who helped by the rise of statistics from Petty (1655) to Graunt and Farr's Life tables who championed the proverb "prevention is better than a cure" [59]. Villerme (1818) and de Chateauneuf showed large differences in mortality and diet between rich and poor in Paris as did a contemporaneous survey in Naples and called for protection against the high price of food: as did Paton (1901) in England and a BMJ leader in 1913 "*..or is it that the wages they command are so low that they cannot purchase the necessities of life*" [60]. Even at the height of "Germ" theory (Robert Koch (1890) and the success of earlier sanitation projects (Edwin Chadwick 1840s) and the first antibiotics some such as William Allison (1830s) and Rene Dubos (1940s) ("think globally, act locally") and Thomas McKeown (1970s) championed a role for diet and the ever- changing ecology to which man has to adapt with microbes being necessary but not sufficient

to cause disease [61, 62]. Nutritional interactions with physical degeneration and infection are complex and bidirectional as was pointed out early by Price (1930s) and Scrimshaw (1960s) and others before and since and here [63–65].

Hopkins (1906) led the charge following others, such as Eijkman, on "unsuspected dietetic factors" then named "vitamins" by Funk presenting the idea that beriberi, rickets, xeropthalmia, scurvy and pellagra were nutritional deficiency diseases. Later Kwashiorkor (described in 1933 on maize diets) was initially felt to be more related to protein malnutrition by many but is cured by milk and theory has reverted to it being a form of juvenile pellagra and a general concentration on the importance of micronutrients. Inadequate income rather than lack of education was a controversy partly eliminated by Boyd-Orr (1936) who with others at the FAO(Food and Agricultural Organisation) founded in 1945 and the World bank (influenced by Berg's "the nutrition factor: its role in national development") tried hard to recognise this as a global not just a national issue such as the self-interested response to the poor height and health of army recruits at the time of South African Wars. Cod liver oil usage (vitamins A & D) became common and fortification of some foods including niacin became mandatory in some countries in 1946 and manufacturers soon included large doses in many foods and drinks following on from a period of "Vitamania". Interactions of nutrition and infection were noted as "mutually aggravating" in a comprehensive monograph in 1968 (as remains true for more recent infections such as HIV). Thomas McKeown (1976) proposed the decline in infectious disease particularly TB was largely down to better diet; this was criticised but is now almost orthodox – the data was available then to link it with meat and nicotinamide (an anti-TB antibiotic) but that had to wait till 2013 [66]. Amongst other anecdotal observations a study with a control group from 1946 had shown that a meat and milk richer diet supplied by the Red Cross reduced the incidence of TB in prisoners of war by 15 fold. From the 1930's to recently repeated studies in many populations showed that milk increased linear growth as did meat and animal products and cognition along with increasing foetal weight relative to gestational age (SGA) and reduced mortality [45, 67–69]. Recommended daily intakes adjusted for physiological stresses, including for nicotinamide, have been in place for many years but are rarely monitored and screening programmes for NAD/Tryptophan deficiency have rarely been used even though eminently possible [70].

4. Poverty and subsistence: Austerity never works

Poverty has long been measured in terms of it's relationship to basic nutritional subsistence and the role of rulers responsibilities in providing calories at least for the proletariat long recognised in early empires. Landmark studies included Eden's "The state of the poor" (1797) that was explicit on the effects of rising food prices and was an empirical foundation for Poor Laws as were Booth and Rowntree's surveys and descriptions of "frugal lines" in the late 19th century. Poverty was often then thought inevitable or necessary to encourage work or was the fault of the poor and their habits and addictions. Poverty Enlightenment in the1800's saw the emergence of a new respect for the poor as people and no longer "shadows in a painting" with the economy seen as a tool for promoting human welfare – an important insight of Adam Smith. By 1890 Marshall in his "Principles of Economics" was writing of the "cumulative evil" of poorly fed children on economic potential and the need for progressive income taxes to help children rise out of poverty. Further enlightenments

saw poverty as a severe constraint both on personal self-fulfilment and on aggregate economic growth and spawned many anti-poverty and better nutritional policies – even as opposition re-surfaced in the 1970's. More recently the dangers of poverty to the well-being of the rich have become better realised whether from war, migration or pandemics. Engel's law as modified by Bennett has been used as a measure of the escape from poverty line and traps and has been substantiated on many occasions whether at a house-hold, country (enabling a move from farming to industrialisation) or at an international level correlating with economic growth. Growth on its own rarely led to reductions in poverty unless it started in the agricultural and service sector enabling lower real food prices and better diets and higher meat intake before there is disposable income to support other aspects of an industrial and consumer society. Once economies are more established (or have used natural resources wisely) this becomes hard to appreciate as agriculture then plays a fairly insignificant role in gross GDP and financialization and "rentier capitalism" that conveniently forgets its roots and responsibilities. Progress is being made given that around 1820 80% of the world population was extremely poor but nutritional status as measured by amount of "wasting" or "stunting" (that includes cognition) is still high and the poor or poor national governance are still being blamed. The example of pellagra demonstrates that most lingering criticisms are however the effect not the cause of poverty in a vicious transgenerational cycle as we will demonstrate.

5. Preconception nutrition: precondition for equality of opportunity for unborn billions

The evidence for the importance of good diet not only early and throughout life but pre-conception and in previous generations continues to mount, building on the epidemiology of the Dutch winter and studies on low birth weight, and affects on both initial (brain) health but also the risk of later onset metabolic disease. This can account for much of the "missing heritability "of many diseases and demonstrates that very early investments (Heckman Curve) can be by far the most cost effective compared with end – of- life health costs- and emphasises the dangers of hunger and austerity measures [71–76] (**Figure 5**). Epigenetic mechanisms include DNA methylation and interactions with NAD/Nicotinamide metabolism with interventions favouring animal based foods and fairly low quantities of milk and eggs having major beneficial effects on cognitive performance and behaviour [77–84]. This also explains the high investment parents will place to allow long successful childhoods so important to our evolution but when impossible comes at the price of reducing social mobility for many but does allow for significant neurodiversity [85–90]. Other periods when brain development is sensitive to environmental and dietary influences are adolescence and "mother brain" with changes in white and grey matter and a pruning of synaptic connections that may be important for brain reserves and ageing well [91, 92]. Improvements of diet throughout life would have short-term and long-term future gains that compound so there is a high discount rate for the current cost for descendant generations fulfilling an obligation to unborn billions for their health and a more cosmopolitan attitude rather than more superficial concerns for local social justice [93, 94]. Better nutrition such as school "breakfast clubs" and free lunches (with dignity) works at all ages and even once in college (or prison, hospital or care homes) it can be shown that hunger on campus affects learning and results, let alone later in life [95, 96].

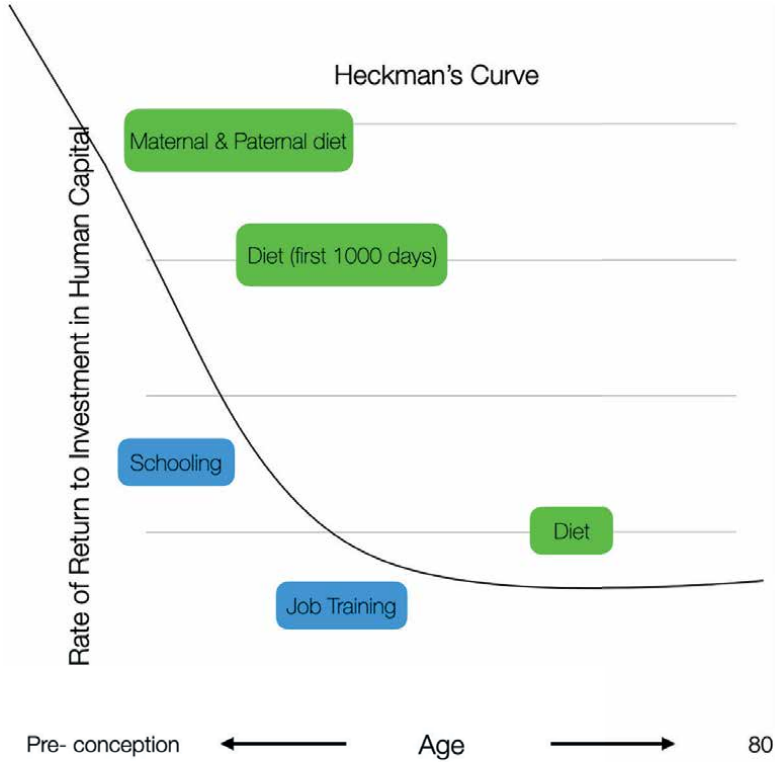

Figure 5.
Heckman's curves illustrate how the rate on return to investment for diet and education rises steeply if begun early - with reductions in many forms of brain and cardiovascular disease. In the case of diet this includes pre-conception parental and even grand-parental diet working through epigenetic and DNA-methylation paths that interact with nicotinamide metabolism. The graph would be steeper for poor countries with short-term benefits merging with long-term compound benefits for future generations. There are limited time windows where catch-up growth can occur with some developmental plasticity but this can create mismatches later in life where ample diets can precipitate metabolic disease and the full gamut encompassed in the developmental origins of adult disease (barker) hypothesis. Low nicotinamide early may cause a phenotype with less neurones more prone to the ravages of ageing but also leads to low induction of nicotinamide methylation that does not forecast a luxury diet and risks nicotinamide toxicity even if diet improves later.

6. NAD history of a key molecule

Harden (1906) discovered NAD as a cofactor whilst investigating fermentation and this was followed by demonstrations of NAD(P)(H) role in anabolism and calcium signalling and NAD(H) in hydride transfers and mitochondrial energetics. Mitochondrial failure is a major feature of many neurological degenerative conditions and often involves other organs. More recently NAD-synthases "feeders" (NMNATs) have been shown to have an important role in (Wallerian) degeneration [97, 98]. NAD-consumers as ADP-Ribose polymerases are known to be important in DNA repair (PARPs) and Sirtuins in ageing (NAD declines with age) with agonists or supplementation extending lifespans and rejuvenating stem cells and promoting tissue regeneration at times of stress, including food scarcity [99–101]. Sirtuin deacetylation (including histones) and NAD affect epigenetic mechanisms regulating genomic and epigenomic stability. NAD turnover is high and supply pool is competed over and is compartmentalised and fluctuates such as with circadian rhythms and is dependent on dietary nicotinamide. There is an endogenous pathway from the degradation of (dietary derived) tryptophan on

the kynurenine pathway that also profoundly affects immune tolerance and is affected by many disease processes and pregnancy [102–104]. Hormetic anti-ageing influences from plant derived compounds, as part of their own defences, such as resveratrol also predominantly act through agonist actions in NAD-Consumer pathways, as does exercise and caloric restriction [105]. NAD connects with the social and sexual dyad relationships through oxytocin regulation [106, 107]. NAD fluxes through energetics and its consumers and signalling is a central master-controller of metabolism and we, in a very real sense, live in a NAD metabolome and microbiome with symbiotic and social breakdowns when the supply fails [108]. Satiety and avoidance of food, sex and gambling addiction and substance abuse from alcohol to cocaine has been linked with circadian NAD replete pathways affecting opioid, nicotine and cannabinoid receptor and dopamine, serotonin, oxytocin and adenosine reward circuits [109]. We may be addicted to these surrogates for NAD as we may be to NAD and its metabolites just like some extreme mutant cancer cells [110]. NAD replacement may work for a wide variety of diseases of ageing as may Nicotinamide N-Methyltransferase (NNMT) inhibition as this enzyme is induced, perhaps by high nicotinamide in diet, in a wide variety of "diseases of modernity" whether metabolic, cancerous or degenerative [109, 111, 112]. We are be in a "NAD World" with many of our senses, metabolism, physiology and actions attuned to obtaining and the optimal use of this supply in our "umwelt" [113, 114].

7. Pellagra's epidemics

Pellagra was first described in the medical literature by Gaspar Casal (1735) in a European epidemic amongst poor polenta eating peasants. He recognised its basis in a poor maize based and low meat diet as had the people affected (one offering to sell her house for a round of butter) [115]. Another famous epidemic was a century ago in the south-eastern "cotton" states of America triggered by economic hardship amongst sharecroppers and slaves. South Africa also had outbreaks triggered by rinderpest in cattle, poverty and apartheid. More recently outbreaks have occurred usually in war-torn African countries. Death rates are high and undiagnosed let alone untreated cases are common [116, 117].

8. Clinical features: 4 D dysfunction & degeneration across generations

Dermatitis was common and sometimes pathognomonic as a seasonal form of sunburn. Darker skins were somewhat protected limiting diagnosis and self-diagnosis that could otherwise lead to self-treatment and eating more meat before specific treatment was even available risking cognitive decline. (During our early history this may have favoured white skinned peoples in more northern climes that also had more meat in diet but less sun). Dementia and poor intellectual development were important features that included a raft of other neuropsychiatric syndromes, including a myoclonic encephalopathy, and poor and antisocial behaviour. Mimics of Parkinson's and Motor Neurone disease were noted. Diarrhoea was common due to inflammation and dysbiotic infections – other dysbiosis included TB – and there was susceptibility to acute infections. Death and premature ageing were common although rarely mentioned by the current ageing literature. Women were affected twice as often as men (and often have less access to meat in the home). Pigmented skin protects against the characteristic sunburn rash but may be a mixed blessing if then poor cognition is overlooked and not (self-) treated particularly as in Africa, Asia and the Americas meat was less available.

Pellagra was thought at the time as being a systems failure and degenerative in the atavistic reverse evolutionary sense of the term (even before the importance of meat in our evolution was realised) let alone being neurodegenerative in the modern sense. Pellagra is also an excellent example to remember in the nature via nurture and in Mind-Gut axis debates [118]. Pathology crossed many current classifications as there was evidence of degeneration, mitochondrial dysfunction, oxidative stress, dysbiosis, amyloidosis and manifestations with no discernible histopathology [41, 119].

9. Addiction: early opioid and other drug endemics and wars

Alcohol addiction and ritual drinking bouts "potationes" was well recognised but by interfering further with NAD status makes things worse and can be a cause of pellagra alongside thiamine deficiency and Wernicke's and Korsakoff syndrome both treated with multivitamin preparations. Addiction to food and feast days is more understandable but other addictions whether sex of gambling played in to developing pellagrins a poor reputation. Self or institutionalised and medicalised treatment with drugs even infants is more surprising. In the 17th century the poor cultivated on an industrial scale and ate poppy seed bread "pavrato" or "pane papaverino" and may well have caused the first "opioid" and "cannabinoid" epidemic. Other pain killing and hallucinatory herbs, including hemp, or spoiled rye with ergotism and St Vitus's dance were as a response to this "disease of wretchedness" benumbing an already stunned undernourished population who could only dream of a land of Cockaigne and a world to be turned upside down "mundus inversus" as often too weak to rebel. Opium has been used since the ancient world but not on this scale that subsequently got magnified with major effects in China, note 19th C "opium wars", and recently as is well documented causing incarcerations (though not of the Sackler's or other manufacturers of fentanyl and analogues) and life expectancy falls particularly in the USA [120–124]. This ultimate in unconscionable abuse of bio-power perhaps started with pellagra-related "deaths of despair" three centuries ago but is only recently recognised as having a link with NAD deficiency helped by NAD infusion [125].

10. Treatment

Joseph Goldberger in the USA during their epidemic beginning in 1902 is rightly credited for renewing the dietary link (proposed for the Nobel Prize three times) as then it was widely thought to be due to a poison in maize or infectious or genetic. He recommended high meat and fresh diets or the use of brewer's yeast to good effect for both prevention and cure and recognised the similarity with "black tongue" in dogs and the link to tryptophan. Conrad Elvehjem discovered nicotinic acid and the link to pellagra (1937) and Tom Spies and colleagues rapidly (Time magazine Team of the Year 1938) treated patients who even in advanced cases could respond.

11. Butterfly castes to butterfly effects: racial, class and other divides are not so black and white

Pellagrins whether white or black were derided as inferior human beings or even as a different race, with many epithets still used against "deplorables", and were known

as the "Butterfly caste" (referring to the characteristic dermatitis) and "problem pellagrins". At various times those from Ireland and Italy have been treated much the same so colour may be a distraction from the real underlying cause of many "them and us" as really "have and have-not" divides and extreme reactions such as the Klu Klux Klan, segregation, apartheid and genocides and the occasional successful revolt such as on Haiti.

Racial and colour awareness can be date back to at least biblical times as in the Christian and Jewish myth of the "curse of black skinned Ham but the origin of whole populations having inferiority complexes has been dated to the 17th century German speaking countries (extraordinary given the later history of racial purity and Aryan supremacy) relative to the French who were dominant in all spheres of life whether material or cultural and was exacerbated by the thirty year war – when German livestock were rounded up and driven away - and these countries were in an early financial crisis with hyperinflation and a credit crunch [126].

Anthropologists travelling the world, such as the neurologist W.H.R.Rivers, dispelled some myths that "primitive" races had sharper perception as their minds used little energy for higher mental functions (the "Spencer hypothesis") although not many were convinced during strong eugenic movements [127–129]. Other anthropologists from the 1930's on have documented behaviour changes and dehumanisation during the "hungry season" (when meat is scarce and pellagra outbreaks start) or when peoples are removed from their hunting grounds noting societal and familial breakdown (with cannibalism and infanticide at the extremes) and include Turnbull's 1960's studies of the Ik tribe "Mountain People" and Scheper-Hughes 1990's Brazilian study "Death without weeping" of slow starvation often medicalised and treated with drugs [130–134]. Similar observations were made in the Ukraine 1930's famine, the Siege of Leningrad in 1941, and many Chinese famines as described for the 1960's Mao responsible famine in "Hungry Ghosts" [135]. Acquired constitutionally poor phenotypes secondary to financial hardship and a slide down Engel's curves precede societal stigma and institutional bias to "wastrels" and discrimination and medicalisation can hide the basic nutritional cause and responsibility even in the face of rebellion [63].

Bacon's 1676 rebellion is remembered as, for once, poor whites and poor blacks united to fight for their rights, yet still failed as did similar attempts later in America, well analysed (by Du Bois around 1900) and South Africa. The calculated response by well fed and nutri-genomically well-endowed northern European groups, who felt superior (and were taller), was that poor whites, often indentured servants or imported criminals, needed preferential material or status enhancing treatment so as not to spoil their own case for supremacy (upset by many shocks such as the Japanese attack on Pearl Harbour) [136, 137]. Hence Jim Crow laws, with apartheid menial jobs with and low incomes then prohibition "wars" first on alcohol and then drugs with incarceration all denying "inferior" groups any realistic chance of levelling up.

As Martin Luther King said in 1968 when about to launch the Poor People's Campaign just before he was assassinated *"in one America people have quality food and education, in the other the best minds can never come out"* [138]. Based on personal reversible experiences, the current mayor of New York has recognised that a diet derived from slavery to unhealthy soul food is a key front line in the fight for civil rights [139]: and, we say, was the original bottom line with a low meat intake affecting physiology and behaviour with a the willful drive to degeneration by further dietary restrictions and then blaming the victims [140–142]. Recent calls support this view that poor diet is the common denominator as in Louis Gates comments in *"America*

beyond the colour line" ."if King came back, he'd say we need another civil rights movement based on class not race" reflecting class divides in people of all colours and the long-term effects of "segregation sequiturs" such as low wealth and income and poor diet - democratic socialism with strong economic rights underpinning diet and (electrical) energy rights is the way forward [143–146]. Pellagra's butterfly effects from origins in the southern states and south Africa bastions to this day of some of these frictions are still the most acute could worsen despite the importance of diet and pellagra prevention being well known for over a century [147].

12. Euthenics not eugenics

Ellen Swallow (1900) is credited with emphasising diet and ecology in human health and combating eugenics with euthenics and social welfare responses to inequality and the vagaries of birth and racial improvement; life not being self-authored [148]. Others despite their interest in eugenics emphasised diets with both proponents for vegetarianism improving the race, such as Graham and Kellogg (1914) and for meat, such as Woods Harrison (1911) - later taken seriously by countries such as Japan and China. McCarrison working in India and Boyd-Orr in Kenya understood that there was an interaction between tribes, races and diet with the Masai and Sikhs benefitting from blood and meat- based diets with taller heights and better health (including less TB) [149]. Even monarchies were at times pioneers of welfarism and sceptical of genealogy or meritocracy as were some social reformers - common prosperity as a mantra is now even championed in China is realised to have a dietary and euthenic habitat related basis – much based on the need for more meat [150].

13. Pellagra prevention

For most of our evolution and history as hunter-gatherers this was pre-solved as our diet was so meat based both as a source of micronutrients and for calories particularly in temperate zones so catastrophes would have caused localised or seasonal famines rather than chronic or widespread or lifelong malnutrition [151–155]. High intake of nicotinamide from hunting may have been important to the evolution of large cooperative brains with pellagra being an atavistic example of evolution in reverse gear. Furthermore there was a very strong sharing culture particularly for meat with anyone attempting to obtain the "lion's" share actively shunned [156]. Storing and preserving meat developed to overcome "seasonal" hungers or other interruptions to the usually ample supply helped by hunting parties leading the global diaspora. However, that led, along with climate change, to megafaunal extinctions on land and sea and a move to smaller prey and the beginnings of herding. After the agricultural neolithic revolution pastoralism developed to help boost the meat supply. The neolithic revolution was overall a net negative meat transition with adverse effects on health, height and brain size whilst populations exploded on a more pellagra-genic diet with malnutrition as hinted at by descriptions on "steles of famine" [157, 158].

Pastoralists and agriculturalists had trading arrangements allowing for a balanced diet (despite some taboos), even if these were at times fraught – much early raiding and warfare can be seen in this light as will be later empires acquiring pastureland. Pastoralists were not only providers of meat but also developed "secondary products", at multiple independent sites, butter/ghee and soured dairy products from milk curds

MACRO & MICRO-NUTRIGENIC ADAPTATIONS - NAD RELATED		
Amylase copy number	-	Starches
Alcohol dehydrogenase	-	Beer / Wine
Lactase persistence (Northern European)	-	Milk
Nicotinamide methylation (Carnivores)	-	Meat / Milk
NAD ENVIRONMENTAL - HOMEOSTATIC INTERFACES		
NAD / NADH (Redox state)	-	Mitochondrial ATP (Brain) power
NAD (P) H	-	Anabolism Xenobiotic detox
NAD - Consumers + sensors (Sirtuins)	-	Circadian rhythms Foraging - meals Master metabolic controls
Signalling / Chromatin making	-	Genetic memory Fetal programming / thrifty phenotype (DoHaD & transgenerational effects)
Nicotinamide / SAM metabolism	-	Ageing (Calorie restriction) Exercise

Figure 6.
There were several nutrigenomic adaptations during our recent evolution that enhanced our NAD diet most notably the development of lactose tolerance. Nicotinamide n-methyl transferase (NNMT) induction protected us from nicotinamide excesses and close control of NAD metabolism evolved through upgrades of NAD -consumers. Close links with environmental stimuli were forged affecting most metabolic and (neuro) physiological pathways.

(and whey) as fermented cheeses and yoghurts with low lactose levels but just as rich in nicotinamide riboside and more easily stored and transported.

In the best example of parallel cultural and genomic convergent evolution, suggesting extremely strong selection pressures lactase persistent genes emerged independently in several pastoralist populations, particularly in northern Europe, to overcome the natural decline in enzymic activity after infancy and avoiding the unpleasant symptoms of lactose intolerance such as flatulence and diarrhoea whilst cultural evolution developed cheeses [159] Other nutrigenomic developments allowed for greater ability to digest starches and alcohol that connect to NAD pathways and NNMT that, as with other carnivores may guard against nicotinamide overload as would many rearrangements in NAD-consumer pathways all of which are active in general and brain metabolism (**Figure 6**) [160].

Some population, such as those in Mesoamerica, had to adapt to low meat diets due to a lack of easy animal domesticates compared to the "big four" of current animal domesticates that were all herding pre-domesticates in the middle east's fertile crescent. A major staple maize co-evolved and achieved God-like status (as did cattle elsewhere as the "food of the Gods") as it is easy to grow and a good source of calories but not of tryptophan or nicotinamide [161–163]. In a cultural evolutionary approach, suggesting strong selection pressures, in the fields it led to the "3 Sisters" joined by beans and squash enabling growth through nitrogen fixation and both protection

of the soil and as sunshade - and a broader diet with extra nicotinamide and amino-acids. As striking was the (subconscious) development of cooking with lime as "nix-tamalization" releasing bound nicotinamide - a practice not always exported to other continents leading to pellagra outbreaks in Europe and elsewhere. There are other examples of cooking practice that evolved to reduce toxicity from cyanogens and other toxins as did enhanced xenobiotic enzymes but this is the most striking example of releasing a micronutrient and reducing toxicity from its potential deficiency [162].

After the discovery of nicotinamide and its relationship to pellagra in the 1940's supplementation programmes were introduced in places starting with bread. Brown bread contains some nicotinamide in the germ but when processed to white bread is largely removed: although white bread was initially the preserve of the rich it became more popular, in a curious and unfortunate inversion, amongst the poor on low meat diets. (Later the pasteurisation of beer had the same effect by removing brewer's yeast an important source of vitamin B3 used as treatment in some epidemics). Manufacturers soon followed first of cereals, as "Vitamania" took hold and later widespread currently in "high energy" drinks and even teas. However, this usually targets the wrong global populations at risk of deficiency and has the disadvantage of being a potential drain on the methylome, unlike adequate meat. Along with effects on NAD-Consumer enzymic activity this could give mechanisms for a hypervitaminosis B3 as is suggested by excessive induction of NNMT in many diseases of "modernity". In other words, creating the worst of all possible "NAD Worlds" with missing treating cases of subclinical endemic pellagra at the same time as increasing the potential for nicotinamide overload and toxicity [17].

14. Endemic pellagra

During the pellagra epidemics, particularly the American outbreak in the southern cotton states a century ago, not only was it recognised that many cases went undiag-nosed but that the rash was often not present and a condition of "pellagra sine pellagra" was endemic and probably had been since well before the Civil War – and may indeed have contributed to the confederate defeat. Low IQ in recruits and poor physical health, such as diarrhoea (now called "environmental enteropathy" or TB, were well recog-nised as a problem at the time: the finding of better IQ scores from black northerners compared with white southerners was an important if inconvenient truth for many. TB disappears once income and diets improve, presumably as nicotinamide is a TB antibiotic, and this has had a profound effect on population health although may lead to the emergence of allergic and auto-immune disease [164, 165] (**Figure 7**). At risk groups on low to very low meat diets may always have harboured sub-clinical cases and may still do whether seen through the lens of class or continent/country. It is worth a short historical detour to investigate this possibility accepting a lack of data due to no biochemical screening tool for NAD/Tryptophan deficiency in use, inexplicable and unacceptable for an easily treatable condition.

15. Class and NAD scales and ceilings: meat pecking orders

Since the Mesolithic and neolithic move down the food chain to a less meat based and more horticultural then cereal and calorific diet hierarchical class-based systems evolved in all sedentary civilisations [19, 152, 166]. If meat is less avail-able it might make some sort of teleological sense to develop an upper ruling and

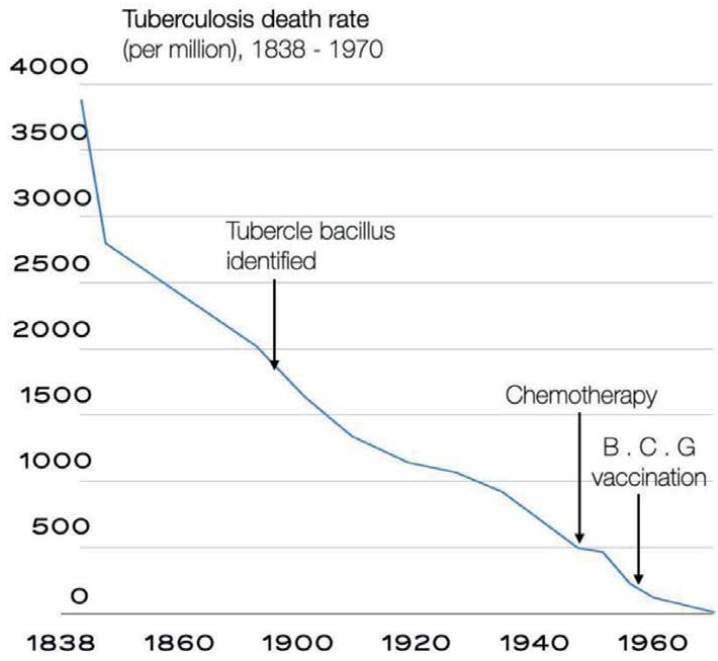

Figure 7.
TB rates fell dramatically before medicines became available and is a hallmark of modernity with a shift that increases life-span but comes with more allergic and auto-immune disease. Sanitation has little effect on this non-water or food-borne microbe and better housing increased rents reducing money for food and has, on documented occasions, led to more TB. Nicotinamide and it's analogues are TB antibiotics so there is a biological explanation and given TB's role in "educating" the immune system absence of this "old friend" may explain it's replacement with the emergence of allergic and auto-immune disease.

officer class on the better diet with high level cognition and a proletariat working and infantry class with, almost by definition, higher fertility. Higher populations allowed for greater divisions of labour and inventiveness. Much of human history can be explained in this light with trading (and wars) with pastoralist (mounted) "barbarians" to obtaining more pastureland by conquest ("Lebenstraum") – given class wars when the ruling classes did not honour their promises to feed the "common" people whose lands and hunting or farming rights they had taken as part of "enclosure" movements (**Figures 8** and **9**). Extreme versions such as wars to obtain captives for human sacrifice rather than land as state sponsored cannibalism for the upper classes in Mesoamerica [167]. Recent versions are evident the history of the working classes and their "snakes and ladders" of failures, whether white or black, if only education and not income or diet is addressed [168–171]. When the political will is there it is possible as examples include successful victualling often cited as being important for victory in all wars and well documented for the Napoleonic wars with significant meat intakes for the sailors compared with their enemies (and non-combatants at home) [172, 173].

High meat, milk, butter and cheese intake amongst the wealthy often amounting to gluttony and "orthorexia" is well documented everywhere that it has been studied for the last 10,000 years with documented effects on height, health, IQ and power as is the opposite effects of forced often monophagic vegetarianism on the working classes or low-income unemployed, especially women and including children [174–176]. Meat as the centrepiece (sometimes along with cheeses) has

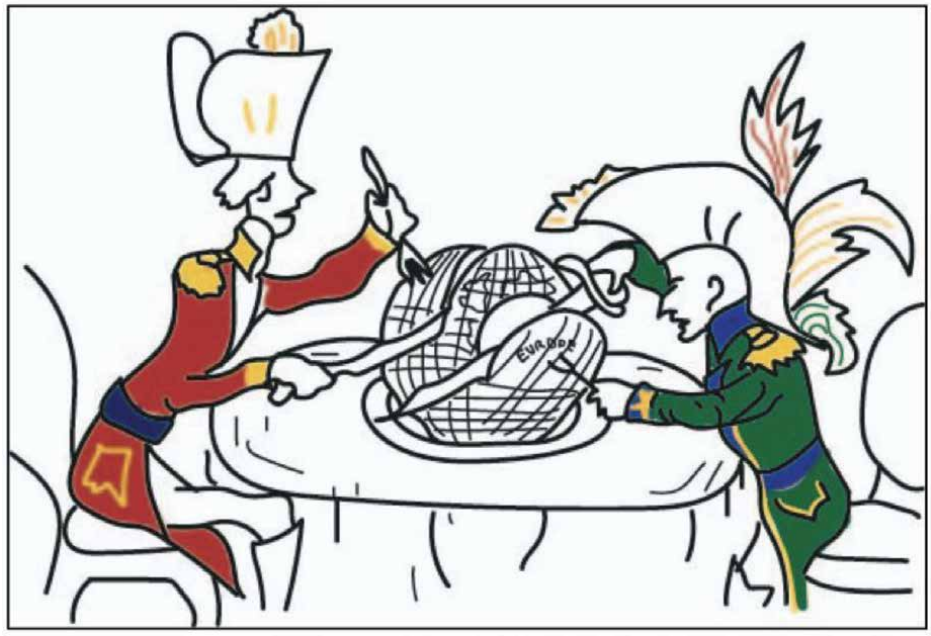

Figure 8.
Gillray's 18thC cartoon may have been the first to illustrate the connection between class differences and cuts of the national "plum pudding" with meats to the king and his courtiers down to the "scrapings" for the labouring poor (the value of roast beef and the evils of alcohol were also well depicted by Hogarth). The carving up of empires between great powers and "state epicures" and" greedy-guts" divided the world to the great detriment of the poor in poor southern nations. Now rather than Palmerston and Napoleon leaders from Eurasian and Western blocs and food monopolies carve up the world – The dangers of this are profound and a common purpose needs to be established fast to correct this basic human right and create a world safer from pandemics.

long been important for the rich and for distribution in feast days - that used to be a lot commoner – or by monasteries (who had a beneficial effect on agriculture even after their dissolution). Peasant dishes can get gentrified, an old example being the addition of meat in medieval times to "frumenty" porridge, with many more examples when dishes were imported to richer climes as in the "hunger for America" diasporas from Europe [177, 178].

The rise of the middle class bourgeoisie on middling and more meaty diets honed in restaurants in countries who by happenstance got ahead on the meat curve is a likely basis for prosperity in a feed-forward cycle given effects on cognition and behaviour and a culture of truth and "matters of fact" that recognises talent from all classes as the history of the Royal Society and other legal and scientific institutions demonstrate [179–183].

Nevertheless a dangerous class divide persists that is known as the "Lockian proviso" and can be summarised as *"if the process of civilization has deprived the members of society of certain liberties (to gather, pasture, engage in the chase) compensation would be due to those persons for whom civilization was a net loss"* allowing a moral argument to steal under those circumstance offers taken up from "Robin Hoods" if there is inadequate pre-or re- distribution to the poor [184–186]. Rulers cannot rule by force alone so a cultural consensus and social contract is normally achieved even if periodic realignments have to be made after periods of austerity and "gilded" ages – we may be in one now exacerbated by Covid with monetary policy in the rich world risking a two-track divergent economic recovery between both classes and countries with their

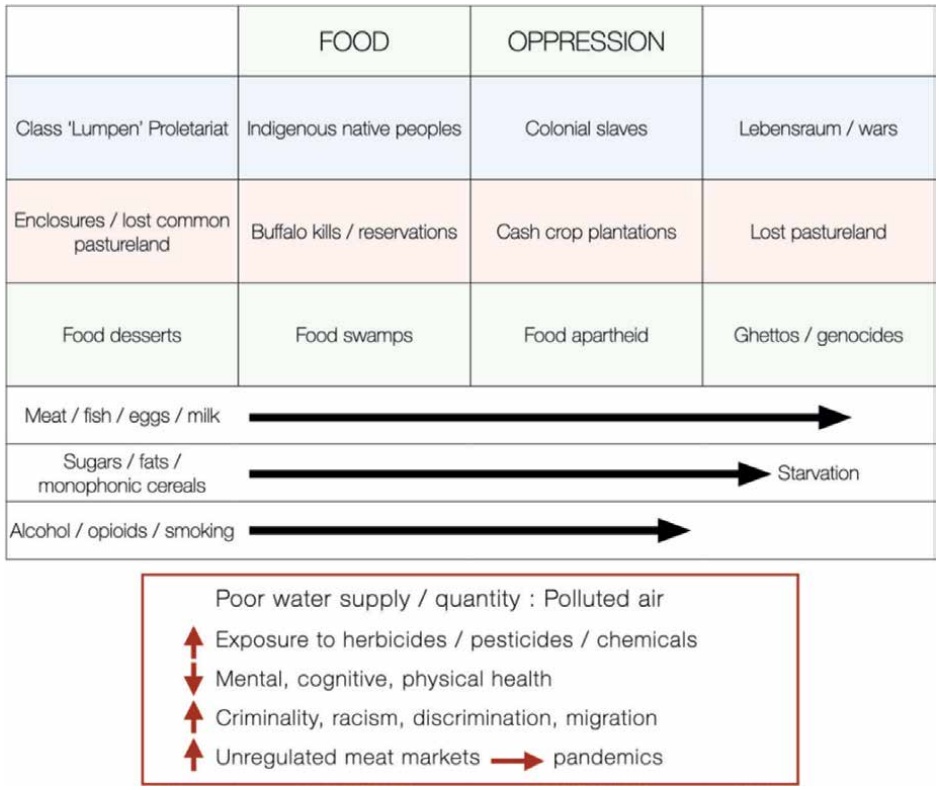

Figure 9.
Most forms of oppression have been crimes of commission (despite being resisted and criticised at the time) mediated by interrupting "swords v ploughshares" food and animal product chains often in (civil or class) and "guns or butter" conflicts, raids and wars. Sometimes these constraints targeted those who started from a poorer dietary base such that infectious disease collaborated in population destruction, such as the Americas, but not always as the bourgeoisie were attacked in the midst of collectivism as with the Russian kulaks and in Cambodia, China - and many Jewish pogroms. Crimes of omission have contributed to at least as much malnutrition and premature deaths or weaponised food supplies.

debt burdens and poor access to increasingly expensive food and agricultural investment funds [187–189]. Cries that we cannot afford more solidarity should remember what Keynes (1942) said *"anything we should actually do, we can afford.*

16. Discussion

Discussions about causation and the origins of class and racial inequalities typically consider only the last 3–400 years and when dysfunctional blame proximate factors such as the need for cheap or surplus labour or, various forms of (neo) slavery and related lack of (hereditary) capital or, "laissez-faire" neoliberalism or, weak democratic institutions and corruption or, property laws and loss of the "commons". However if one takes a longer view it is clear that our pre-history ancestors were far more egalitarian in general and particularly so over the sharing of meat. Later class gradients of meat eating emerged and perhaps allowed some increased diversity in a largely isogenic species with high human capital when meat intake was high but higher fertility amongst the proletariat that may have

been of overall benefit. However, when taken to extremes with very low intakes "precariats" and "underclasses" let alone frank pellagra developed that became racialised and has caused much friction over the last few millennia. This underlying dietary motor has become obscured although poor diet as a transgenerational and within lives mechanism for exacerbating or causing racial, sexual and transgenerational inequalities is gaining traction and is, we believe, a constructive and practical way of dealing with reparations by eliminating food deserts and swamps with their "empty" calories and "amputation capitals" and other metabolic ghettoes – we should re-invent being" together at the table" and adequate sustenance with sustainability for all [190].

Reducing resource stress and food insecurity improves cognition and reduces loss of cognitive bandwidth by having to spend less time on earning to provide a basic diet over and above calories and giving more time to spend on education and family - with no need for breaking laws.

17. Conclusions

Engel's Law (1857), is one of the most robust regularities in economics, showing an uncanny fit both within and across countries with increasing incomes (or falls in prices) leading to a decline in the share of family income spent on food. Indeed, given other necessities such as heating, clothes, shelter and entertainment, it can be used as a measure of poverty. Bennetts (1941) modification demonstrated that as income rises less is spent on starches or cereals and more on milk and meat and fruit and vegetables up to a point where it then can fall off for meat. Indeed, we have previously proposed a hypervitaminosis B3 and there are other signals that too much meat may be toxic. Engel's curves are subject to major distortions if calories become very cheap but meat fruit and vegetables remain expensive as then this normal progression will become attenuated – especially if there is also competition from other "luxuries" with remarkable penetration such as mobile phones. These destroy the market for meat as demand seems to fall as there is not enough disposable income to support a safe market encouraging dangerous black markets in "bushmeat". No wonder there is no longer the same clear divide between the move from infectious to auto-immune disease and obesity now becoming common and now a feature of poverty due to the emphasis on cereals and oils and sugars and empty calories in food swamps creating a "double whammy" and sick societies [191].

We have given some background on NAD metabolism with pellagra being the "tip of a metabolic iceberg" and the importance of animal products as the source of nicotinamide and how it's deficiency can cause many disease, dysbiotic and social phenotypes that include poor cognition and anti-social behaviour with addictions creating classes that become dysfunctional. In *"Silencing the past: power and the production of history"* Trouillot (1995) insisted that *"the ultimate mark of power maybe it's invisibility; the ultimate challenge, the exposition of it's roots"* and this meat-power relationship needs to be made visible so that it can be corrected and allow multiple "Phoenixes" to rise.

Acknowledgements

This study was funded by QEHB Charity, Birmingham, UK.

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Author details

Adrian C. Williams[1*], Christina Wood[1] and Lisa J. Hill[2]

1 Department of Neurology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

2 School of Biomedical Sciences, Institute of Clinical Sciences, University of Birmingham, UK

*Address all correspondence to: adrian.williams1949@gmail.com

References

[1] Arora N. The Lottery of Birth: On Inherited Social Inequalities. India: Three Essays Collective; 2017

[2] Smil V. Energy and Civilization: A History. MIT Press; 2017

[3] Marshall M. The Genesis Quest: The Geniuses and Eccentrics on a Journey to Uncover the Origin of Life on Earth. University of Chicago Press; 2020

[4] Pinson J. The rise and reign of the mammals: A new history, from the shadow of the dinosaurs to us. In: Amer Assoc Advancement Science. New York, Washington, DC; 2022

[5] Scheidel W. The Great Leveler. Princeton University Press; 2018

[6] Kent S. Farmers as Hunters: The Implications of Sedentism. Cambridge University Press; 1989

[7] Shepard P. The Others: How Animals Made us. Human: Island Press; 1997

[8] Maestripieri D. Games Primates Play: An Undercover Investigation of the Evolution and Economics of Human Relationships. Basic Books; 2012

[9] Kean H, Howell P. The Routledge Companion to Animal-Human History. Routledge; 2018

[10] Morris B. The Power of Animals: An Ethnography. Taylor & Francis; 2020

[11] von Hippel W. The social leap: The new evolutionary science of who we are. In: Where we Come from, and What Makes us Happy. Harper Collins; 2018

[12] Jebelli J. How the Mind Changed: A Human History of our Evolving Brain. Little, Brown; 2022

[13] Pollan M. This Is your Mind on Plants. Penguin Publishing Group; 2021

[14] Burton FD. Fire: The Spark That Ignited Human Evolution. University of New Mexico Press; 2011

[15] Berg AD, Muscat RJ. The Nutrition Factor; its Role in National Development [by] Alan Berg (Portions with Robert J). Muscat: Brookings Institution; 1973

[16] Pimentel D, Marcia H, Pimentel MS. Food, Energy, and Society. Third ed. CRC Press; 2007

[17] Williams AC, Hill LJ. Inequality: The dangers of meat haves and have-nots in a nicotinamide-adenine-dinucleotide world. In: Meat and Nutrition. Vol. 3. London, UK: Intech Open; 2021

[18] Bowles S et al. Poverty Traps. Princeton University Press; 2011

[19] Outram AK, Bogaard A. Subsistence and Society in Prehistory: New Directions in Economic Archaeology. Cambridge University Press; 2019

[20] Altieri MA. Agroecology: The Science of Sustainable Agriculture. CRC Press; 2018

[21] Weis T. The Ecological Hoofprint: The Global Burden of Industrial Livestock. Bloomsbury Publishing; 2013

[22] de Wit MM. Abolitionist Agroecology, Food Sovereignty and Pandemic Prevention. Daraja Press; 2021

[23] de Blij H. Why Geography Matters, more than Ever. USA: OUP; 2012

[24] Rieff D. The Reproach of Hunger: Food, Justice, and Money in the Twenty-First Century. Simon & Schuster; 2016

[25] Ungar PS, Teaford MF. Human Diet: Its Origin and Evolution. Bergin & Garvey; 2002

[26] Baccini P, Brunner PH. Metabolism of the Anthroposphere, Second Edition: Analysis, Evaluation, Design. MIT Press; 2012

[27] Bailey KD. Social Entropy Theory. State University of New York Press; 1990

[28] Clark RP. The Global Imperative: An Interpretive History of the Spread of Humankind. Taylor & Francis; 2018

[29] Frank AG. ReOrient: Global Economy in the Asian Age. Univ of California Press; 1998

[30] Ayres RU, Simonis UE. Industrial Metabolism: Restructuring for Sustainable Development. United Nations University Press; 1994

[31] Lessenich S. Living Well at Others' Expense: The Hidden Costs of Western Prosperity. John Wiley & Sons; 2019

[32] Parr T et al. Active Inference: The Free Energy Principle in Mind, Brain, and Behaviour. MIT Press; 2022

[33] Prigogine I. Order out of Chaos: Man's New Dialogue with Nature. Verso; 2017

[34] Thomas L. The Intersectional Environmentalist: How to Dismantle Systems of Oppression to Protect People +Planet. Little, Brown; 2022

[35] Williams AC, Hill LJ. Meat and Vitamin B3: Getting a Grip on Engel's Curve. Intech Open; 2021

[36] Clapp J, Moseley WG. This food crisis is different: COVID-19 and the fragility of the neoliberal food security order. The Journal of Peasant Studies. 2020;**47**(7):1393-1417

[37] Federico G. Feeding the World: An Economic History of Agriculture, 1800-2000. Princeton University Press; 2010

[38] Food M, C. Energy and the Creation of Industriousness: Work and Material Culture in Agrarian England, 1550-1780. Cambridge University Press; 2011

[39] Pilcher JM. Food in World History. Taylor & Francis; 2017

[40] Standage T. An Edible History of Humanity. Bloomsbury Publishing; 2009

[41] Williams AC, Hill LJ. Poverty and Pellagra's penumbras. In: B-complex Vitamins. London, UK: Intech Open; 2021

[42] Escribano AJ et al. Instant Insights: Integrated Crop-Livestock Systems. Burleigh Dodds Science Publishing Limited; 2021

[43] Headey DD, Alderman HH. The relative caloric prices of healthy and unhealthy foods differ systematically across income levels and continents. The Journal of Nutrition. 2019;**149**(11):2020-2033

[44] Forouzanfar MH et al. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: A systematic analysis for the

global burden of disease study 2015. The Lancet. 2016;**388**(10053):1659-1724

[45] Health MC. Food and Social Inequality: Critical Perspectives on the Supply and Marketing of Food. Taylor & Francis; 2015

[46] Shaw I, Aldridge A. Consumerism, health and social order. Social Policy and Society. 2003;**2**(1):35-43

[47] Reckwitz A. The End of Illusions: Politics, Economy, and Culture in Late Modernity. John Wiley & Sons; 2021

[48] Tupy ML, Pooley GL. Superabundance: The Story of Population Growth, Innovation, and Human Flourishing on an Infinitely Bountiful Planet. Cato Institute; 2022

[49] Purkiss D. English Food: A Social History of England Told through the Food on its Tables. William Collins; 2022

[50] Fanzo J, Davis C. Global Food Systems, Diets, and Nutrition: Linking Science, Economics, and Policy. Springer International Publishing; 2021

[51] Unger PK, Press OU. Living High and Letting Die: Our Illusion of Innocence. Oxford University Press; 1996

[52] Stop LP. Thief!: The Commons, Enclosures, and Resistance. PM Press; 2014

[53] Sen A. Poverty and Famines: An Essay on Entitlement and Deprivation. Oxford: OUP; 1983

[54] Slocum R, Saldanha A. Geographies of Race and Food: Fields, Bodies, Markets. Taylor & Francis; 2016

[55] Piketty T. A Brief History of Equality. Harvard University Press; 2022

[56] Collier P. The Bottom Billion: Why the Poorest Countries Are Failing and What Can be Done about it. USA: Oxford University Press; 2008

[57] Smith D. Zygmunt Bauman: Prophet of Postmodernity. John Wiley & Sons; 2013

[58] Robertson C. What the future holds: Democracy, corruption, ESG and emigration. In: The Time-Travelling Economist. Springer; 2022. pp. 219-242

[59] Newman G. The Building of a Nation's Health. Garland; 1985

[60] de Pee S et al. Nutrition and Health in a Developing World. Springer International Publishing; 2017

[61] McMichael AJ. Planetary Overload: Global Environmental Change and the Health of the Human Species. Cambridge University Press; 1993

[62] Dubos RÃJ. So Human an Animal: How we Are Shaped by Surroundings and Events. Scribner; 1968

[63] Price WA, Nguyen T. Nutrition and Physical Degeneration: A Comparison of Primitive and Modern Diets and their Effects. EnCognitive.com; 2016

[64] Scrimshaw NS et al. Interactions of nutrition and infection. Monograph Series. World Health Organization. 1968;**57**:3-329

[65] Pammi M et al. Nutrition-Infection Interactions and Impacts on Human Health. Taylor & Francis; 2014

[66] Williams AC, Dunbar RI. Big brains, meat, tuberculosis, and the nicotinamide switches: co-evolutionary relationships with modern repercussions? International Journal of Tryptophan Research. 2013;**6**:S12838

[67] Patel R. Stuffed and Starved: The Hidden Battle for the Food System. Brooklyn: Melville House Publishing; 2007

[68] Schindler B. Eat like a Human: Nourishing Foods and Ancient Ways of Cooking to Revolutionise your Health. Hodder & Stoughton; 2022

[69] Simpson SJ, Raubenheimer D. The Nature of Nutrition: A Unifying Framework from Animal Adaptation to Human Obesity. Princeton University Press; 2012

[70] Liu Y et al. Quantitation of NAD+: Why do we need to measure it? Biochimica et Biophysica Acta (BBA)-General Subjects. 2018;**1862**(12):2527-2532

[71] Gluckman P, Hanson M. Mismatch: The Lifestyle Diseases Timebomb. Oxford University Press on Demand; 2008

[72] Austerity BM. The History of a Dangerous Idea. Oxford University Press; 2013

[73] Scott P. The wolf at the door: The trade union movement and overseas multinationals in Britain during the 1930s. Social History. 1998;**23**(2):195-210

[74] Titmuss RM. Birth, Poverty and Wealth. A Study of Infant Mortality. Read Books; 1943

[75] Russell SA. The hunger experiment. The Wilson Quarterly (1976). 2005;**29**(3):66-82

[76] Cattan S et al. Early Childhood Inequalities. Institute for Fiscal Studies; 2022. p. 1

[77] Leyton G. Effects of slow starvation. Lancet. 1946;**248**:73-79

[78] Allen LH, Dror DK. Effects of animal source foods, with emphasis on milk, in the diet of children in low-income countries. Milk and Milk Products in Human Nutrition. 2011;**67**:113-130

[79] Hulett JL et al. Animal source foods have a positive impact on the primary school test scores of Kenyan schoolchildren in a cluster-randomised, controlled feeding intervention trial. British Journal of Nutrition. 2014;**111**(5):875-886

[80] Pollitt E et al. Nutrition in early life and the fulfillment of intellectual potential. The Journal of Nutrition. 1995;**125**(suppl_4):1111S-1118S

[81] Sitwell W. Eggs or Anarchy: The Remarkable Story of the Man Tasked with the Impossible: To Feed a Nation at War. UK: Simon & Schuster; 2016

[82] Balehegn M et al. Animal-sourced foods for improved cognitive development. Animal Frontiers. 2019;**9**(4):50-57

[83] Black RE et al. Maternal and child undernutrition: Global and regional exposures and health consequences. The Lancet. 2008;**371**(9608):243-260

[84] Iannotti LL et al. Eggs in early complementary feeding and child growth: A randomized controlled trial. Pediatrics. 2017;**140**(1):e20163459

[85] Duffy B. Generations: Does When You're Born Shape Who you Are? Atlantic Books; 2021

[86] Hassett B. Growing up Human: The Evolution of Childhood. Bloomsbury USA; 2022

[87] Doepke M, Zilibotti F. Love, Money, and Parenting: How Economics Explains

the Way we Raise our Kids. Princeton University Press; 2020

[88] Bourne H. Am I Normal Yet? Usborne Publishing Limited; 2015

[89] Singer J. Neurodiversity: The Birth of an Idea. Judy Singer; 2017

[90] David W. The Pinch: How the Baby Boomers Took their Children's Future and Why they Should Give it Back. Atlantic Books; 2010

[91] Blakemore SJ. Inventing Ourselves: The Secret Life of the Teenage Brain. Transworld; 2018

[92] Conaboy C. Mother Brain: How Neuroscience Is Rewriting the Story of Parenthood. Henry Holt and Company; 2022

[93] MacAskill W. What we Owe the Future. Basic Books; 2022

[94] Doyle A. The New Puritans: How the Religion of Social Justice Captured the Western World. Little, Brown Book Group; 2022

[95] Goldrick-Rab S. Paying the Price: College Costs, Financial Aid, and the Betrayal of the American Dream. University of Chicago Press; 2016

[96] Mandery E. Poison ivy: How Elite Colleges Divide us. New Press; 2022

[97] Nikiforov A et al. The human NAD metabolome: Functions, metabolism and compartmentalization. Critical Reviews in Biochemistry and Molecular Biology. 2015;**50**(4):284-297

[98] Zhou M et al. Neuronal death induced by misfolded prion protein is due to NAD+ depletion and can be relieved in vitro and in vivo by NAD+ replenishment. Brain. 2015;**138**(Pt 4):992-1008

[99] Brenner C. Why is mom stressed: Homeorhesis as the potential problem and nicotinamide riboside as the potential solution. Journal of Experimental Neuroscience. 2019;**13**:1179069519869679

[100] Ear PH et al. Maternal nicotinamide riboside enhances postpartum weight loss, juvenile offspring development, and neurogenesis of adult offspring. Cell Reports. 2019;**26**(4):969-983.e964

[101] Platten M et al. Treatment of autoimmune neuroinflammation with a synthetic tryptophan metabolite. Science. 2005;**310**(5749):850-855

[102] Chang RQ et al. The role of indoleamine-2, 3-dioxygenase in normal and pathological pregnancies. American Journal of Reproductive Immunology. 2017;**79**:e12786

[103] Xu J et al. Brain SIRT1 mediates metabolic homeostasis and neuroprotection. Frontiers in Endocrinology (Lausanne). 2018;**9**:702

[104] Deng Q, Barbieri JT. Molecular mechanisms of the cytotoxicity of ADP-ribosylating toxins. Annual Review of Microbiology. 2008;**62**:271-288

[105] Calabrese EJ. Hormesis: Path and progression to significance. International Journal of Molecular Sciences. 2018;**19**(10):2871

[106] Gerasimenko M et al. Nicotinamide riboside supplementation corrects deficits in oxytocin, sociability and anxiety of CD157 mutants in a mouse model of autism spectrum disorder. Scientific Reports. 2020;**10**(1):1-12

[107] Salmina AB et al. Integrative neurochemistry and neurobiology of social recognition and behavior analyzed with respect to CD38-dependent brain

oxytocin secretion. Current Topics in Medicinal Chemistry. 2013;**13**:2965-2977

[108] Imai S-i. The NAD world 2.0: The importance of the inter-tissue communication mediated by NAMPT/NAD+/SIRT1 in mammalian aging and longevity control. NPJ Systems Biology and Applications. 2016;**2**(1):1-9

[109] Braidy N et al. Sobriety and satiety: Is NAD+ the answer? Antioxidants. 2020;**9**(5):425

[110] Tateishi K et al. Extreme vulnerability of IDH1 mutant cancers to NAD+ depletion. Cancer Cell. 2015;**28**(6):773-784

[111] Conlon N, Ford D. A systems-approach to NAD+ restoration. Biochemical Pharmacology. 2022;**198**:114946

[112] Gao Y et al. Nicotinamide N-methyl transferase (NNMT): An emerging therapeutic target. Drug Discovery Today. 2021;**26**:2699-2706

[113] Ball P. The Book of Minds: How to Understand Ourselves and Other Beings, from Animals to AI to Aliens. University of Chicago Press; 2022

[114] Yong E. An Immense World: How Animal Senses Reveal the Hidden Realms around us. (THE SUNDAY TIMES BESTSELLER): Random House; 2022

[115] Harris S. Clinical Pellagra. St. Louis: C. V. Mosby Company; 1941

[116] Williams AC, Ramsden DB. Pellagra: A clue as to why energy failure causes diseases? Medical Hypotheses. 2007;**69**(3):618-628

[117] Roe DA. A Plague of Corn: The Social History of Pellagra. Cornell University Press; 1973

[118] Deary IJ. Intelligence: A Very Short Introduction. Oxford University Press; 2020

[119] Mayer E. The Gut-Immune Connection: How Understanding the Connection between Food and Immunity Can Help us Regain our Health. HarperCollins; 2021

[120] Camporesi P. Bread of Dreams: Food and Fantasy in Early Modern Europe. Polity Press; 1996

[121] Inglis L. Milk of Paradise: A History of Opium. Pan Macmillan; 2018

[122] Jay M. High Society: Mind-Altering Drugs in History and Culture. Thames and Hudson Limited; 2013

[123] Pleij H, Webb D. Dreaming of Cockaigne: Medieval Fantasies of the Perfect Life. Columbia University Press; 2003

[124] Westhoff B. Fentanyl, Inc.: How Rogue Chemists Are Creating the Deadliest Wave of the Opioid Epidemic. Scribe Publications Pty Limited; 2019

[125] Higham S, Horwitz S. American Cartel: Inside the Battle to Bring down the Opioid Industry. Grand Central Publishing; 2022

[126] Bonney R. The Thirty Years' War 1618-1648. USA: Bloomsbury; 2002

[127] Chaplin JE. Subject Matter: Technology, the Body, and Science on the Anglo-American Frontier, 1500-1676. Harvard University Press; 2003

[128] Linstrum E. Ruling Minds: Psychology in the British Empire. Harvard University Press; 2016

[129] Taylor G. Buying Whiteness: Race, Culture, and Identity from Columbus to Hip Hop. Springer; 2005

[130] Carrasco D. City of Sacrifice: The Aztec Empire and the Role of Violence in Civilization. Beacon Press; 1999

[131] Hogarth RA. Medicalizing Blackness: Making Racial Difference in the Atlantic World, 1780-1840. University of North Carolina Press; 2017

[132] Russell SA. Hunger: An Unnatural History. Basic Books; 2006

[133] Scheper-Hughes N. Death without Weeping: The Violence of Everyday Life in Brazil. University of California Press; 1993

[134] Turnbull CM. The Mountain People. Triad/Paladin Books; 1984

[135] Snyder TD, Dillow SA. Digest of education statistics 2013. In: NCES 2015-011. National Center for Education Statistics; 2015

[136] Lake M, Reynolds H. Drawing the Global Colour Line: White men's Countries and the Question of Racial Equality. Melbourne Univ. Publishing; 2008

[137] Suranyi A. Indentured Servitude: Unfree Labour and Citizenship in the British Colonies. McGill-Queen's University Press; 2021

[138] Hägglund M. This Life: Why Mortality Makes us Free. Profile; 2019

[139] Adams E. Healthy at Last: A Plant-Based Approach to Preventing and Reversing Diabetes and Other Chronic Illnesses. Hay House, Inc.; 2021

[140] Eliav-Feldon M et al. The Origins of Racism in the West. Cambridge University Press; 2013

[141] Hinton E. From the War on Poverty to the War on Crime: The Making of Mass Incarceration in America. Harvard University Press; 2016

[142] Smith DL. Making Monsters: The Uncanny Power of Dehumanization. Harvard University Press; 2021

[143] Hatch AR. Blood Sugar: Racial Pharmacology and Food Justice in Black America. University of Minnesota Press; 2016

[144] Reed A. Class Notes: Posing as Politics and Other Thoughts on the American Scene. New Press; 2021

[145] Rogers JA. Nature Knows No Color-Line. Wesleyan University Press; 2012

[146] Reed AL. The South: Jim Crow and its Afterlives. Verso Books; 2022

[147] Bailey R, Wellesley L. Chokepoints and Vulnerabilities in Global Food Trade. London, UK: Chatham House; 2017

[148] Richards EH. Euthenics, the Science of Controllable Environment: A Plea for Better Living Conditions as a First Step toward Higher Human Efficiency. Good Press; 2019

[149] Hazareesingh S. Black Spartacus: The Epic Life of Toussaint Louverture. Penguin Books Limited; 2020

[150] Warren WJ. Meat Makes People Powerful: A Global History of the Modern Era. University of Iowa Press; 2018

[151] Gráda CÓ. Famine: A Short History. Princeton University Press; 2021

[152] Harris M. Cannibals and Kings: Origins of Cultures. Knopf Doubleday Publishing Group; 2011

[153] Kelly RL. The Foraging Spectrum. Washington, DC: Smithsonian Institution Press; 1995

[154] Le S. 100 Million Years of Food: What our Ancestors Ate and Why it Matters Today. Picador; 2016

[155] Stanford CB, Bunn HT. Meat-Eating and Human Evolution. Oxford University Press; 2001

[156] Widerquist K, McCall GS. Prehistoric Myths in Modern Political Philosophy: Challenging Stone Age Stories. Edinburgh University Press; 2017

[157] Bocquet-Appel JP, Bar-Yosef O. The Neolithic Demographic Transition and its Consequences. Netherlands: Springer; 2008

[158] Cohen MN. Health and the Rise of Civilization. Yale University Press; 1989

[159] Mendelson A. Milk: The Surprising Story of Milk through the Ages: Alfred a. Knopf; 2008

[160] Carlberg C et al. Nutrigenomics: How Science Works. Springer International Publishing; 2020

[161] Fussell BH. The Story of Corn. Albuquerque: University of New Mexico Press; 1992

[162] Johns T. With Bitter Herbs they Shall Eat it: Chemical Ecology and the Origins of Human Diet and Medicine. University of Arizona Press; 1990

[163] Jones MO. Corn: A Global History. Reaktion Books; 2017

[164] Krishnan V. Phantom Plague: How Tuberculosis Shaped History. Public Affairs; 2022

[165] Offer A et al. Insecurity, Inequality, and Obesity in Affluent Societies. Oxford University Press; 2012

[166] Kohler TA, Smith ME. Ten Thousand Years of Inequality: The Archaeology of Wealth Differences. University of Arizona Press; 2019

[167] Carrasco D. City of Sacrifice: The Aztec Empire and the Role of Violence in Civilization. Beacon Press; 2000

[168] Baradaran M. The Color of Money: Black Banks and the Racial Wealth. Gap: Harvard University Press; 2017

[169] Jones GS. Outcast London: A Study in the Relationship between Classes in Victorian Society. Verso Books; 2014

[170] Todd S. The People: The Rise and Fall of the Working Class, 1910-2010. John Murray Press; 2014

[171] Todd S. Snakes and Ladders: The Great British Social Mobility Myth. Random House; 2021

[172] Knight R. Britain against Napoleon: The Organization of Victory, 1793-1815. Penguin Books Limited; 2013

[173] Grainger I et al. The Royal Navy Victualling Yard, East Smithfield. London: Museum of London Archaeology; 2010

[174] Cederström C, Spicer A. The Wellness Syndrome. John Wiley & Sons; 2015

[175] Johnston J, Baumann S. Foodies. Taylor & Francis; 2015

[176] Poole S. You Aren't What you Eat: Fed up with Gastroculture. Aurum Press; 2012

[177] Colas A. Food, Politics, and Society: Social Theory and the Modern Food System. University of California Press; 2018

[178] Diner HR. Hungering for America. Harvard University Press; 2009

[179] McCloskey DN. Bourgeois Equality. University of Chicago Press; 2021

[180] Rauch J. The Constitution of Knowledge: A Defense of Truth. Brookings Institution Press; 2021

[181] Shapiro BJ. A Culture of Fact: England, 1550-1720. Cornell University Press; 2000

[182] Sitwell W. The Restaurant: A History of Eating out. UK: Simon & Schuster; 2020

[183] Stjernø S. Solidarity in Europe: The History of an Idea. Cambridge University Press; 2009

[184] Nelson PJ. Global Development and Human Rights: The Sustainable Development Goals and beyond. University of Toronto Press, Scholarly Publishing Division; 2021

[185] Nozick R. Anarchy, State, and Utopia. New York: Basic Books; 1974

[186] Holt JC. Robin Hood. Thames & Hudson; 2011

[187] Banerjee AV, Duflo E. Good Economics for Hard Times. Juggernaut Books; 2019

[188] Green T. The Covid Consensus: The New Politics of Global Inequality. Hurst Publishers; 2021

[189] Rosin C et al. Food Systems Failure: The Global Food Crisis and the Future of Agriculture. Taylor & Francis; 2013

[190] Allen P. Together at the Table: Sustainability and Sustenance in the American Agrifood System. Penn State University Press; 2015

[191] Stuckler D, Siegel K. Sick Societies: Responding to the Global Challenge of Chronic Disease. Oxford: OUP; 2011

Chapter 4

Pellagra: Down Not Out If Down and Out (and South) – Part 2

Adrian C. Williams, Christina Wood and Lisa J. Hill

Abstract

North-South variation in the supply of meat has always been present. Sharing of meat was the rule but in the multi-centric Neolithic revolution when domestication of animals and plants co-evolved class differences became pronounced-aristocrats and inferior proletariats and "lesser breeds and lower orders" started to form. The distribution of natural domesticates was uneven with the near-east and a temperate band across Europe well off compared with Africa and the Americas. The Columbian exchange changed this as meat became abundant in the New World who then exported to Europe. Wars, expropriations and genocides were over the meat supply and acquiring pastureland or water. Colonial plantation profits paid for meat imports from "settler colonies" indigenous or poor peoples on low meat pro-pellagrous diets were considered inferior whatever their colour and had poorer health and life expectancy. Attempts to correct hunger in the resultant ramshackle "Third world" concentrated on calories fuelling population booms and busts and delaying demographic, epidemiological and economic transitions. High meat variances are narrowing in China and Asia but need help elsewhere in the South. Dangers of not developing with a safe and sufficient meat supply include the emergence of zoonoses and mass migration. Reparations, rehabilitation and rejuvenation should concentrate on reconstituting a meat commons giving us a shot at redemption and survival.

Keywords: NAD, meat transitions, demographic transitions, epidemiological transitions, TB, poverty traps, metabolic syndromes, genocide

1. Introduction

Almost from time immemorial luminaries such as Cato, Cicero, de Quesney, Turbot, and Smith up until the present day have debated whether agriculture or industry or new energy sources or free trade created wealth and progress. Concepts on the "Biopower and Biopolitical" uses of diet can be dated back to Aristotle and Plato and elaborated on by Foucault and followers. Omnivorous diets for all as a prerequisite tailwind for firing on all body and brain cylinders neverthelessis rarely heralded (even by neurologists or psychiatrists) and even then the links between the "Grand Transitions" involving demographics, economics and epidemiology and the "Mega-threats" of pandemics and climate change are rarely made at a diet- metabolic level [1–7].

In Part 1 we discussed the consequences of being "down and out" or on "skid row" from meat and milk and therefore nicotinamide deprivation and mitochondrial energy within countries since the neolithic agricultural revolution and the domestication of crops and animals—here we shall discuss meat privilege on a broader canvas across time and space and the implications for human and planetary health. All agree that it's "inequality that kills" but how does this actually work? Sub-clinical pellagra stunts and slows individuals and fails to develop prosperity and a bourgeoisie creating bradykinetic macroeconomics and poverty from the pathology of ill health [8–10]. First, however, lets recap on some basic building blocks of civilisations starting with water but then majoring on meat and nicotinamide.

Splitting water by photosynthesis supplies oxygen and combined with CO_2 carbohydrates (CHO) and subsequently NADH to mitochondrial oxidative phosphorylation to produce energy as ATP. Water and water vapour, as a green-house gas, with a supply of photons makes the world habitable. Riparian "river cultures" such as by the Euphrates, Tigris, Nile, Indus and Yellow River with their floodplains and alluvial soils comprised the majority of early civilisations. "Hydraulic" empires, such as Rome, China or the desert kingdoms can be compared with those, some in Europe, with easier rainfall patterns or those with monsoon seasons, for their necessary adaptations for crops and the prodigious amounts of water needed to raise cattle and for their responses to climate changes-often inadequate causing collapses ("the Curse of Akkad"). Water is important for hydropower and trade routes (and Sea power states such as Athens, Carthage, Venice, Netherlands or Britain) and affects the politics of dams and canals and landscapes, such as terracing, and social structures, sanitation programmes, and wars when mutual interest fails [11–17]. A Gordian knot and nexus exists between water, air and diet and (for the last century) oil.

The role of diet, particularly grain in the rise, often with " ecological windfalls" or "ecological imperialism" and fall of empires or other collapses, often with "ecocides" from exploitation of the earth's resources (from Sumeria to Egypt to the Mayan and Roman empires and Easter Island) has been discussed: some enlarge on a role for meat and steppe nomads and, here we emphasise the importance of a sustainable balance between cereals and meat and, innovatively, discuss a metabolic mechanism suggested by the narrative of pellagra and NAD deficiency for both class and country effects [18–26]. Although air is free, unlike meat, but like water often not clean, asphyxiation has been a metaphor (and not always a metaphor thinking of lynching, Covid or George Floyd) for how to subjugate people—and their collective struggle for resources or to breathe as Franz Fanon (1959) said it is *"oxygen that invents a new humanity"*—but NAD deficiency (considered a "pseudo-hypoxia") is a more plausible mechanism [27–29].

2. Hypothesis: Short Story

Geographical gradients of meat intake have always existed but in the last few centuries they diverged and more recently have converged except in parts of the South where some billion people live on below $1.90 a day—the World Bank's definition of extreme poverty and so become enforced and often monophagic vegetarians with effects on health and longevity (**Figure 1**). Initially a more plant-based diet in the Neolithic may have increased fertility and a population growth that allowed for division of labour and high collective intelligence as the " Human Swarm" even as health and height deteriorated; but this may now be a developmental over-run producing "underclasses/countries" [30, 31]. Here we attempt to describe how and why all this happened, hoping to illuminate a universal from the specific of pellagra, and that high meat intake is both

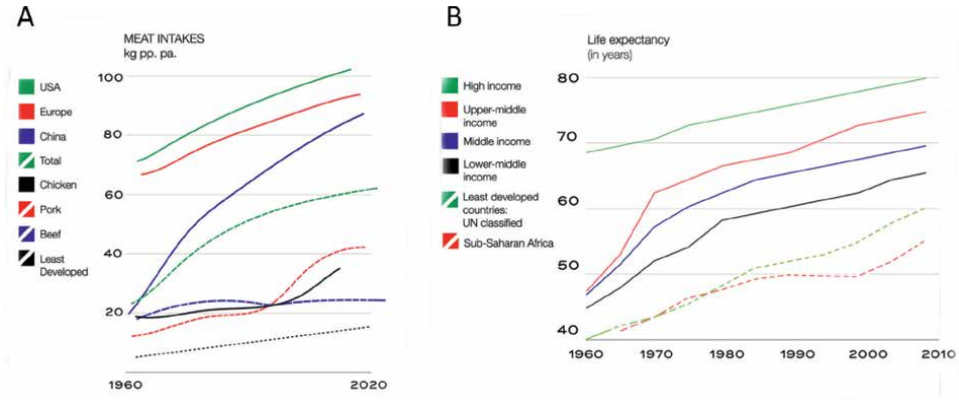

Figure 1.
(A) Meat by type & intakes by continent 1960-now. China shows a remarkable increase as have other "Asian Tigers". Europe and the USA long term leaders on intake are beginning to drop. India is in the middle on intake (better in the south), but Sub-Saharan and some other African countries are stalling as are their epidemiological and demographic transitions. Beef and ruminant intake worldwide have stabilised with pork (omnivorous scavengers) and industrially farmed chicken showing remarkable increases. (B) International Life expectancy by income. Remarkable increases shown here from 1960 but starting much earlier before medicine would have had much impact implying that public health measures such as clean water and a better diet were more important. Nicotinamide metabolism is important to most models of longevity in all species suggesting that high meat/milk intake could be causative.

the cause and the effect of economic progress (generally considered an unresolved "wicked problem"). Countries and continents have different epidemiological and demographic trajectories that may link to timing of safe meat transitions. If inequality is to be overcome its root cause and the source of biopower relationships, whether by class or by nation, needs to be understood and may lie with quality diets and quality populations. Sorting this may be the moral and safe way forward—and intersects with solutions for climate change and reducing civil unrest and pandemics [32–39].

3. More background and current relevance

Plows and petroleum have largely fuelled the food systems but despite successes has not served the poor or the planet that well [40–42] (**Figures 2** and **3**). Food insecurity underlies widespread micro- and macro-nutrient malnutrition, emigration and pandemics in this "nomadic" and "pandemic era" spread by commerce from zoonotic microbial cauldrons [43–46]. Such mega-challenges to feed with "sustainable intensification" increasing populations in the South rarely discuss a relationship between diet and fertility and the interactions with climate change [47–49]. There is a need for a mega-Marshall plan that as Bruntland's classic commission of 1987 said "*meets the needs of the present poor without compromising the needs of future generations*", that may include novel foods and fermented or cultured meat or exceeding "planetary boundaries" will cause a "ecological shock" with loss of biodiversity and further climate change [50–53]. Poor meat food-chains facilitate "bushcraft" and species-jumping zoonoses and decreases resistance to infectious pathology. Wars, including civil wars, and land enclosures and confiscations and land-grabs can be related to "lebenstraum" and the appropriation of well-watered and fertilised pastureland or the oil to support high intensity farming and a better diet-traditionally at others, usually in the global south's, expense. Geopolitical tensions and the follies of war include "slash and burn" tactics, unplanted or unharvested

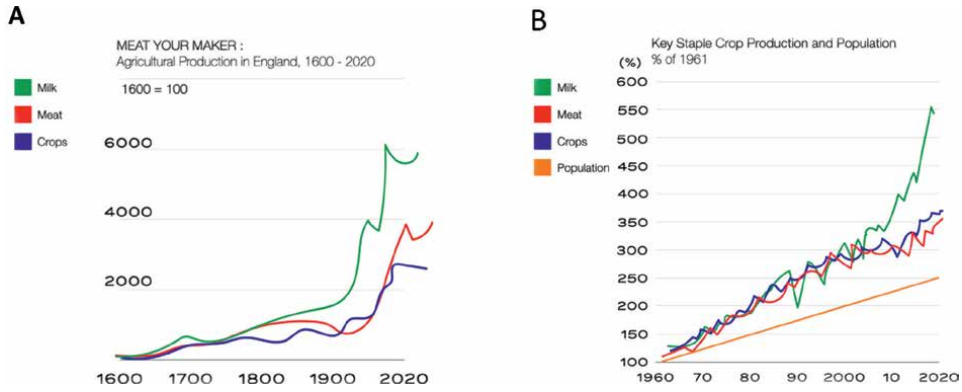

Figure 2.
(A) Meat production England 1600–2020. Meat production increased but barely kept up with population growth. Imports paid for by the profits from the cotton and sugar trade caused the real improvements helped by the repeal of the corn laws and better transportation and refrigeration allowing imports from the "settler" colonies and states. (B) Crop production yields have increased significantly over the last 50 years. Some GM crops contain vitamin A such as golden rice and recently vitamin D in tomatoes otherwise sourced from animal produce (or sunlight). Breads and cereals are often supplemented with vitamins, including nicotinamide, but less often in poor countries and are expensive. Oatmilk is now popular but does not contain as much nicotinamide-riboside as dairy milk.

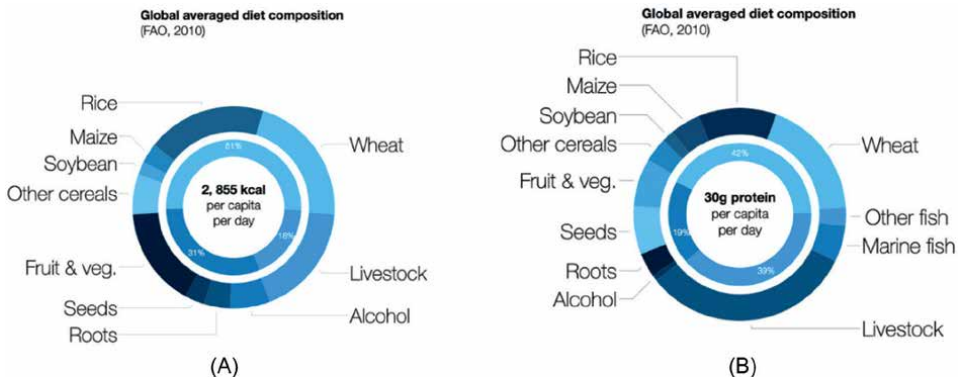

Figure 3.
(A) Global averaged diet composition. However, it is the extremes not the averages that are the problem with the danger of undiagnosed and untreated "pellagra sine pellagra" on the one hand and a possible hypervitaminosis B3 on the other. Switching from one extreme to the other within lifetimes can risk metabolic syndromes. Switching over generations to more meat and milk can lead to demographic, economic and epidemiological transitions. (B) Global sources of protein. All sources are not equal as far as Tryptophan is concerned as an alternative precursor to NAD where animal sources are better, as they are for nicotinamide. Other sources exist such as insects and larval forms—mealworms—that may play an increasing role in the future as may algae and macroalgae seaweeds such as kelps—and artificial laboratory grown meats from stem-cells.

crops, pillaging, stock-piling, blocked ports and sea channels, and sieges and often genocidal "hunger-plans" that along with price rises or tariff arrangements create a vicious cycle and more deprivation, again worst felt by the poor and in the South.

Existential threats such as climate change are both caused by and effect food systems (an initial boost to plant growth by high CO_2 is rapidly cancelled out by drought, floods and fires and locusts). Shorter-lived but potent methane as a greenhouse gas ($80xCO_2$) is largely derived from microbial synthesis in expanding wetlands and thawing permafrost "thermocrast" lakes as well as ruminants (and has increased markedly from 2007 in a vicious cycle that could form a "methane bomb"). Alongside

the effect on CO_2 and nitrous oxide emissions this raises major concerns on meat intake and linked agricultural methods that increase emissions, such as transportation and excess use of fertilisers or tillage that destroy carbon sinks on land and acidified seas. Well maintained pastureland (of no use for crops) and perennial and tree silvacultures can however, like the sea, be massive carbon sinks [54].

High meat intake in the affluent west needs to drop but we will argue that for those on a low income, usually in the south in Asia or Africa it needs to increase (or its synthetic cell-based or safer non-ruminant/insect or plant/fungi and algae substitutes or at least with fortification of vitamins) to allow healthy demographic and epidemiological transitions. "Farmerian" structural violence has been attributed to poor food distribution networks and unfair property laws and metabolic and behavioural dysfunction in ghettoes as well as the incidence of infectious disease and early death [55–57]. A thought experiment imagining a "Dog-land" within the USA showed dogs to be at a high average global meat intake for humans [58].

High meat intake is not so much the problem, although the Delphic ΜΗΔΕΝ ΑΤΑΝ (Nothing in Excess) applies, as high global variances and lowering these drastically is the solution as a wholesale move to a plant-based diet often with ultra-processed high calorific but cheap foods is problematic [59–63]. The Lancet EAT commission suggested as much but was criticised for not explaining how the under-developed world was going to afford to eat a more varied vegetarian diet or for not fully recognising the need for some animal-sourced produce [64–66]. Despite living in a "Superabundant" world with a "breakfast bounty" whereby the price of meat and eggs has fallen for blue-collar workers by over 90% in real terms as measured by how long it takes to work to pay for them many of the poor within countries have not benefited and many countries in the south are no richer than the UK was in 1800 with per capita GDP still not exceeding 10$ a day [67, 68]. English breakfasts indeed became popular largely at the time when the international meat trade really took off with chilled American beef and deep frozen Argentinian and Australasian meat carried by refrigerated ships (such as the Circassia) in the 1880s such that by the eve of WW1 40% of the meat consumed by Britons came from abroad, a trade that shaped the world [69]. But let us start again toward the beginning as this all relates to how the high meat variances and quality of diets between nations as well as classes developed during our history, that were not part of our initial evolutionary trajectory. Not addressing this may de-rail our " slouch toward Utopia" instead directing us toward apocalyptic dystopias, if we do not develop climate smart food supplies and an "ethical omnivory" sensitive to animal rights and refrain from "milking" the poor [70–78].

4. Continental NAD divides

At the time of the Neolithic agricultural revolution all was not equal when it came to available animal domesticates and therefore the meat and milk supply even if sharing meat in our social leap was the early norm hierarchy, exploitations, enslavement and inequality rapidly developed [79, 80]. The middle east and then Europe and the Asian steppes were well off for amenable hoofed ruminants such as goats, sheep and cattle [24]. Africa the "cradle of mankind" having been a meat cornucopia with abundant wild herbivores in the savanna had few natural domesticates and more than their fair share of animal diseases (such as trypanosomiasis (sleeping sickness) in the wide tsetse belt and in the nineteenth century rinderpest introduced from Europe) and competing large carnivores. Nomads and pastoralists and relationships with other animals were important components of our history and culture [81, 82].

Cattle, Chattels and Capital all derive from the same etymology and in practices such as bride-wealth. More damaging was cattle rustling and the concept of "terra nullius" that allows for pastureland not obviously farmed by indigenous people to be appropriated and territorial gains through war or land-grabs and were all meat related as was cannibalism [83]. The New world after the original animal population was decimated by hunters had few natural domesticates other than turkeys and guinea pigs; China had foraging pigs, chickens and many ducks so was reasonably well supplied at times, but still largely cereal based and famine prone [84, 85].

5. Columbian exchange of NAD suppliers and attitudes to other peoples

The Columbian exchange changed the New World dramatically by developing settler states that improved their own and then others supply of meat (**Figure 4**). Cattle, sheep, goats and horses rapidly bred in this new ecology and on ranches [86–88]. This was usually to the detriment of indigenous peoples and the slaves, as illustrated by the manmade deplorable "Trail of Tears" and "Middle Passage", even although Africans had helped by smuggling (Black) rice across the Atlantic and contributed their considerable agricultural and even medicinal skills [89–93]. Some appreciation that native Americans were not, after all, monsters or savages having their own civilisations was there as a philosophy of "All Mankind is One" was supported by the Spanish monk Las Casas and even had royal support but did not unfortunately translate for long. As Montesquieu (1748) said (sarcastically) in his Spirit of the Laws

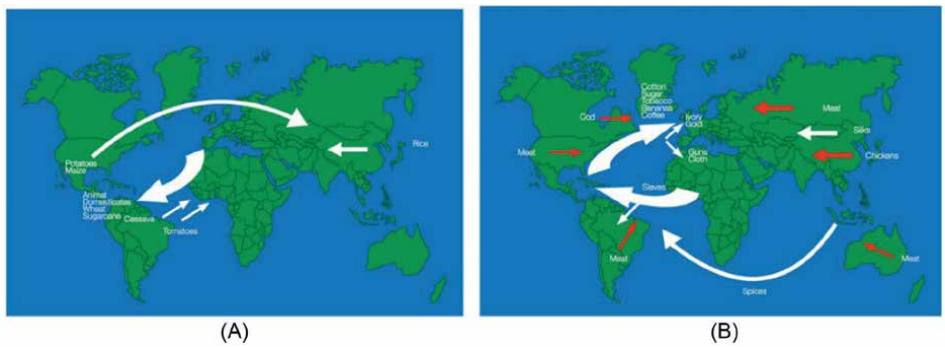

Figure 4.
(A) Columbian exchange. Animal Domesticates, such as sheep and cattle, were introduced to the New World that otherwise had very few such as turkeys and guinea pigs. Earlier megafauna had, as elsewhere, been killed off by hunters and climate change, and later bison were killed by (white)hunters to the detriment of indigenous tribes. Imported ungulates rapidly expanded swarming in the lush new pastures "ghost acres" tripling the pastureland for England and other European powers further aided by cowboys, barbed wire and ranching with the import of new breeds. Later feeds replaced grassland and the "livestock complex" was born. Maize and potatoes went East fuelling population booms and busts. (B) The slave trade by supporting sugar, tobacco and cotton indirectly supported the meat trade as the profits held by Europe paid for the meat imports as had silver and gold. Settler colonies exported meat, now frozen and easily transported, and usually had enough for their own benefit. Others with or without plantations had their farming systems damaged and their peasants taxed (salt and tea taxes provoked rebellions in India and America). Diets deteriorated (such as the Bengal famines). Indigenous peoples contributed much on farming technique and introduced crops such as rice in the West and medicinal "secret cures of slaves" (such as quinine) and commercial plants (such as rubber) of great value that like the silver, gold and (blood)diamonds were basically stolen as "primitive accumulation" to fund capitalist ventures and more profit for the centre. In the Irish famine and even quite recently examples of exporting meat whilst the supply to the local population declined markedly include Guatemala and Costa Rica in the 1960s [26].

"having extirpated the natives Europeans had no choice but to make slaves of Africans besides which sugar would be too dear" may provide the explanation along with other expropriations of useful materials and free or cheap labour from indentured servants.

Previously many racial differences had been attributed to "environmentalism" and climate or diet but the mood changed as Europeans, except when they inter-married (miscegenation may have even saved us from a speciation event) did not change their phenotype and so genetics became a more favoured explanation with whites genes being superior. The underclass and "cultures of poverty" were invented (with planters pitting working class whites and "hillbillies" against people of colour)—a self-fulfilling prophesy when the indigenous natural diets were destroyed in favour of producing cereals and sugar/molasses, and a pellagrogenic diet allowing for "class cluelessness and callousness" [94, 95]. Furthermore "divide and rule" policies by elites and "dog whistle" racial politics were encouraged on the plantations and thereafter stalled many worker class rebellions. More subtly on Haiti in 2008 food price increases were bailed out with strings attached that are damaging longer term for the nutritionally weakened poor—(even though they were the base of agriculture and capitalism in general)— all old and new methods that create superficial frictions that include pitching disadvantaged racial and tribal groups against each other [96–99]. This is now known as the "Southern Strategy" though moved North with the mass great migrations of African Americans after the Civil War (Underground Railroad) and is a "Pluto Populism" and "Racecraft" and often evangelical and nationalistic policy with vote gerrymandering and other suppressions much copied (including ironically by the party of Abraham Lincoln) to this day.

Some original abolitionists retaliated with criticism of eating slave-foods (such as sugar), and other forms of plant robbery such as rubber and cinchona (quinine anti-malarial) sentiments that continue with fair trade movements (but the connection with the meat trade was not realised) [100–103]. Gold and silver and later profits from the slave-based sugar and cotton industry paid for massive levels of meat and fish imports to Europe particularly after the invention of steam engines for ships and the railways, and refrigeration. Colonised settler states after the Americas included Australasia exporting meat; other colonies contributed indirectly such as India and Africa (inspired by Cecil Rhodes) were taxed or used to boost income from mining and "cash mono-crops" using cheap labour advantaging the European core at the expense of the "periphery." Outbreaks of pellagra, in the poor southern "cotton states" of the USA and later in "banana republics" were the tip of a malnutrition iceberg. Advances in farming beyond "hoe-culture" were discouraged as was the manufacture of goods, even traditional cotton clothing—all helped to create a now dependant "Third World" [104, 105].

Cash crops such as from peanuts, cacoa or tea took precedence over staples such as rice or yams often in the name of comparative advantage (that then had to be imported with no control over price) and destroyed mixed farming and the meat supply for all except surviving pastoralists. Ironically the Masai were even admired by their colonial masters for their height and health. As Daniel Defoe author and pamphleteer, said at the time *"No African trade, no negroes, no sugar, indicoes, cotton; no islands, no continent no (meat) trade"* and change or even insight has come slowly. This all allowed the "great subsistence crisis" in the north-western world triggered by war, volcanic eruption (Tambora 1815) and the "year without summer" and effects from El Nino to be the last crisis in the North but came at the expense of the South [106–108]. Modern equivalent practices include the export of Palm Oil and soybean (used as animal fodder in industrial farms) causing much local ecological damage—swaths of the Brazilian Cerrado region turned in to cropland and rainforests cleared

for grazing cattle contributing to both local and global climate change and destroying much biodiversity in order to supply the west with more meat or biofuels [109, 110].

6. The West then the rest: meat as propellant. More circumstantial evidence

Ink (and blood) has been spilled over the issue of the reason for the rise of the west and we have added meat centrality to previous arguments relevant to all empire building and as advice to their builders [111–122]. Poor cooperation between agricultural empires, such as the Roman and the Ming empires (who decried milk and its products in an anti-Mongol gesture except in Zhangua province that fared better), and their "barbarian" pastoralist neighbours has been implicated in their falls (perhaps answering Needham's puzzle in the case of China as to why they were overtaken) [123, 124]. Similar issues have emerged for the Ottoman and Mughal empires with lack of animal fodder or exhausted irrigation systems and ecocides leading to "high equilibrium traps and inadvertent selection for quantity rather than quality population growth in low meat economies [125–127].

Julius Caesar noted of British tribes in 54BC "lacte et carne vivant" but most observers date Britain's success to the response to the 14th C Black Death that itself followed on from a great famine (and is thought to have originated in the East and spread along the Silk Road by Mongols as a zoonosis involving the fur trade in marmots and grain supplies eaten by both man and rats with their fleas all in close proximity with gruesome stories of early biological warfare catapulting the dead into a city (Caffa) under siege [128]). Here, the argument goes, the high death rate led to a shortage of peasants and yeomen so, despite early aristocratic resistance, wages rose and agrarian fields turned to pastureland innovations such as turnips for winter fodder avoiding autumnal culls and spring seasonal hardship (when pellagra often emerged). Meat intake increased markedly for several centuries—all reflected in increasing height and perhaps, IQ [129–134]. The need for labour saving devices became the "mother of inventions" for agriculture then industry. Studies have used estimates of affordable "baskets" at various times with international variations and fluctuations in the incidence of the more pellagra-genic basket support these claims [135–137] (**Figure 5**).

Elsewhere populations exploded on more cereal (and now maize) based diets and agricultural reforms lagged with many other obstacles in the East and South that involved ecological and unresolved water and irrigation issues that were not so difficult in rainy Europe [138]. The rise of the northern white protestants on a high dairy diet in the reformation compares with the poorer but more fertile Catholics which may have been another divergence in the making [139, 140]. In England population grew slowly for centuries but then populations boomed, at the time of Malthus, as there were dietary setbacks so by the 1800s many of the poor were enforced vegetarians culminating in the "hungry forties" before another meat transition took place.

Reforms of corn laws and deflation of food prices along with cotton and other profits allowing importation of meat on a grand scale meant that for once the poorest gained and could afford a better diet. This allowed for an expansion of the middle classes and the rise of "hawkers" of street meat and "fishwives", taverns and restaurants helped. The Chartist movement and the rise of trade's unions avoided the concurrent hunger inspired revolutions in Europe at least until the 1930's hunger

	Basket	2-3000 calories
	Respectable: quantity pp, per year	Bare bones subsistence: pp, per year: Pellagrongenic
Beans / Peas	34 kg	20 kg
Beer	182 litres	
Bread	182 kg	
Oatmeal / grain		170 kg
Meat	26 kg	5 kg
Butter	5.2 kg	3 kg
Cheese	5.2 kg	
Eggs	5.2 kg	
Fuel	5.0 MDBT	2.0 MDBT
Linen / Cotton	5 metres	3 metres

Figure 5.
Subsistence baskets. Food baskets have been estimated for many countries over many centuries. Such baskets can be tracked—In England they deteriorated before the Black Death but then improved as income (after opposition) increased for centuries. The birth of the lead in agriculture and the industrial revolution has been attributed to this high meat intake and enough money for consumers to spend on luxuries developing commerce (once sumptuary laws were abandoned). Poor harvests and wars had led to economic failures widespread vegetarianism culminating in the "hungry" 1840s. Many then escaped from bare bones pellagrogenic diets and continued the lead in Europe but then were overtaken by the USA with China catching up more recently. These dietary divergences and convergences can be linked to the rise and fall of empires and civilisations.

marches. In England (and later America) and in Amsterdam and Antwerp's "glory years" butchers and their guilds prospered in the *luilrkkerland* (delicious-land) with stories depicting houses made of pancakes and bacon with pre-roasted pigs walking—butchers could not keep up with the nouveaux riche [141, 142].

Many observers have touched upon diet being important for talent, "industriousness" and progress: "Rosbifs" and "Roast Beef of Old England" were immortalised in paintings and song and Shakespeare's plays, such as Henry Vth [143]. Other dietary explanations have included a spice or "sugar rush" (although the dangers of sugar were pointed out by Thomas Willis around 1670 as diabetes "mellitus"). Importation of tea (that became part of the British identity despite no tea plantations in the UK) and coffee displaced beer, a safer source of liquid than water at the time, and distilled spirit addiction "drunk for a penny, dead drunk for tuppence" even feeding infants

as depicted by Hogarth's Gin Alley, as preferable stimulants rather than depressants (whilst at the same time driving the opium trade depressing China may all have led to some international advantage). But back to meat important trades spices (curry becoming emblematic of the UK) relates to the preservation and taste of meat, or by camouflaging the added salt, along with other forms of charcuterie [144–148].

7. Nicotinamide not sugar rush: intellectual "savants and tinkerers"

We propose a meat and nicotinamide "rush" as a more likely explanation for moving the dial with non-dietary correlations such as coal and steam enabling improvements in the supply as would profits from sugar and cotton plantations [116, 149–152] (**Figure 6**). Long rotating global waves of prosperity allowing more (patentable) innovation noted by Kondratieff may have a basis in agricultural success and lower prices or higher wages and could relate to meat transitions that in turn are related to

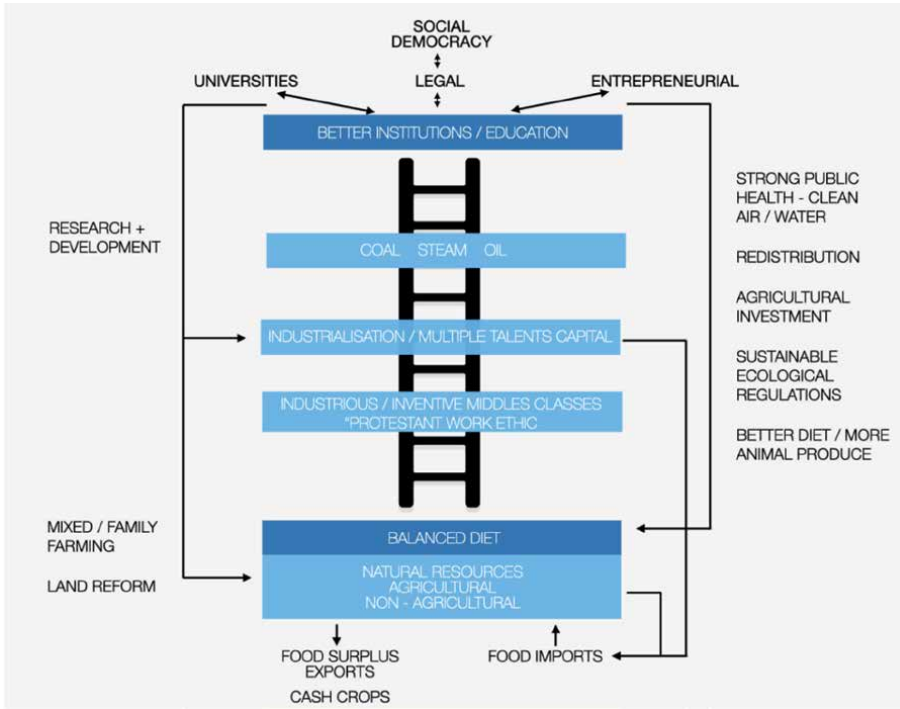

Figure 6.
Ladder of development. Better institutions and governance are the conventional wisdom and thought, after Weber, to be the major drivers of progress and may prove proximate causes. However, it is our contention that this develops only after a critical mass of the population have high human capital from an adequate and balanced diet. This became a positive feed-back loop in the nineteenth C helped by the rise of restaurants (and chefs no longer needed by the (French)aristocracy) further improving diet that gives the illusion that better diet is a consequence, but we would claim reverse causation. History does suggest this was learnt the hard way obscured with friction and peasant rebellions (such as Jack Kade's in 1450 over enclosures and privatisation of land usually for wool rather than meat that then became too expensive for the poor unless they worked)—and indeed has still not been learnt. Weber's example of protestants in northern Europe had high meat and dairy/butter intake and were lactose tolerant compared with southern Europe with less mixed farming and olive oil rather than butter that has a higher nicotinamide content. Southern Europe was the site of the first recorded pellagra outbreaks, by Casal, in the 18th century. Perhaps subconscious cultural lessons were learnt as Italy now has the most democratic of diets and this "Mediterranean" diet leads to relatively good health outcomes [153].

local agricultural and import opportunities all favouring good dinners for some; but let us look again at the example of nineteenth century Britain [153, 154].

8. Tectonic plates: meat, epidemiological and demographic transitions meet early in the UK

Agriculture evolved in Europe with fallows enriched by grasses and legumes "Ley farming" improving the soil and nitrogen content, and the rise and fall of tillage improving the soil microbiome, with alternation of crops and livestock with integrated systems demonstrated by Jethro Tull (1751) and "Turnip" Townsend for winter forage [155, 156]. Stock breeding and "High farming" were introduced by pioneers such as Robert Bakewell and John Webster as the UK became the world's "Stud Farm" and proponent of feedlots. England compared with many other countries including France had a high ratio of pasture to arable land supporting high meat intakes and horsepower along with ample manure for crops and was an important pre-requisite for the industrial revolution [157]. The fishing industry particularly for (dried and salted) herring, cod and whale took off supplying much meat as the "Northern Hunt Trades" and fourteenth C carp fish farming, helped by being allowed to eat fish on the many religious fasting/meat-free days, but soon was in trouble from over-fishing and later farms such as those for shrimp damaged the ecology of mangrove swamps as important carbon sinks even though done properly fish-farms may re-emerge as important sources of nicotinamide [158–160].

The astonishing rise of the chicken and egg market began to contribute [161]. However, with population increases numbers could not keep pace with demand. The well documented [60, 162–164] meat transition occurred early in the UK (1850–1900) with intake almost doubling for the general population although the idea that people and slaves need any more than subsistence died hard "scarcity promotes industry and less drunkenness" being a common view as was starvation as being a natural Malthusian population correction (as expressed by government in the Irish and Bengal famines). Better wages later became popularised by Henry Ford, as did conveyor belt manufacturing after observing the meat packing industry and is the basis of consumer society and luxury markets with all relating to Engel's curves.

The pattern of disease changed dramatically with far less infections and early deaths most notably for TB [165–169]. Sanitation or at least better housing and fresh air and clean water have been considered important in this pre-antibiotic era, but evidence is surprisingly unsupportive for TB perhaps because rents rose squeezing family budgets. There are many other correlations, such as increased sugar intake, but the only one, to our eyes, with a convincing biological explanation is more meat as meat is a source of nicotinamide. Nicotinamide has antibiotic activity against TB (and other organisms including Mycobacterium leprae that also "disappeared" in the western world in the earlier sixteenth century meat transition) and many TB antibiotics developed are nicotinamide analogues. Furthermore, TB excretes nicotinamide (used as a test for pathogenic strains) suggesting that it may be a nutritional symbiont that turns dysbiotic if relied upon too heavily [170]. As TB disappeared diseases of modernity particularly allergic and auto-immune diseases appeared [168, 171].

Biological explanations are to hand as the Tryptophan-NAD intrinsic pathway would not be activated on a NAD-precursor rich diet and is well known to be the immune tolerance pathway so over-reaction to otherwise harmless antigens might be expected (that might include the foetus); and absence of "Old Friends" could lead to loss of immune education again leading to immune over-reactions [171]. Relative

infertility indeed rose once death rates had fallen as part of the demographic transitions that causes temporary population explosions and then stability—and then population declines as fertility falls below that needed for replacement. Such demographic patterns happen with modernity but the element of modernity responsible has never been identified (many happened before effective birth control was available or education improved.) Rather than talking of "African exceptionalism", for instance, diet should be reconsidered as there is a longer history of meat being held responsible for low fertility and cereal dependency or poor diet short of starvation for high fertility amongst the proletariat causing much alarm about "replacement" by "inferior" peoples, but little action. Higher quality of population rather than higher numbers should be the aim ("K" v. "r" selection) and that can be done starting with better diet [172].

9. Nineteenth-twentieth century meat exchanges: rural and third worlds

Observers ,such as de Sant Pierre (1769) noted that "*coffee and sugar were not essential to Europe but brought wretchedness and misery upon America and Africa*" including becoming reliant on local "bushmeat" eating their own, now rare, wild animals from elephants to monkeys and losing some indigenous cereals, that often have lower calories and more micronutrients let alone being a source of cultural and biodiversity that may become important with climate change. During the later colonial period meat and tropical goods flowed from the periphery in to the European core aided by refrigeration and canning and "Free Trade" using cotton and sugar profits to pay for the imports and essentially living well at others expense creating "Victorian Holocausts" in the tropics often exacerbated or even capitalising on climate change [106, 173–177] (**Figure 7**). Current telling examples can be seen in Madagascar currently and occasionally in the centre as in the 1930s Dust Bowl on the American prairies that are worrying signs for a future of climate change in coastal and natural deserts, even California [178].

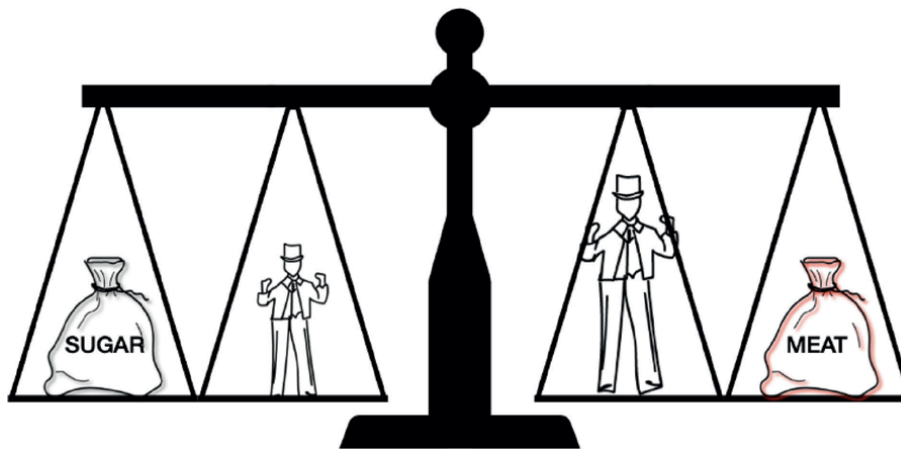

Figure 7.
Sugar in Europe and the settler colonies was balanced by higher meat intake. This was not true for poor people particularly those in the Caribbean and "cotton" (and pellagra) southern states of the USA fed with high quantities of molasses (and rum) and little meat. This was a recipe for pellagra and poor nutrition throughout life and transgenerational epigenetic effects including metabolic syndromes. Reparations might be well directed to preventing this happening in the future. The same argument is true for poor peoples in rich economies where cheap calories with 2 for 1 deals and junk food do not help people ascend Engel's curves.

Within the core there were extraordinary concentrations of cattle and meat flowing from rural areas to magnets large towns and cities that majored in animal husbandry and use of pigs as well as horses, hens and cows contributing to "metabolic rifts". As Jenner rhymed (1772) *"Fat droves of sheep and oxen, consigned from Lincoln fens, that swearing drovers beat to Smithfield pens."* This need spread and the Scottish clearances and the "colonisation" of Ireland caused much hardship and emigration in order to supply meat centrally at the expense of the "crofters". Smithfield market is an exemplar in its Georgian day of a dominant 800-year-old industry of live animals "meat on the hoof" driven into the city for food and transport (and dung not easily re-cycled) dwarfing other better-known industries, such as sugar and coffee, and helped by advances in stockbreeding for meat and dairy. Abattoirs then moved out of town and out of view of the consumers with new tensions for animal rights by making the "cognitive dissonance" over killing animals easier.

10. Pellagra: plus Kwashiorkor

Pellagra epidemics re-emerged in the periphery, namely South Africa, where it had been unknown until 1914, as did poverty, racism and disease—chiefly infectious or nutritional such as Kwashiorkor, well- illustrated by Oxfam, and felt by many to be infantile pellagra particularly after the protein hypothesis was discarded [179–182]. Post WW2 local initiatives and cereal exports and some meat from the developed world supported some feed-lot cattle in the underdeveloped world allowing for their own meat transitions that drove demographic and epidemiological transitions [105, 183–188]. However, this was highly heterogeneous (often aid was linked with political and anti-communist motives or a way of exporting subsidised surpluses that did nothing for local

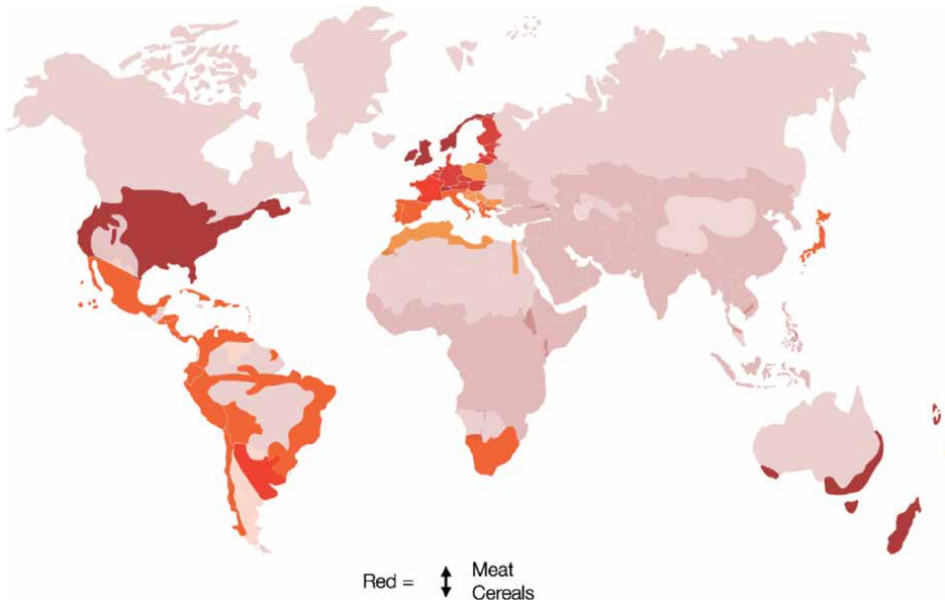

Figure 8.
Countries in shades of red whose cereal consumption fell as meat consumption rose correlate with high or very high (darker red) economic activity. This is Engel's/Bennett's law at an international level. Poor countries are trapped by high food and energy prices where they also make up a larger share of the national inflation basket.

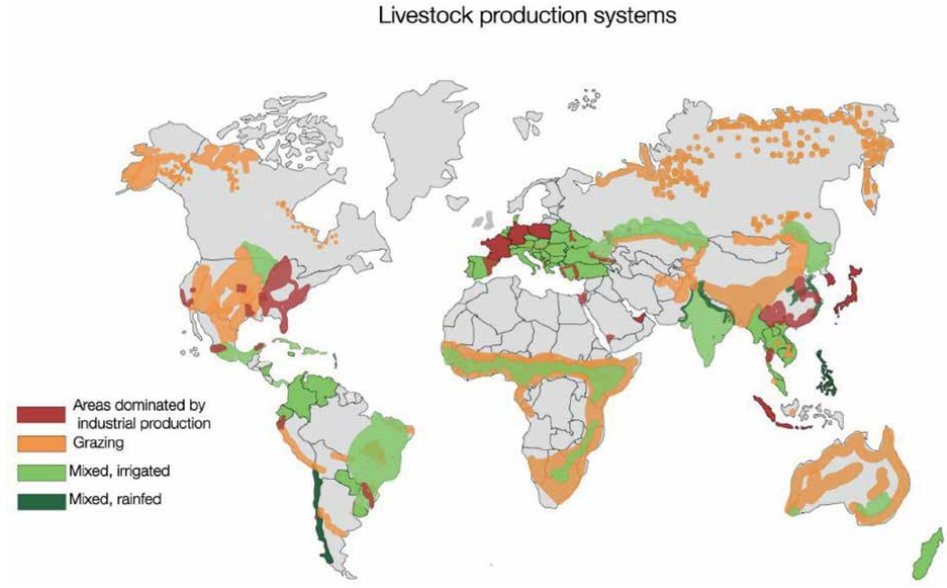

Figure 9.
Meat and wheat international trades are high as is maize and soyabean with much used to support meat industrialisation (and biofuels). Sources and industrialisation of meat is geographically very heterogeneous. More local production with mixed farming or pastoralism would help reduce variances across the globe and reduce the need for artificial fertilisers.

farmers) and more commonly being cereal based may have given rise to population explosions as much as alleviating hunger. Transitions are still incomplete in southern Asia and most of Africa where poverty, stunting and chronic infectious disease with population explosions remain common and, we suspect subclinical pellagra is common.

Such countries may be the victims of excessive cerealization then calorificization with "empty calories" and "junk foods" and other temptations by-passing the normal function of Engel's law [189, 190]. The so called "resource curse" may be when states get lucky with natural underground resources whether oil or minerals, or cash crops they do not spend it on improving diet where it is poor—by chance or design Europe did not do that with their wool and cotton trades and may have narrowly escaped this trap—probably "a damm close run thing" as Wellington said of Waterloo (**Figures 8** and **9**).

11. Poverty pathogenesis converges on NAD mechanisms

Stephen J Gould's comment channels as "*I am, somehow, less interested in the weight and convolutions of Einstein's brain than in the near certainty that people of equal talent have lived and died in cotton fields and sweat shops*"—much talent and brain power is indeed being wasted for lack of NAD-as William Blake said (in 1793) "Reason is the bound circumference of Energy". The poor (and particularly women as men commonly got the "Lion's share" of meat) have a NAD deficient headwind to contend with and an NAD-related degenerative pathology and functional neuropsychiatric effects ("feebleminded" and ripe at times for enforced sterilization or extirpation) from both low dietary intake and increased consumption as they are exposed to more than their fair share of environmental genotoxic and other toxins and infections [191, 192]. Chemical revolutions have shaped our world from chlorine (releasing bleaching fields for pastureland) (1785) to soap and

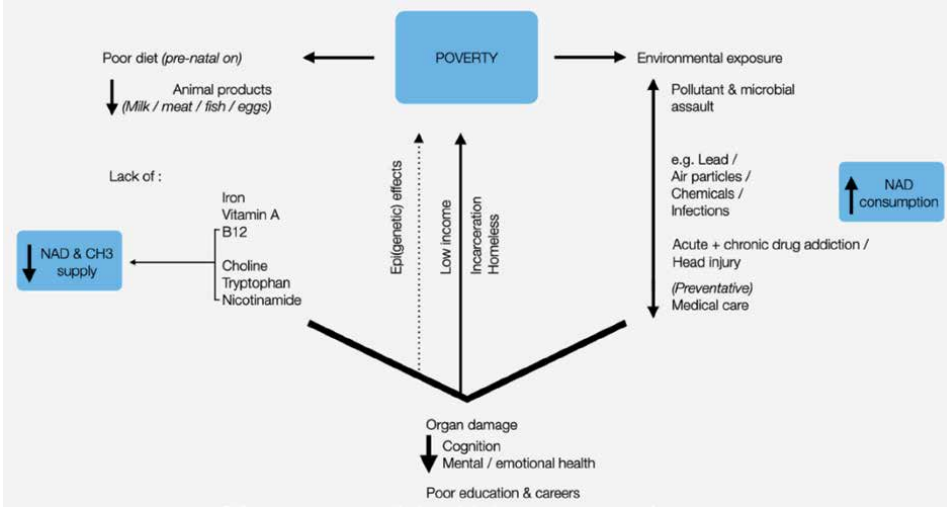

Figure 10.
A balanced diet has to include adequate nicotinamide supply along with other micronutrients that, until supplementation was introduced, had to come from animal produce. Supplementation and "nutritionism" may be an emergency procedure of value but is a technological fix (as is Golden Rice) to try to fix an economic problem and ignores broader cultural and health issues that rarely work and in the case of nicotinamide can drain the methylome [196]. Poor diet and poverty are interlinked in cycles of despair and increased environmental hazards adding insult to injury that are trans-generational.

cleaning water (1850) to refining sugar to artificial fertilizers to DDT and organophosphates and neonicotinoids to leaded gasoline and poison gases and safe refrigeration, (that enabled the meat trade) but all have come at a (neurotoxic)price and unforeseen consequences particularly in poor neighbourhoods [193–195] (**Figure 10**). Incentives for "credit invisible" disadvantaged people to set up business in the USA (as part of Nixon's "black capitalism" even concentrated on fast food outlets and franchises "force feeding junk" (although admittedly hamburgers, kebabs and "cod fish sandwiches" like fish and chips in Britain increase meat intake)rather than grocery stores as did targeted advertising and "Foodopolies" and all not helped by traditions of "soul/slave" food [197, 198]. Poor neurobiology has previously been blamed on genetics, but this plays a secondary role perpetuating the problem through epigenetic means well after the environmental assault [199]. Epigenesis may have direct effects through chromatin marks or in a wider sense of the term lead to poorer education both within and outside the family or access to (preventive) medical care or exercise. A large volume of evidence supports the idea that animal products such as milk and meat are important in child development in good studies in many countries over many years: given the evidence that increased income is spent on ascending Engel's curves this explains the beneficial effects of universal income and services being cost effective with improved labour outcomes and productivity and the failure of austerity programmes [129, 133, 200, 201].

12. Living high: letting die

The moral position on this *"thou shalt not kill"* is clear as many ethicists and philosophers from Aristotle on have pointed out that all should be allowed to flourish [202–205] (**Figure 11**). Many diseases of poverty can be related to meat deprivation and the "western diet" linked with allergy and auto-immune disease and (food) allergies often attributed

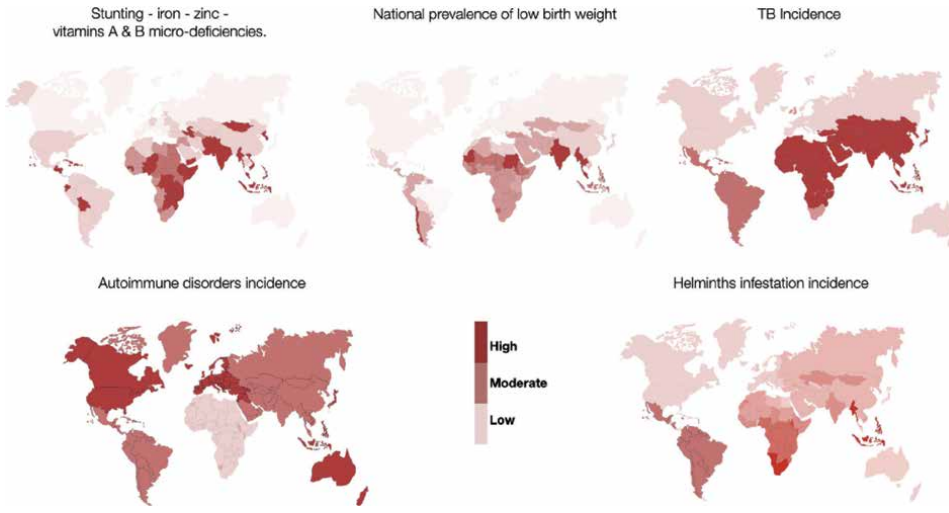

Figure 11.
Stunting whether measured by height or IQ tests is very geographic and correlates with poor diets. So do low birth weights that then even if diet improves runs the risk of metabolic syndromes. TB decreases over time if meat intake increases as it did in Victorian England but is still common in countries where meat intake is low. Nicotinamide has antibiotic actions against TB and many helminths. As TB and Helminth incidence decrease allergic and auto-immune disease quickly and consistently rise in incidence as does longevity and some age- related inflammatory, degenerative and cancerous conditions.

to lack of fibre and ultra-processed foods could be a direct effect of higher nicotinamide doses and that the theories merge as less fibre with changes in the gut microbiome and less butyrate and other short-chain fatty acids (SCFAs) affects the niacin receptors such as GPR43 and GPR109A and both T cell function and NAD metabolism [206–209].

We did not emerge from Hobbesian state of "solitary, poor, nasty, brutish and short" but from a (meat)affluent society. As Rousseau, Locke, Paine, John Stuart Mill and many since have pointed out the essence of the social contract and property rights with enclosures is that there is then an obligation to feed those whose land, pasture and hunting rights have been expropriated. Indeed that has often been taken as the hallmark of civilisation even if codes are regularly broken [210]. Many revolts, revolutions and even world wars have been based on the right to subsistence, or used food as a weapon such as the Nazi Hungerplan (see "The taste of war"-Collingham 2012 – for many relevant examples emphasising the need for meat). Some nearly succeeded such as the French revolution's "le droit a la subsistence" supervised by the "Comite de Mendicite" of 1790 that after long years of malnutrition under the Ancien Regime was working well until adverse finances due to the Napoleonic wars intervened [211–215].

The basis of a good diet is well known even if detail changes with fashions rather than evidence: Hippocratic and Aristotle's biopower recommendations for individuals and states on dietary and exercise regiments are not that different to modern recommendations or as observed in healthy "Blue Zones" [64, 216]. The problem is that for millions within even wealthy countries and billions globally this advice is not affordable or even available—and not because the poor cannot manage their domestic budget or cook properly but because high calorific foods are cheap and there is less waste and they keep you alive even if "starving on a full stomach" [66]. Cost of thriving indices (Coti) suggest that even the (crucial) middle classes in rich countries are over the last 50 years struggling for the basics including the nutritious food baskets – at lease on one income. Statesman like actions to alleviate intergenerational friction from "baby boomer"

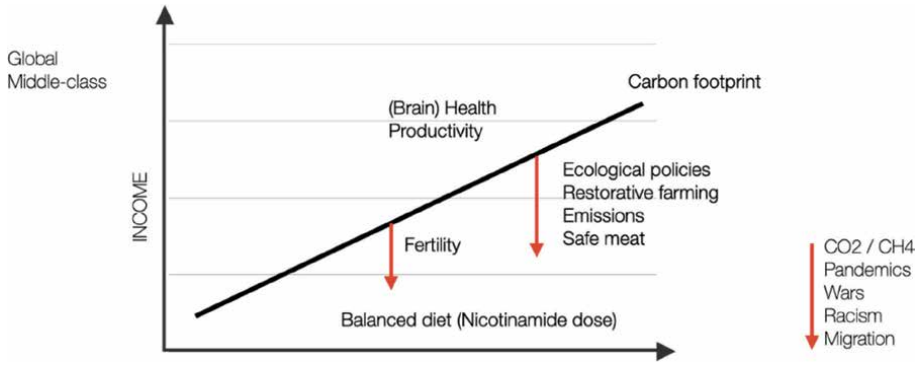

Figure 12.
A balanced diet leads to better demographics with high quality but lower numbers of offspring that raise productivity and inventiveness and eventually lowers emissions after an initial sharp rise at least in the past. This is different to the cereal related boom-bust demographics of the neolithic and recent green revolutions with their emphasis on calories that become demographic and health "time bombs".

pinches on subsequent generations prosperity and diet need accepting as breaks in the contract between generations (after Edmund Burke). A move back to "kitchen table" issues rather than the distraction of post-materialist cultural concerns treating lower status non-elites better may counteract populism and waves of migration along a metabolic gradient unstoppable by "Canute-like" border controls and walls [217].

13. Poverty traps

Previous worries about alleviating poverty and encouraging laziness or high fertility can now be shown, and the pellagra example helps, to be wrong—better diet cures laziness and poor or even criminal behaviour patterns and may decrease fertility (to the point it becomes a concern as the demographic dividend from more young people dissipates and immigration can become a necessity) [218] (**Figure 12**). The original Neolithic move to a more cereal based diet may have been a "Faustian" bargain increasing fertility and populations that could develop divisions of labour but at the expense of poorer health and human capital for some—a bargain we should recognise and take active steps to avoid.

"Tragedy of the commons" [219] claims that peasant cooperatives overgraze pastureland are rare whilst capitalist corporations frequently have short term non-sustainable profit orientated approaches that damage the soil and use artificial fertilisers and pesticides to such an extent that they damage ecosystems and diminish biodiversity. Mixed farming cooperatives usually do the more sustainable reverse unless driven out of the market when if close to starvation "seed corn" may get eaten or corn sold cheaply that has to be bought back early in the next season at greater expense or, not eating (or even destroying) cattle as it is the only source of wealth—classic poverty double traps that happen [220].

14. Politics and economics

No political or economic ideology has had unalloyed success in feeding their own populations (or of consistently helping others)—a key measure of the legitimacy of

any government. Neoliberal policies emphasise industrial agribusiness' efficiency with monopolies and profits to shareholders, compared with earlier "Fordist" capitalist systems that encouraged higher pay leading to better diets and consumerism for workers and gains for subordinate classes, have not served meat equality well [221, 222]. Neither has the Ricardian economics of "comparative advantage" that makes some sense when exporting tropical goods (or wine from Portugal versus cloth from England) and free trade but taken too far can destroy local mixed farming and even staples that then have to be "offshored" to unreliable or expensive sources leading to food insecurity [223].

State involvement as socialist and collectivist experiments also often fail such as in China or in the Soviet Union as witnessed by the Ukrainian Holdamor with starvation even in the "breadbasket" of Russia [224]. Other widespread famines and Stalin's Russia "Terror-Famine" in the 1930s and China's and Mao's "Secret Famine" in the 1960s—neither put nutrition first but industrialisation. Meat issues and differentially successful agrarian policies may have been behind both the rise and fall of the Iron Curtain—McDonald's in Moscow was reduced to ersatz meat and meat queues were deeply unpopular in east Germany and Poland [225]. The need for square meals was re-discovered in the 1930s great depression in the capitalist USA and in Britain stimulated by hunger and job marches and both had to take a more socialist stance as in Roosevelt's "New Deal" [226, 227]. This deal incorporated anti-monopolist laws that dissolved the "Beef Trust" (alongside the more remembered Standard Oil) and supported the earlier populist movement of farmer cooperatives and the "Granger" movement notably and unusually from all "races" in the 1870s although "Big Ag" later has regained power [228–231].

The more capitalist and scientific focus (as with the "green" scientific hybrid and GM approaches) have been mainly on yields and calories rather than on nutrition and improving human capital—paradoxically reducing overt starvation but perhaps fuelling population booms on a "Sisyphean task" as far as keeping everyone well fed is concerned [26, 232–235]. There have been attempts to prioritise economies to basic human needs [236–240]. These sometimes put diet and meat via either jobs or direct cash ahead of other human or political or even international legal values (that often favour the rich) and could "unshackle" some economies (such as in India relative to China's undemocratic policies) as a (hopefully) temporary trade-off [241–243].

15. Big food—small holders

A basic challenge is to decouple growth from its reliance on fossil fuels and fertilisers (from bones to guano to potash, phosphorus and artificial oil fuelled nitrogen fixation) in a way that does not make things worse for the planet or its inhabitants: compound "green growth" is likely to require a combination of some reversion to traditional crop-pastureland recycling practices and technological innovation from vertical farming to artificial meat to methane-eating bacteria in dairy farms and measuring progress using Human Development indices not GDP [244–247].

Agribusiness has been guilty of short-term emission heavy and other "Silent Spring" approaches that contribute to climate change and will eventually lead to less suitable agricultural land being available. Somehow a way forward with "local for local" (as was true for almost the whole of our evolution) "10 mile diets" insourcing more sustainable farming and ranching needs to be found [248–251]. Loss of biodiversity includes loss of the rarer foods that might be needed later and include some sources of meat [252]. Goldschmidt's 1978 "As you Sow" research showed profound effects on

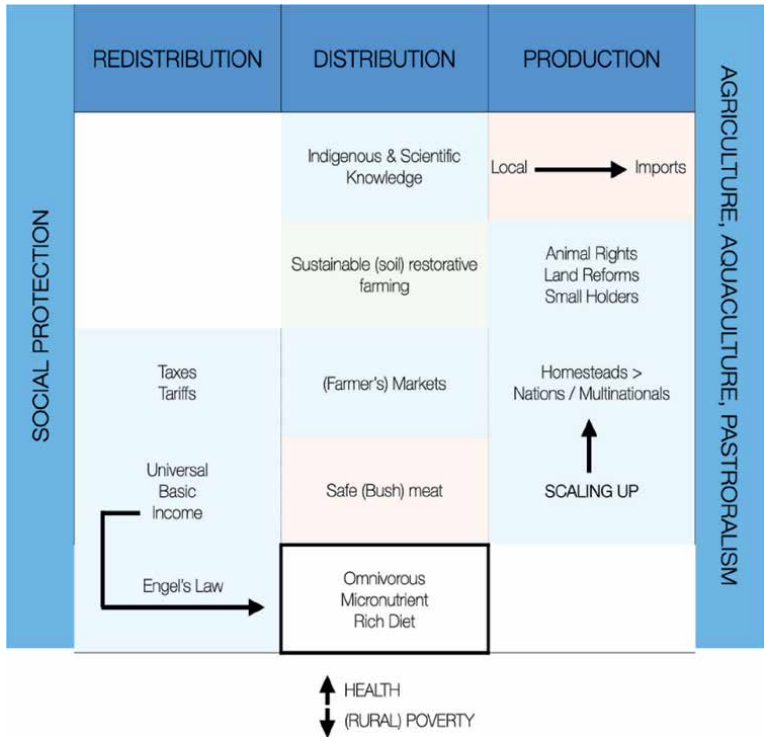

Figure 13.
Answers are likely to come from a combination of social protection of income ideally through well-paid jobs and better educational infrastructure in deprived areas as "pre-distribution" or, redistribution with universal lifelines for meat (and energy) consumption up to a certain point with food subsidies or cash payments. Local production of foods and the best of the scientific and indigenous knowledge approaches with restorative farming and better and safer distribution networks will help.

the community affecting poverty and health of industrial agriculture adversely versus family owned farms [253].

There are many suggestions and experiments ongoing that could solve these problems that integrate crop—livestock systems—if these decentralised systems can satisfy be scaled up creating a world system rather than globalisation with its high food miles and waste [254–267]. Local economies with food sovereignty going beyond food security with international peasant, slow food, cooperative solidarity movements like *La Via Campesina and Gruppi di Acquisto Solidale* with the many versions of food hubs may cut out middle-men and monopolies or speculators making produce cheaper, safer and closer products suitable to diverse dietary needs [244, 268]. Regenerative farming and agroecology, sometimes less strict than organic farming that does not allow weed-killers, with less tillage or chemicals and "soil doctors" may heal poor soil health and make them both more productive and more resilient to climate change (whether temperature, drought or floods) as well as habitat for a rich ecosystem for micro-organisms and a storage sink for carbon - but this is often only solvable by local measures as there is no "one size fits all" solution [269–272] (**Figure 13**). Care needs to be taken as radical overhauls such as banning all fertilisers and pesticides can cause a low yield crisis, as suggested by the experience of Sri Lanka. Laboratory grown meat has come a long way since the first burger (2013 and

$330,000) as have shifts from beef and lamb toward chicken and tofu but may remain too expensive for the poor and unacceptable "Frankenfoods" to the rich [273].

16. Is more data needed?

Cartesian logic says that when we have enough knowledge of a balanced diet, we do not need the "logic" of the marketplace to help us valorise or price meat. Neither do we need more data to act. The long overdue measurement and screening of NAD pathways in populations should still be done and would act as a lever to target deficient individuals and to adjust dosage at times of stress.

A simple goal reclaiming a meat and diet commons should be set that would quite possibly pay for itself several-fold in productivity, resilience and safety [274–277].

17. Pro-pandemic meat variances: poor plagues can plague the rich world

If altruistic and moral arguments do not suffice, then fear of pandemics and climate change might tip the balance toward further action. The meat supply has long been a source for concern from nineteenth century meat packers in Americas "Red meat Republic" and Chicago's "Porkopolis" as depicted by Cronon and Sinclair in "the Jungle" with dangers to the packers and the consumers triggering legal constraints on labour and consumer safety (the birth of the FDA). This did not stop the variant

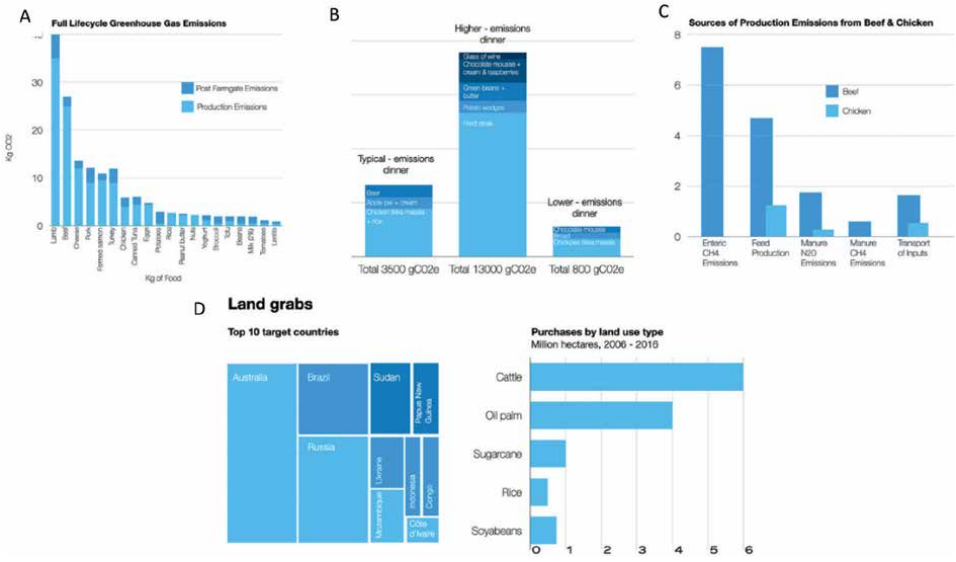

Figure 14.
(A) Greenhouse emissions by food type. (B) Emissions from beef and chicken. (C) High to low emission meals. (D) Land grabs and their main uses. Ruthless pastureland and cropland appropriations and exploitations have been important drivers of our history. Territorial gains (Ukraine excepted) are now rare but the goal of most deals remains to feed the western centre or create profits from cash crops, oil or mining increasingly of rare metals. All benefitting from information technology and "offshoring" with cheaper labour rather than improving the farms or the diet of the local inhabitants [294–296]. When local governments are astute to avoid "resource curse" or the "Dutch disease" they use profit to farm and feed their population properly and do not become too dependent on others for aid or their food surpluses or manufactured goods.

CJD outbreak in the UK from unnatural farming and feeding practices associated with "industrial meat regimes" or in China "dragonhead enterprises"—COVID-19 highlights the need for better and safer meat supplies as did other earlier emergent zoonoses; pathogen spillover is more likely when there are rapid changes in bat ecology including climate change and deforestation and when they are hungry and nomadic themselves bringing them closer to intermediate viral hosts and the human food-chain [62, 278–284].

The quest for meat is strong enough that risks get taken both by the poor in desperation, such as widespread poaching endangering species, and equally by the bored uber-rich desiring exotic foods usually meat. Bush meat and other wildlife hunting or farming particularly in deforested areas can bring species together so closely that it allows for microbial/viral species-jumping an important source of new (and old) zoonoses and food poisoning. Animal culls from emergent veterinary infection or known pathogens that could have been avoided by better vaccination programmes can impair the meat supply and cause price spikes. Regulating the market with a visible hand banning illegal wildlife, improving livestock densities and revamping with less cruelty to animals and fish, tidier slaughterhouse conditions combined with early warning systems are urgent to correct this "biological experiment" as are fresh looks at conservation in zoos and parks with public health in mind [285–288]. Restricting the rich in a "meat retreat" but supplying the poor is the crucial point that must be kept central to policies and not compatible with calls to abolish livestock farming and replace with veganism and microbial ferments (reminiscent of the dystopian 1973 film Soylent Green) [45, 289–293] (**Figure 14**).

NAD depleted populations are prone to infections and more likely to infect others with the infections further depleting NAD from tissue damage and perhaps impaired uptake of tryptophan in a metabolic trap. Indeed some manifestations of COVID and other infections (and long lasting side-effects such as chronic fatigue) may be new versions of pellagra with its documented disturbances of nicotinamide metabolism [297].

18. Answers: nutritional repairs as reparation and route to prosperity

Well-meaning attempts, and utopian ideals, have been made to alleviate nutritional poverty from feasts and potlatches in feudal times to poor laws and charity including from churches and monasteries and later foundling hospitals, school meals and food banks—and the far less well-meaning depictions of the "undeserving poor" and establishment of workhouses [298]. The usual reason for support was to provide enough basic subsistence to socially "produce and reproduce" a surplus workforce in case needed for industry or for "cannon-fodder". More enlightened policies exist but often rush to education or electricity or fertility control or good institutions without much mention of diet the gift that underpins these worthy goals [299–303] (**Figure 15**). In other words a meat and fish ("Blue") Commons and a "Glocalisation" foodscape needs to be recreated counteracting the "Lauderdale paradox" (as the "Charter of the Forest" a part of the Magna Carta had attempted in 1217 as later did the 17th C Leveller and Digger upheavals in the English Civil War, with "warning tears of the oppressed", and later the Quakers and Chartists). However, the rich still enriched themselves "contrived scarcity" of what had been abundant and was to become super-abundant. The worries of "Grim reaper" Malthusians such as Paul Ehrlich (as in his 1980 bet with the cornucopian Julian Simon) are perhaps resolvable by high "K" quality populations on good diets not "r" "population bombs" [304]. On the whole up to now the optimists have been right with Human

Figure 15.
Food spend as % of income remains high in many countries and will be a lot worse for the poorest families. Engel's/Bennett's law is clear cheap empty calories will be the first priority and meat/milk and vegetables will be squeezed out. By contrast rich people in rich countries spend a negligible proportion of their income on food that is in effect free as it barely affects their disposable income. Overindulgence can however be exacerbated by excessive fortification in foods and drinks running the risk of hypervitaminoses B3 for the affluent.

Development reports showing reductions from 60% to 10% of peoples in extreme poverty (less than 2$ a day) since 1950 with increases in schooling, life expectancy and happiness but this has been unequally spread; the pandemic has reversed progress in a detour that may last given an "uncertainty complex" in a "polycrisis" or ticking "cluster bombs" best avoided by returning to basics such as wholesome diets.

Global problems, we have illustrated can be dated to unlucky geographies exacerbated by colonialism and post-colonial self-determination and the long shadow of slavery or neo-slavery, such as indentured servants and child labour, frequently resulting in pro-pellagrous diets [305–311]. Indeed, some good data is on catch-up growth after the stunting of American slave children that gives hope, as do many other studies across the world on migrants that diet with more animal products and protein can improve height cognition and behaviour and life chances within and across generations. Massive reparations were made to the slave owners not the slaves and reconstruction deals such as " Forty acres and a mule" that would have helped were soon reneged on [28]. If we set our minds we could disallow a range of black-white disparities in the prevalence of chronic disease including (Caribbean) "amputation capitals" caused by metabolic and "blood sugar" syndromes as well as excessive deaths from infection. Targeting the vulnerable may be more effective, more workable and more affordable than other proposals or repatriating looted cultural artefacts and could be off-set by other stolen assets from corrupt dictators laundered in the West as more recent "sins of the fathers" [57, 312–319].

Reparations, it will be remembered were poorly managed in Versailles in 1919 with fatal consequences (paving the way to WW2), despite help from the American Red Cross and "Save the Children" (who against opposition also helped starving Russians).

By common assent the German famines led to fascism, further *lebenstraum (that was a factor initiating WW1 seeking "a place in the sun" for both Germany and Japan)* and WW2: The "Hungerplan" to starve Soviets and Jews mixed up such nutritional policies, racism and later genocide and "Holocausts" (whilst the world watched "*a grotesque dream is forming*"—Joseph Roth 1924) [212, 320, 321]. Half-starving people on a low meat diet turns them into versions of pellagrins, underlined by Primo Levi's description of the "Musselman" who close to death "*with head dropped and shoulders curved whose face and eyes not a trace of thought was to be seen*"—that then "proves" them inferior.

In the WW2 case this chain of events was defined (by Lemkin and Lauterpacht -1945/6) as "genocide" and "crimes against humanity" and their "Final Solution" of euthanized death [302–304, 322–324]. Many genocides can also be seen in the light of dividing pastoralist and farmer groups and deciding they are ethnically different as evidenced in the history of the San (hunted as bushmen) or frictions over dairy farming in Kenya (the Mau Mau uprising in 1952) or in Rwanda or Darfur or inventing national borders that encourage ethnolinguistic diversity and friction as in Africa and India/Pakistan with similar colonial-settler like frictions and "indiginocides" in Gaza, Sri Lanka and Myanmar [323].

In these self-fulfilling policies half-starving people on a low meat diet turns them into versions of pellagrins 'legitimising' denationalisation followed by dehumanization and should be incorporated into Stanton's "10 stages of genocide" under ecological and economic headings. We should re-think development emphasising the opposite outcome from a better diet turning the investment of reducing famine and malnutrition and circumvent various vested interests to avoid future criticisms and our own "autogenocide" [245, 325–331]. This is particularly important for Africa and some parts of Asia allowing them to complete their demographic and epidemiological transitions to everyone's advantage [274, 332–336]. The remarkable success of countries such as South Korea, a war-torn "basket case" in the 1950s concentrating on agriculture, land reform, exportable goods and culture shows that "Shrimp to Whale" progress can be done [337].

19. Better policies: nutrition front and centre "to each according to their needs"

Food stamps and maternal support and attempts to maximise employment or provide universal basic incomes have had some luck [338]. Multiple studies over nearly a century in many countries have shown the benefits of animal sourced foods the tall Masai relate to pastoralism and the tall Dutch to high milk intake in the Netherlands—international IQ comparisons may similarly relate to diet [339–353]. Universal basic income first suggested in Thomas More's old Utopian dream and enacted in Speenhamland (1795) almost became American policy in 1969 as part of the "War on Poverty" and many recent studies have shown large cost-effective gains in many measures across the board—this may well reflect Engel's curves in improving the amount of milk and meat in diet [354]. Universal basic services is a closely related idea that would have similar results if it included diet as a priority rather than jump to welfare objectives such as free education and health by-passing diet [355, 356]. A reinvention of "gas and water" municipal socialism (as instigated by Chamberlain in Birmingham) and "New Jerusalem's" with communes driven then by labour unions and strikes to include diet and international subsistence revolts often led by women ("Rebecca food riots") andhelp to local farmers and their markets may be a the exemplar narrative and pre-requisite for success [357–362].

Policies that encourage rather than marginalise pastoralism (as a protected local industry as important as other forms of security such as energy, computer, ships or military technology) and invest in "precision" mixed farming and sustainable regenerative agriculture and aquaponics combining local indigenous knowledge with the best of the scientific approaches—and learning from well—constructed trials sensitive to local opportunities and cultural needs have to make sense [53, 76, 256, 266, 363–370]. Pastoralists are particularly at risk of climate change and its effects on forestation such as the advance of Boreal forests and reindeer populations or, their loss from fires, and is in the Sahal a flashpoint for outbreaks of violence [371].

Furthermore, agriculture and silviculture improve biodiversity reflecting the co-evolution between man, birds, bees and other insects, and symbiotic microbes in our gut and in the soil [372–374]. Neonicotinoids and other pesticides have damaged insect populations and the use of antibiotics to encourage growth in animals contributes to changes in our microbiome with antibiotic resistance and the emergence of "superbugs" now a major health hazard [375].

20. Humanitarianism: re-igniting a concern for distant others

Humanitarianism and its institutions have a history that some date from the consequences of decisions in Paris (1919) and Biafra (1970), where pellagra was well described, was another historical stimulus—that is still relevant to poor nutrition and population explosions in Nigeria [364, 376–379]. Charity organisations, such as Medicins Sans Frontières and the NGO Oxfam [380] with local development is the way forward including supporting pastoralists. The need for migration should then be manageable with less friction—after all behaviourally modern *Homo Sapiens* has been on a transcontinental global quest for meat or fish along eastern and western coastal "kelp and salmon highways" (and remember the Polynesians and Thule Inuit and the more commercial Basques) for 200,000 years or so and only migrates away from family when it is forced to [381, 382].

Calls for internationalisation of the meat, milk and egg supply pointing out the related failures of water privatisation and to the overall success of national meat rationing in time of war may be in order [11, 383, 384]. Such combined national and international approaches with a broader view of "A Duty of Care" [385–387] should lessen the loaded dice of being born in the wrong place with little chance up upward mobility (on the Gatsby curve) and may even be helped by technology and increased ability to virtually see the world from other perspectives, although runs the risk of flaming inequality, with gamers even playing farming games (originally "Harvest Moon") rather than shooting "baddies" and rewards for being kind not vengeful [388, 389].

21. NAD ups and downs over time and place—"Only one Earth"

Pellagra, often familial, is an outstanding example, alongside eco-genetic opposite side of the genetic coin examples, such as phenylketonuria also cured by dietary intervention, of good nature via good nurture [390]. Cotton market failures led to pellagra outbreaks just as loss of ship building led to a dietary and health collapse in Glasgow [391, 392]. Although the rest of "Bad Food Britain" or the USA is far from ideal (with many food-banks necessary) hope comes from Mediterranean countries where the class food divide is not so marked, and neither are health inequalities. Perhaps as

they were in the eye of the original pellagra storm lessons were learnt Elsewhere the "fallacy of composition" states that because many have access to luxuries one must not presume that necessities are catered for as heavy marketing of new technologies distort Engel's law even in slums and "shanty towns" [393].

Politics should lower its sights and deal with Masferrer's (1929) "El minimum vital" regardless of the hand dealt by fate and as Berthold Brecht said in his Three Penny Opera "*You may proclaim, good sirs, your fine philosophy but till you feed us right and wrong can wait*" or Scott Fitzgerald (1925 -Jazz age) in the Great Gatsby "*No human difference is so profound as between the sick and the well*" and this failure to allow ascension up the food chain is the real source of (brain)health inequality [382, 394–397]. A "Constitution of knowledge" or "Adaptive intelligence" or "Metacognition" depend upon diet and if these do not function well neither science or the arts or political and democratic institutions can emerge capable of solving the major problems facing the planet and our own survival [263, 296, 380, 398–404].

Poor nutrition commonly gets medicalised shifting the blame and responsibility from the state to the individual and then blaming willpower or incarcerating or driving to drug and food addictive behaviour with opioid epidemics and mappable deaths of despair as was even documented three centuries ago in the pellagra epidemics [78, 405]. Failure to progress nutrition and human capital may explain the "Great economic disappointment" of the last 20 years [406]. Poor classes and countries particularly in the South face a NAD headwind that results in a developmental and degenerative pathology of poverty and inferiority, as judged by many in richer habitats who choose to forget the quote from Corinthians "*What do you have that you did not receive? And if you received it, why do you boast as if it were not a gift.*" Or the meritocrats conveniently forget "*Der Mensh was iBt*" (Feuerbach 1850) that can now be shown by stable isotope research, that has tracked our meat: plant dietary history, to be literally true that we are what (and where) we eat [407–409]. Rich gastronomy and exotic diets look decadent at best if the south is included in "Only One Earth" (Ward 1972) and contributes to a dangerous syndemic and as said to the rich after Belshazzars feast in the Book of Daniel "*thou art weighed in the balances, and found wanting".* Meat is not a luxury for billions and should be democratised or as Benjamin Franklin (1758) stated "For want of a nail, the kingdom was lost". Metabolic rifts allow for dangerous metabolic ghettoes with poor brain development crucial for abstract thought, language writing and arithmetic and the many Neuro- prefixed disciplines that "supersize the mind" [312, 316, 410, 411]. A more moral economy should focus on this need as did the "physiocrats" and "levellers" several centuries ago—and was Confucian philosophy long before that [186, 397, 412]. Meat markets are (Pareto) inefficient as it would be possible to make many people better off without making anyone worse off (indeed they may well be better off too; giving money would pay for the meat and would not be wasted as predicted by Engel and has been shown in several randomised trials (see Banerjee and Duflo's Nobel prize winning studies).

22. Postcript 1: current concerns

Much of the heated controversies over the rights and wrongs of meat based or plant-based diets can be resolved if seen in the light of needing homeostasis and NAD(H) based metabolism [284, 413–420] that may yet rhyme with a green hydrogen energy revolution [421]. The writing is on the wall over the ethics and safety of allowing billions to be poorly fed so we need to sort this out or any future generations will obloquy us in the same way as we criticise the diet-mediated slave trade and most genocides [269, 422].

Stagflation with increasing prices and no growth was triggered in the 1970s by energy and then food price spikes and may happen again turbocharged by current shocks—for every percentage point increase in food prices another 10mn people are pushed into extreme poverty and developed countries are far from immune to this effect (prices are up 30% this year) with households paying over 50% of income on food. Heavy current subsidies of foods may become unaffordable for some countries and already concentrate on calories encouraging junk food and "buy one get one free" deals. Repeating dated mantras such as the poor needing help with cooking and domestic budgeting or, protectionism with export bans over foods or fertilisers are not an answer.

Recent events in Ukraine bring to a head longstanding problem in the food-chain affecting everyone but particularly those teetering in countries affected by conflict—including Yemen, Ethiopia Sudan and Egypt—risking another "Arab uprising" that began symbolically with the self-immolation of a Tunisian vegetable vendor and were followed by Sudanese and other protests over the price of bread [423].

Individuals may be best served by free money but some states need "Special Drawing Rights" and support via World Food Programmes and combined with investment to improve agricultural yields such as in Africa and incentives to cut down

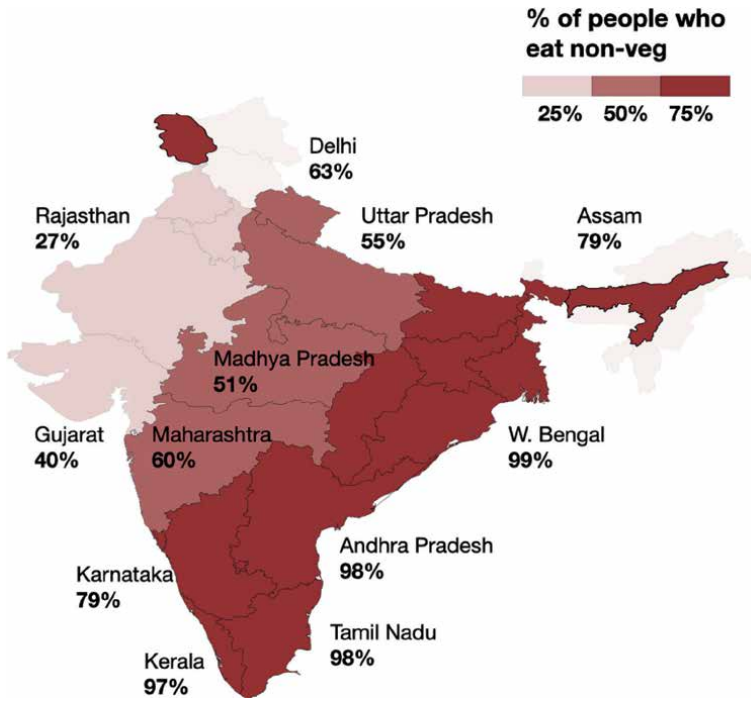

Figure 16.
Southern v, Northern India may be as close to a controlled experiment as it is possible to get compared to the natural experiments we have described. A child born in the South is far less likely to die in their first year of life or lose her mother in childbirth. She will receive better nutrition with free midday meals and go to school and stay in school longer then attend college and secure employment with better pay. She will have fewer children who in turn will be healthier and more educated than her. Southern India, and Kerala in particular, over the last 50 years has developed meat and especially beef as a secular dish cutting across class, caste and religion—the latter of course is complex historically with taboos that remain influential in the North. Initially the extra expense may have been kick-started by Gulf migration and remittance monies sent home but is now self-sustaining due to economic success and high meat production as well as consumption.

on scandalous food waste (as in European "butter mountains" and "milk lakes") and overindulgence in the developed world [424–426].

23. Postcript 2: QED?

These are man-made disasters, as was overt pellagra. Hope should come from realising that darkest London of 200 years ago was not that different to the poorest regions of the world now. Strong correlations with progress such as fossil-fuel dependency that may have tempted emerging economies, such as in Africa, to believe that they cannot leap-frog to green economies can be shown that the legacy carbon path, or at least an extreme form of it, is not necessary if a balanced diet is prioritised.

Concrete optimism could spring from an almost randomised series of experiments in India where the southern states have overtaken the Northern states in educational and economic terms with better health (such as infant mortality or TB incidence) with enlightened policies on meat/milk/eggs eating and midday school meals [427] (**Figure 16**).

Improved diet would increase resistance to infection more than the most powerful antibiotics and avoid "superbugs" and improve gene maintenance, expression, regenesis (including of neurones) and alter our inheritance in a way that glitzy gene therapies—for the rare and rich—could only dream of (although it has been suggested that such technology could by using gene-drives reduce the desire for meat and make us more altruistic) [278, 428–431]. At the same time the nightmare of more inequality would be avoided as so much unmet need would be addressed. The fairly high hereditability of traits such as height and IQ and many diseases are much less if poor suggesting that diet is the crucial, cheaper and fairer intervention [432].

24. Discussion

It does not take a paranoid or an anxious mind-set to sense trouble ahead if food-security and nutrition is not taken more seriously—the Maputo declaration of 2003 committed African leaders to devote 10% of budgetary allocations to agriculture; few have come close but placate populations with food imports that they increasingly cannot afford and should rely less on free trade but produce more at home or "friend-shore" rather than deal with international monopolies with few value based rules [433–435]. Commerce and market forces along with some optimism over new technology could, if it prioritised diet, create its long- promised potential for peace, (as first suggested by Montesquieu (1748) and Angell (1910)) and " freedom" and democracy between interdependent classes and countries that currently are made dependant on those with (non-seasonal and varied) affluent dietary and other (decadent) appetites—and could stop us all hurtling toward disaster [436–438].

A post liberal cosmopolitan economics that considers others more, and agrees with Joesph Roth (1938) " People aren't pigments and the world is not a palette!" and is not about the survival of the richest (even planning escapes to Mars (!) or eternal lives) or even a "golden billion" and other "great replacement" conspiracy theories by remembering Benjamin Franklin's 1776 dictum "we must hang together or surely we shall hang separately" is in order [439–441]. Originally race was closely linked to class and poverty (as are immigration and other white laws) exemplified by parochial commentaries such as "the Bethnal Green poor are a caste apart, a race of whom we

know nothing" force-feeding inferiority that then needed to be despised or civilised in hostile environments cloaked in superficial markers such as colour or religion, as noted by WEB. Du Bois when visiting a Warsaw ghetto in 1949 [442].

Better diet for all should speed up our "slouch toward Utopia" rather than "molecular utopianism" for the few. We finally begin to answer Keynes' 1924 criticism that "*we lack a coherent scheme of progress*" as that means meat for metabolic progress, not meat as a sign of progress or for "showing-off". Poverty alongside affluence definable as "stuffed and starved" metabolic diseases with pathologies not due to "status anxiety". A flatter not fatter earth with reduced meat variances is required and need not wreck the world and may save it [188, 443–446]. As (Sir)Bob Geldof, influenced by the history of *An Gorta Mor*—the Irish Great Hunger of the 1850s when governments also stood-by—recently said "*Development is not some feel-good virtue-signalling function, it is a critical necessity of humanity or the spores of poverty find fertile ground in the poisonous fields of ethnicity, populism and nationalism- ask Putin*". Giving in to our altruistic urge with something of a moral revolution may help when combined with a "fear factor" of pandemics and climate change and a concern for our kids and future generations and generational injustice [447–452].

Bernard Kouchner, the originator of Medecins Sans Frontiers, (1993) having observed starvation and pellagra in the Biafran war wrote in his memoir "*Le malheur des autres*"—"A quoi servaient medicins s'ils n'alertaint pas le monde du blocus alimentaire.....silencieux nous etions complices du massacre systematique". Preventative and moral medicine needs to avoid being accomplices amongst the geopolitical chaos and speak and act up over malnutrition and pandemic avoidance with safer meat supplies—and in keeping with Ernest Hemmingway's "*if the story is so simple it can be said in 6 words*" and to avoid the weight of circumstantial but (we hope) percipient material dragging our argument down we say loud and clear Square Meals—Poverty and Pandemics Gone. The lesson of the Black Death or of imports from "settler colonies" is that doubling meat intake for the peasants creates "Golden Ages" with more equality of early developmental outcomes and opportunities but this could be done without more plagues or creating more third worlds in the post-colonial age that could "boomerang" [453, 454]. As a critique of development policies, states: the silence on unequal (metabolic) rights for rich and poor made unequal by dietary not genetic or cultural "tangles of pathology",—and the lack of trust to make their own subsistence and other decisions has to end with less emphasis on blaming the victims and punishing laws and orders [455]. "Races" may correlate with skin colour but this oppressive social construct disconnects from causation as it includes Jews, Gypsies, Romas and many other poor economically disempowered white classes on poor diets (in the past including the Irish and Italians or indeed anyone non-Nordic), subject to (immigration) discrimination and genocide, that profoundly affects plastic phenotypes [456–459].

*His story relevant to child malnutrition was "*Baby shoes for Sale. Never used*"

Acknowledgements

This study was funded by QEHB Charity, Birmingham, UK.

Author contributions

ACW and LJH drafted review, CW produced figures/tables, all authors proofed and authorised submission.

Funding

This study was funded by QEHB Charity, Birmingham, UK.

Conflicts of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Author details

Adrian C. Williams[1*], Christina Wood[1] and Lisa J. Hill[2]

1 Department of Neurology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

2 School of Biomedical Sciences, Institute of Clinical Sciences, University of Birmingham, UK

*Address all correspondence to: adrian.williams1949@gmail.com

References

[1] Hyman M. Food Fix: How to Save Our Health, Our Economy, Our Communities and Our Planet–One Bite at a Time. Hachette UK; 2020

[2] Smil V. Grand Transitions: How the Modern World Was Made. Oxford University Press; 2021

[3] Thunberg G. The Climate Book. Penguin Books Limited; 2022

[4] Waters A. We are What We Eat: A Slow Food Manifesto. Penguin; 2022

[5] Vardi L. The Physiocrats and the World of the Enlightenment. Cambridge University Press; 2012

[6] Carolan M. The Sociology of Food and Agriculture. Taylor & Francis; 2016

[7] Misra UK, Kalita J. Neurological Consequences of Nutritional Disorders: CRC Press; 2021.

[8] Bernstein WJ. The Birth of Plenty: How the Prosperity of the Modern Work was Created. McGraw Hill LLC; 2010

[9] McCloskey DN, Carden A. Leave Me Alone and I'll Make You Rich: How the Bourgeois Deal Enriched the World. University of Chicago Press; 2020

[10] Miles D et al. Macroeconomics: Understanding the Global Economy. Wiley; 2012

[11] Water SS. The Epic Struggle for Wealth, Power, and Civilization. HarperCollins; 2010

[12] Wilson-Lee E. A History of Water: Being an Account of a Murder, an Epic and Two Visions of Global History. HarperCollins Publishers Limited; 2022

[13] Jones TC. Desert Kingdom: How Oil and Water Forged Modern Saudi Arabia. Harvard University Press; 2010

[14] Halliday S. Water: A Turbulent History. Sutton Gloucestershire; 2004

[15] Boccaletti G. Water: A Biography. Knopf Doubleday Publishing Group; 2021

[16] Lambert A. Seapower States: Maritime Culture, Continental Empires and the Conflict That Made the Modern World: Yale University Press; 2018.

[17] Howarth DA. British Sea Power. Basic Books; 2003

[18] Davidson A et al. The Oxford Companion to Food. Oxford University Press; 2014

[19] Fraser EDG, Rimas A. Empires of Food: Feast, Famine and the Rise and Fall of Civilizations. Arrow Books; 2011

[20] Rimas A, Fraser E. Beef: The Untold Story of How Milk, Meat, and Muscle Shaped the World. Harper Collins; 2008

[21] Jacob HE, Winston RC. Six Thousand Years of Bread: Its Holy and Unholy History. Hauraki Publishing; 2016

[22] Tannahill R. Food in History. Paw Prints; 2008

[23] Khosrova E. Butter: A Rich History. Algonquin Books; 2017

[24] Scott JC. Against the Grain: A Deep History of the Earliest States. Yale University Press; 2017

[25] Crosby AW. Ecological Imperialism. Cambridge University Press; 2015

[26] Ponting C. A New Green History of the World: The Environment and the Collapse of Great Civilizations. Random House; 2011

[27] Fanon F. Studies in a Dying Colonialism. Earthscan; 1989

[28] Foner E. A Short History of Reconstruction, Updated Edition. HarperCollins; 2015

[29] Gomes AP et al. Declining NAD+ induces a pseudohypoxic state disrupting nuclear-mitochondrial communication during aging. Cell. 2013;**155**(7):1624-1638

[30] Bocquet-Appel JP, Bar-Yosef O. The Neolithic Demographic Transition and its Consequences. Springer Netherlands; 2008

[31] Kohler TA, Smith ME. Ten Thousand Years of Inequality: The Archaeology of Wealth Differences. University of Arizona Press; 2019

[32] Huber MT. Climate Change as Class War: Building Socialism on a Warming Planet. Verso Books; 2022

[33] Lieven A. Climate Change and the Nation State: The Case for Nationalism in a Warming World. Oxford University Press; 2020

[34] Parfit D. Reasons and Persons. OUP Oxford; 1986

[35] MacAskill W. What We Owe the Future. Basic Books; 2022

[36] Davis M. The Monster Enters: COVID-19, Avian Flu, and the Plagues of Capitalism. Verso Books; 2022

[37] McAlevey J. No Shortcuts: Organizing for Power in the New Gilded Age. Oxford University Press; 2016

[38] Zaretsky R. Victories Never Last: Reading and Caregiving in a Time of Plague. University of Chicago Press; 2022

[39] Medicine NAo. Global Roadmap for Healthy Longevity. Washington, DC: The National Academies Press; 2022. 320 p

[40] Ruddiman WF. Plows, Plagues, and Petroleum: How Humans Took Control of Climate. Princeton University Press; 2010

[41] Pfeiffer DA. Eating Fossil Fuels: Oil, Food, and the Coming Crisis in Agriculture. New Society Publishers; 2006

[42] Porritt J. Hope in Hell: A Decade to Confront the Climate Emergency. Simon & Schuster UK; 2020

[43] Vince G. Nomad Century: How Climate Migration Will Reshape Our World. Flatiron Books; 2022

[44] Harper K. Plagues Upon the Earth: Disease and the Course of Human History. Princeton University Press; 2021

[45] Harrison M. Contagion: How Commerce Has Spread Disease. Yale University Press; 2012

[46] Chan A, Ridley M. Viral: The Search for the Origin of Covid-19. HarperCollins Publishers; 2021

[47] Bess MD. Planet in Peril: Humanity's Four Greatest Challenges and How We Can Overcome Them. Cambridge University Press; 2022

[48] Roubini N. Megathreats: The Ten Trends that Imperil Our Future, and How to Survive Them. John Murray; 2022

[49] Yergin D. The New Map: Energy, Climate, and the Clash of Nations. Penguin Publishing Group; 2020

[50] Rockström J et al. Planetary boundaries: Exploring the safe operating space for humanity. Ecology and Society. 2009;**14**(2)

[51] Ninan KN. The Economics of Biodiversity Conservation: Valuation in Tropical Forest Ecosystems. Taylor & Francis Group; 2012

[52] Pretty J et al. Sustainable Intensification: Increasing Productivity in African Food and Agricultural Systems. Earthscan; 2011

[53] Rees M. If Science is to Save Us. Polity Press; 2022

[54] Toensmeier E, Herren H. The Carbon Farming Solution: A Global Toolkit of Perennial Crops and Regenerative Agriculture Practices for Climate Change Mitigation and Food Security. Chelsea Green Publishing; 2016

[55] Malm A. The Progress of This Storm: Nature and Society in a Warming World. Verso Books; 2020

[56] Baccini P, Brunner PH. Metabolism of the Anthroposphere, Second Edition: Analysis, Evaluation, Design. MIT Press; 2012

[57] Wells JCK. The Metabolic Ghetto: An Evolutionary Perspective on Nutrition, Power Relations and Chronic Disease. Cambridge University Press; 2016

[58] Korzeniewicz RP, Moran TP. Unveiling Inequality: A World-Historical Perspective. Russell Sage Foundation; 2009

[59] Fanzo J. Can Fixing Dinner Fix the Planet? Johns Hopkins University Press; 2021

[60] Otter C. Diet for a Large Planet: Industrial Britain, Food Systems, and World Ecology. University of Chicago Press; 2020

[61] Steinfeld H et al. Livestock's Long Shadow: Environmental Issues and Options. Food and Agriculture Organization of the United Nations; 2006

[62] Cronon W. Nature's Metropolis: Chicago and the Great West. W.W. Norton; 2009

[63] Monbiot G. Regenesis: Feeding the World Without Devouring the Planet. Penguin Books Limited; 2022

[64] Willett W et al. Food in the Anthropocene: The EAT–Lancet Commission on healthy diets from sustainable food systems. The Lancet. 2019;**393**(10170):447-492

[65] Hirvonen K et al. Affordability of the EAT–Lancet reference diet: A global analysis. The Lancet Global Health. 2020;**8**(1):e59-e66

[66] Wylie D, Societies ACoL. Starving on a Full Stomach: Hunger and the Triumph of Cultural Racism in Modern South Africa. University Press of Virginia; 2001

[67] Tupy ML, Pooley GL. Superabundance: The Story of Population Growth, Innovation, and Human Flourishing on an Infinitely Bountiful Planet. Cato Institute; 2022

[68] Koyama M, Rubin J. How the World Became Rich: The Historical Origins of Economic Growth. Wiley; 2022

[69] Bernstein WJ. A Splendid Exchange: How Trade Shaped the World. Grove Atlantic; 2009

[70] Scialabba G. Slouching Toward Utopia: Essays and Reviews. Pressed Wafer; 2018

[71] Godin S. The Carbon Almanac. Penguin; 2022

[72] Gibson M. The Feeding of Nations: Redefining Food Security for the 21st Century. CRC Press; 2016

[73] Reay D. Climate-Smart Food. Springer International Publishing; 2019

[74] Bridle S. Food and Climate Change Without the Hot Air. UIT Cambridge; 2020

[75] Randers J. A Global Forecast for the Next Forty Years. Chelsea Green Publishing; 2052. p. 2012

[76] Steel C. Sitopia: How Food Can Save the World. Random House; 2020

[77] Hunter J. The Making of the Crofting Community. Birlinn; 2018

[78] Percival R. The Meat Paradox: 'Brilliantly Provocative, Original, Electrifying' Bee Wilson, Financial Times. Little, Brown Book Group; 2022

[79] Kaplan RD. The Revenge of Geography: What the Map Tells Us About Coming Conflicts and the Battle Against Fate. Random House Publishing Group; 2012

[80] von Hippel W. The Social Leap: The New Evolutionary Science of Who We Are, Where We Come From, and What Makes Us Happy. HarperCollins; 2018

[81] Sattin A. Nomads: The Wanderers Who Shaped Our World. John Murray Press; 2022

[82] Gray J. Straw Dogs: Thoughts On Humans And Other Animals. Granta Publications; 2015

[83] Harvey D. Spaces of Global Capitalism: A Theory of Uneven Geographical Development. Verso Books; 2019

[84] Wolch JR, Emel J. Animal Geographies: Place, Politics, and Identity in the Nature-culture Borderlands. Verso; 1998

[85] Wilcox S, Rutherford S. Historical Animal Geographies. Taylor & Francis Group; 2018

[86] Crosby AW. The Columbian Exchange: Biological and Cultural Consequences of 1492. Greenwood Publishing Group; 2003

[87] Crosby AW. Ecological Imperialism: The Biological Expansion of Europe, 900-1900. Cambridge University Press; 1993

[88] Suranyi A. The Atlantic Connection: A History of the Atlantic World, 1450-1900. Taylor & Francis; 2015

[89] Schiebinger L. Secret Cures of Slaves: People, Plants, and Medicine in the Eighteenth-Century Atlantic World. Stanford University Press; 2017

[90] Elliott JH, Societies ACoL. The Old World and the New: 1492-1650. Cambridge University Press; 1992

[91] Boorstin DJ. The Discoverers. Knopf Doubleday Publishing Group; 2011

[92] Clark RP. The Global Imperative: An Interpretive History of the Spread of Humankind. Taylor & Francis; 2018

[93] Penniman L, Washington K. Farming While Black: Soul Fire Farm's Practical Guide to Liberation on the Land. Chelsea Green Publishing; 2018

[94] Williams JC, Cuban M. White Working Class, With a New Foreword by Mark Cuban and a New Preface by the Author: Overcoming Class Cluelessness in America. Harvard Business Review Press; 2019

[95] Vance JD. Hillbilly Elegy: A Memoir of a Family and Culture in Crisis. HarperCollins Publishers; 2016

[96] Baptist EE. The Half has Never Been Told: Slavery and the Making of American Capitalism. Basic Books; 2016

[97] Fryer P. Staying Power: The History of Black People in Britain. PlutoPress; 2018

[98] Sbicca J. Food Justice Now!: Deepening the Roots of Social Struggle. University of Minnesota Press; 2018

[99] Strings S. Fearing the Black Body: The Racial Origins of Fat Phobia. NYU Press; 2019

[100] Everill B. Not Made by Slaves: Ethical Capitalism in the Age of Abolition. Harvard University Press; 2020

[101] Stiglitz JE, Charlton A. Fair Trade for All: How Trade Can Promote Development. Oxford University Press; 2007

[102] Ind N, Horlings S. Brands with a Conscience: How to Build a Successful and Responsible Brand. Kogan Page; 2016

[103] Jackson J. The Thief at the End of the World: Rubber, Power, and the Seeds of Empire. Penguin Publishing Group; 2008

[104] Belich J. Replenishing the Earth: The Settler Revolution and the Rise of the Angloworld. OUP Oxford; 2011

[105] Rodney W. How Europe Underdeveloped Africa. Bogle-L'Ouverture Publications; 1972

[106] Linden E. The Winds of Change: Climate, Weather, and the Destruction of Civilizations. Simon & Schuster; 2006

[107] Keys D. Catastrophe: An Investigation Into the Origins of the Modern World. Ballantine Pub.; 2000

[108] Miller EM. The Last Great Subsistence Crisis in the Western World. JSTOR; 1978

[109] Robins JE. Oil Palm: A Global History. University of North Carolina Press; 2021

[110] Turzi M. The Political Economy of Agricultural Booms: Managing Soybean Production in Argentina, Brazil, and Paraguay. Springer International Publishing; 2016

[111] Edgerton D. The Rise and Fall of the British Nation: A twentieth-Century History. Penguin UK; 2018

[112] Goldstone JA. Why Europe? The Rise of the West in World History 1500-1850. McGraw-Hill Higher Education; 2009

[113] Goody J. The Eurasian Miracle. Polity; 2010

[114] Jones E. The European Miracle: Environments, Economies and Geopolitics in the History of Europe and Asia. Cambridge University Press; 2003

[115] Tainter J. The Collapse of Complex Societies. Cambridge University Press; 1988

[116] Vries P. State, Economy and the Great Divergence: Great Britain and China, 1680s-1850s. Bloomsbury Publishing; 2015

[117] Cannadine D. Victorious Century: The United Kingdom, 1800-1906. Penguin Books Limited; 2017

[118] Turchin P. Ages of Discord: A Structural-demographic Analysis of American History. Beresta Books; 2016

[119] Slobodian Q. Globalists: The End of Empire and the Birth of Neoliberalism. Harvard University Press; 2020

[120] Parthasarathi P. Why Europe Grew Rich and Asia Did Not: Global Economic Divergence, 1600-1850. Cambridge University Press; 2011

[121] Ravallion M. The Economics of Poverty: History, Measurement, and Policy. Oxford University Press; 2016

[122] Smith N. Uneven Development: Nature, Capital, and the Production of Space. University of Georgia Press; 2010

[123] Elvin M. The Retreat of the Elephants. The Retreat of the Elephants. Yale University Press; 2008

[124] Frank AG. ReOrient: Global Economy in the Asian Age. Univ of California Press; 1998

[125] De Vries J. The Economy of Europe in an Age of Crisis, 1600-1750. Cambridge University Press; 1976

[126] Kaplan H et al. A theory of human life history evolution: Diet, intelligence, and longevity. Evolutionary Anthropology: Issues, News, and Reviews. 2000;**9**(4):156-185

[127] O'Rourke KH. The European grain invasion, 1870-1913. The Journal of Economic History. 1997;**57**(4):775-801

[128] Welford M. Geographies of Plague Pandemics: The Spatial-Temporal Behavior of Plague to the Modern Day. Taylor & Francis; 2018

[129] Case A, Paxson CH. Stature and Status: Height, Ability, and Labor Market Outcomes. SSRN; 2010

[130] Deaton A. The Great Escape: Health, Wealth, and the Origins of Inequality. Princeton University Press; 2013

[131] Dyer C. Standards of Living in the Later Middle Ages: Social Change in England C.1200-1520. Cambridge University Press; 1989

[132] Floud R et al. Height, Health and History: Nutritional Status in the United Kingdom, 1750-1980. Cambridge University Press; 2006

[133] Manary M et al. Protein quality and growth in malnourished children. Food and Nutrition Bulletin. 2016;**37**(1_suppl):S29-S36

[134] Steckel RH, Research NBoE. Heights and Human Welfare: Recent Developments and New Directions. National Bureau of Economic Research; 2008

[135] Allen RC. The British Industrial Revolution in Global Perspective: How Commerce Created the Industrial Revolution and Modern Economic Growth. Oxford: Oxford University Press; 2006

[136] Findlay R, O'Rourke KH. Power and Plenty: Trade, War, and the World Economy in the Second Millennium. Princeton University Press; 2009

[137] Van Zanden JL. The Long Road to the Industrial Revolution: The European Economy in a Global Perspective, 1000-1800. Brill; 2009

[138] Daly J. The Rise of Western Power: A Comparative History of Western Civilization. A&C Black; 2013

[139] Gregory BS. The Unintended Reformation: How a Religious Revolution Secularized Society. Harvard University Press; 2015

[140] Ryrie A. Protestants: The Radicals Who Made the Modern World. William Collins; 2017

[141] Diner HR. Hungering for America. Harvard University Press; 2009

[142] Pye M. Antwerp: The Glory Years. Penguin Books, Limited; 2022

[143] Muldrew C. Food, Energy and the Creation of Industriousness: Work and Material Culture in Agrarian England, 1550-1780. Cambridge University Press; 2011

[144] Turner J. Spice: The History of a Temptation. Vintage; 2008

[145] Allen SL. The Devil's Cup: Coffee, the Driving Force in History. Canongate; 2001

[146] Schivelbusch W. Tastes of Paradise: A Social History of Spices, Stimulants, and Intoxicants. Vintage Books; 1993

[147] Keay J. The Spice Route: A History. John Murray; 2006

[148] Moss M. Salt, Sugar, Fat: How the Food Giants Hooked Us. Ebury Publishing; 2013

[149] Mintz SW. Sweetness and Power: The Place of Sugar in Modern History. Penguin; 1986

[150] O'Brien PK. The Economies of Imperial China and Western Europe: Debating the Great Divergence. Springer International Publishing; 2020

[151] Pomeranz K. The Great Divergence: China, Europe, and the Making of the Modern World Economy. Princeton University Press; 2009

[152] Walvin J. Sugar: The World Corrupted, From Slavery to Obesity. Little, Brown Book Group; 2017

[153] Viestad A. Dinner in Rome: A History of the World in One Meal. Reaktion Books; 2022

[154] Kondratieff ND. The long waves in economic life. Review (Fernand Braudel Center). 1979:519-562

[155] Overton M. Agricultural Revolution in England: The Transformation of the Agrarian Economy 1500-1850. Cambridge University Press; 1996

[156] Sheldrake M. Entangled Life: How Fungi Make Our Worlds, Change Our Minds & Shape Our Futures. Random House Publishing Group; 2021

[157] Wrigley EA. Continuity, Chance and Change: The Character of the Industrial Revolution in England. Cambridge University Press; 1990

[158] Kurlansky M. Cod. Random House; 2011

[159] Deaton A, Muellbauer J. Economics and Consumer Behavior. Cambridge University Press; 1980

[160] Clover C. Rewilding the Sea: How to Save our Oceans. Ebury Publishing; 2022

[161] Barber J. The Chicken: A Natural History. Ivy Press; 2018

[162] Kurlansky M. Cod: A Biography of the Fish that Changed the World. Vintage; 1999

[163] Oddy DJ, Miller DS. Making of the Modern British Diet. 1976

[164] Perren R. The Meat Trade in Britain, 1840-1914. Routledge and Kegan Paul; 1978

[165] Caballero B. The Nutrition Transition: Diet and Disease in the Developing World. Elsevier Science; 2002

[166] Lindeberg S. Food and Western Disease: Health and Nutrition from an Evolutionary Perspective. Wiley; 2010

[167] Pajuelo D et al. NAD(+) depletion triggers macrophage necroptosis, a cell death pathway exploited by Mycobacterium tuberculosis. Cell Reports. 2018;**24**(2):429-440

[168] Smith FB. The Retreat of Tuberculosis, 1850-1950. Croom Helm; 1988

[169] Tak U et al. The tuberculosis necrotizing toxin is an NAD+ and NADP+ glycohydrolase with distinct enzymatic properties. Journal of Biological Chemistry. 2019;**294**(9):3024-3036

[170] Williams AC, Dunbar RI. Big brains, meat, tuberculosis, and the nicotinamide switches: Co-evolutionary relationships with modern repercussions? International Journal of Tryptophan Research. 2013;**6**:73-88

[171] Rook G. The Hygiene Hypothesis and Darwinian Medicine. Birkhäuser Basel; 2009

[172] Meij J et al. Quality–quantity trade-off of human offspring under adverse environmental conditions. Journal of Evolutionary Biology. 2009;**22**(5):1014-1023

[173] McMichael P. Development and Social Change: A Global Perspective. Thousand Oaks, US: Pine Forge; 2008

[174] McMichael P. Food Regimes and Agrarian Questions. Practical Action Publishing; 2014

[175] Williamson JG. Trade and Poverty: When the Third World Fell Behind. MIT Press; 2013

[176] Lessenich S. Living Well at Others' Expense: The Hidden Costs of Western Prosperity. John Wiley & Sons; 2019

[177] Davis M. Late Victorian Holocausts: El Niño Famines and the Making of the Third World. Verso; 2001

[178] Richard A. The Sloth Lemur's Song: Madagascar from the Deep Past to the Uncertain Present. University of Chicago Press; 2022

[179] Collingham EM. Imperial Bodies: The Physical Experience of the Raj, C. 1800-1947. Wiley; 2001

[180] Downs J. Maladies of Empire: How Colonialism, Slavery, and War Transformed Medicine. Harvard University Press; 2021

[181] Stamp LD. The Geography of Life and Death. Collins; 1964

[182] de Castro J. The Geopolitics of Hunger. Monthly Review Press; 1977

[183] Davis M. Late Victorian Holocausts: El Niño Famines and the Making of the Third World. Verso Books; 2002

[184] Dixon J. The Changing Chicken: Chooks, Cooks and Culinary Culture. UNSW Press; 2002

[185] Hickel J. The Divide: A Brief Guide to Global Inequality and its Solutions. Random House; 2017

[186] Hopkins AG, Bruchey SW. An Economic History of West Africa. Columbia University Press; 1973

[187] Josephson PR. Chicken: A History from Farmyard to Factory. Polity Press; 2020

[188] Patel R. Stuffed and Starved: The hidden Battle for the Food System. Brooklyn: Melville House Publishing; 2007

[189] Laudan R. Cuisine and Empire: Cooking in World History. University of California Press; 2015

[190] Leyton G. Effects of slow starvation. Lancet. 1946:73-79

[191] Osmani SR. Nutrition and Poverty. Oxford University Press; 1992

[192] Perlmutter D. Grain Brain: The Surprising Truth about Wheat, Carbs, and Sugar--Your Brain's Silent Killers. Hachette UK; 2018

[193] McGrayne SB. Prometheans in the Lab: Chemistry and the Making of the Modern World. McGraw-Hill; 2001

[194] Phillips K. An Ethnography of Hunger: Politics, Subsistence, and the Unpredictable Grace of the Sun. Indiana University Press; 2018

[195] Washington HA. A Terrible Thing to Waste: Environmental Racism and Its Assault on the American Mind. Little, Brown; 2019

[196] Scrinis G. Nutritionism: The Science and Politics of Dietary Advice. Columbia University Press; 2013

[197] Bittman M. Animal, Vegetable, Junk: A History of Food, from Sustainable to Suicidal. Houghton Mifflin Harcourt; 2021

[198] Jou C. Supersizing Urban America: How Inner Cities Got Fast Food with Government Help. University of Chicago Press; 2017

[199] Hogarth RA. Medicalizing Blackness: Making Racial Difference in the Atlantic World, 1780-1840. University of North Carolina Press; 2017

[200] Haagh L. The Case for Universal Basic Income. Polity Press; 2019

[201] Van Parijs P, Vanderborght Y. Basic Income: A Radical Proposal for a Free Society and a Sane Economy. Harvard University Press; 2017

[202] Aiken W, LaFollette H. World Hunger and Morality. Prentice Hall; 1996

[203] Seligman MEP. Flourish: A Visionary New Understanding of Happiness and Well-being. Atria Books; 2012

[204] Singer P. Practical Ethics. Cambridge University Press; 2011

[205] Unger PK, Press OU. Living High and Letting Die: Our Illusion of Innocence. Oxford University Press; 1996

[206] Singh N et al. Activation of Gpr109a, receptor for niacin and the commensal metabolite butyrate, suppresses colonic inflammation and carcinogenesis. Immunity. 2014;**40**(1):128-139

[207] Macia L et al. Metabolite-sensing receptors GPR43 and GPR109A facilitate dietary fibre-induced gut homeostasis through regulation of the inflammasome. Nature Communications. 2015;**6**(1):1-15

[208] Tan J et al. Dietary fiber and bacterial SCFA enhance oral tolerance and protect against food allergy through diverse cellular pathways. Cell Reports. 2016;**15**(12):2809-2824

[209] Langley MR et al. Critical role of astrocyte NAD+ glycohydrolase in myelin injury and regeneration. Journal of Neuroscience. 2021;**41**(41):8644-8667

[210] McCabe H. John Stuart Mill, Socialist. McGill-Queen's University Press; 2021

[211] Offer A, Offer REHA. The First World War: An Agrarian Interpretation. Clarendon Press; 1989

[212] Gerhard G. Nazi Hunger Politics: A History of Food in the Third Reich. Rowman & Littlefield Publishers; 2015

[213] Forrest AI. The French Revolution and the Poor. B. Blackwell; 1981

[214] Hufton OH. The Poor of Eighteenth-century France 1750-1789. Clarendon Press; 1974

[215] McMeekin S. The Russian Origins of the First World War. Harvard University Press; 2013

[216] Buettner D. The Blue Zones Solution: Eating and Living Like the World's Healthiest People. National Geographic; 2015

[217] Harding J. Border Vigils: Keeping Migrants Out of the Rich World. Verso Books; 2012

[218] Soss J et al. Disciplining the Poor: Neoliberal Paternalism and the Persistent Power of Race. University of Chicago Press; 2011

[219] Linebaugh P. Stop, Thief!: The Commons, Enclosures, and Resistance. PM Press; 2014

[220] Bowles S et al. Poverty Traps. Princeton University Press; 2011

[221] Hobsbawm EJ, Wrigley C. Industry and Empire: From 1750 to the Present Day. The New Press; 1999

[222] Wolf S, Bonanno A. The neoliberal regime in the agri-food sector. Crisis, resilience. 2014

[223] Emmanuel A et al. Unequal Exchange: A Study of the Imperialism of Trade. Monthly Review Press; 1969

[224] Conquest R. The Harvest of Sorrow: Soviet Collectivisation and the Terror-Famine. Random House; 2018

[225] Conradi P. Who Lost Russia?: How the World Entered a New Cold War. Oneworld Publications; 2018

[226] Ziegelman J, Coe A. A Square Meal: A Culinary History of the Great Depression. HarperCollins; 2016

[227] Stevenson J, Cook C. The Slump: Britain in the Great Depression. Taylor & Francis; 2013

[228] Goodwyn L. Democratic Promise: The Populist Moment in America. Oxford University Press; 1976

[229] Leonard C. The Meat Racket: The Secret Takeover of America's Food Business. Simon & Schuster; 2014

[230] Lynn BC. Liberty from All Masters: The New American Autocracy vs. the Will of the People. St. Martin's Publishing Group; 2020

[231] Teachout Z, Sanders B. Break 'Em Up: Recovering Our Freedom from Big Ag, Big Tech, and Big Money. St. Martin's Publishing Group; 2020

[232] Barrett CB, Maxwell D. Food Aid After Fifty Years: Recasting its Role. Taylor & Francis; 2007

[233] Hayter T. Aid as imperialism. 1971

[234] Jun F et al. China's Agriculture and Rural Development in the Post-reform Era. ACA Publishing Limited; 2017

[235] Moskoff W. Perestroika in the Countryside: Agricultural Reform in the Gorbachev Era. Taylor & Francis; 2019

[236] Zadek S. The Civil Corporation. Earthscan; 2007

[237] Buller A. The Value of a Whale: On the Illusions of Green Capitalism. Manchester University Press; 2022

[238] Henderson R. Reimagining Capitalism in a World on Fire: Shortlisted for the FT & McKinsey Business Book of the Year Award 2020. Penguin Books Limited; 2021

[239] Mackey J et al. Conscious Capitalism, With a New Preface by the Authors:

Liberating the Heroic Spirit of Business. Harvard Business Review Press; 2014

[240] Esping-Andersen G. The Three Worlds of Welfare Capitalism. Princeton University Press; 1990

[241] Chhibber A, Soz SA. Unshackling India: Hard Truths and Clear Choices for Economic Revival. HarperCollins; 2021

[242] Tcherneva PR. The Case for a Job Guarantee. Polity Press; 2020

[243] Pistor K. The Code of Capital: How the Law Creates Wealth and Inequality. Princeton University Press; 2020

[244] Stoknes PE, Hawken P. Tomorrow's Economy: A Guide to Creating Healthy Green Growth. MIT Press; 2022

[245] Hawken P et al. Natural Capitalism. Little, Brown; 2007

[246] Moore JW. Capitalism in the Web of Life: Ecology and the Accumulation of Capital. Verso Books; 2015

[247] Handfield RB, Linton TK. Flow: How the Best Supply Chains Thrive. University of Toronto Press; 2022

[248] Robin V. Blessing the Hands that Feed Us: What Eating Closer to Home Can Teach Us about Food, Community, and Our Place on Earth. Thorndike Press; 2014

[249] Lent J. The Web of Meaning: Integrating Science and Traditional Wisdom to Find Our Place in the Universe. Profile; 2021

[250] Yunkaporta T. Sand Talk: How Indigenous Thinking Can Save the World. Text Publishing Company; 2019

[251] Howard PH. Concentration and Power in the Food System: Who Controls What We Eat? Revised ed. Bloomsbury Publishing; 2021

[252] Saladino D. Eating to Extinction: The World's Rarest Foods and Why We Need to Save Them. Random House; 2021

[253] Lobao LM. Locality and Inequality: Farm and Industry Structure and Socioeconomic Conditions. State University of New York Press; 1990

[254] Dixon JA et al. Farming Systems and Poverty: Improving Farmers' Livelihoods in a Changing World. FAO; 2001

[255] Shepard M. Restoration Agriculture: Real-world Permaculture for Farmers. Acres U.S.A.; 2013

[256] De Luna KM. Collecting Food, Cultivating People: Subsistence and Society in Central Africa. Yale University Press; 2016

[257] Antle JM, Ray S. Sustainable Agricultural Development: An Economic Perspective. Springer International Publishing; 2020

[258] Shaw HJ, Shaw JJA. Corporate Social Responsibility, Social Justice and the Global Food Supply Chain: Towards an Ethical Food Policy for Sustainable Supermarkets. Taylor & Francis; 2019

[259] Zhou ZY. Global Food Security: What Matters? Taylor & Francis; 2019

[260] Walia SS, Walia US. Farming System and Sustainable Agriculture. Scientific Publishers; 2020

[261] Yao S. Agricultural Reforms and Grain Production in China. Palgrave Macmillan UK; 2016

[262] Wolf SA, Bonanno A. The Neoliberal Regime in the Agri-Food Sector: Crisis, Resilience, and Restructuring. Taylor & Francis; 2013

[263] Rosin C et al. Food Systems Failure: The Global Food Crisis and the Future of Agriculture. Taylor & Francis; 2013

[264] Plague HJ. Population and the English Economy 1348-1530. Macmillan; 1977

[265] Cole DH, Ostrom E. Property in Land and Other Resources. Lincoln Institute of Land Policy; 2012

[266] Escribano AJ et al. Instant Insights: Integrated Crop-Livestock Systems. Burleigh Dodds Science Publishing Limited; 2021

[267] Dixon J et al. Farming Systems and Food Security in Africa: Priorities for Science and Policy Under Global Change. Taylor & Francis Limited; 2021

[268] Judge K. Direct: The Rise of the Middleman Economy and the Power of Going to the Source. HarperCollins; 2022

[269] Fiennes J. Land Healer: How Farming Can Save Britain's Countryside. Ebury Publishing; 2022

[270] Kassam A et al. Successful Experiences and Lessons from Conservation Agriculture Worldwide. Agronomy. 2022;**12**(4):769

[271] Kassam A, Kassam L. Rethinking Food and Agriculture: New Ways Forward. Elsevier Science; 2020

[272] Rooted SL. Stories of Life, Land and a Farming revolution. Viking; 2022. 368 p

[273] Hong TK et al. Current issues and technical advances in cultured meat production: A review. Food Science of Animal Resources. 2021;**41**(3):355-372

[274] Canning D et al. Africa's Demographic Transition: Dividend or Disaster? World Bank Publications; 2015

[275] Goodhart C, Pradhan M. The Great Demographic Reversal: Ageing Societies, Waning Inequality, and an Inflation Revival. Springer International Publishing; 2020

[276] Harrison M. Contagion: How Commerce Has Spread Disease. Yale University Press; 2013

[277] Paice E. Youthquake: Why African Demography Should Matter to the World. Head of Zeus; 2021

[278] de Wit MM. Abolitionist Agroecology, Food Sovereignty and Pandemic Prevention. Daraja Press; 2021

[279] Will RG et al. A new variant of Creutzfeldt-Jakob disease in the UK. The Lancet. 1996;**347**(9006):921-925

[280] Ritchie DL et al. Variant CJD: Reflections a Quarter of a Century on. Pathogens. 2021;**10**(11):1413

[281] Sinclair U. The Jungle. OUP Oxford; 2010

[282] Greger M. How to Survive a Pandemic. Pan Macmillan; 2020

[283] Davis M. The Monster at Our Door: The Global Threat of Avian Flu. Henry Holt and Company; 2006

[284] Specht J. Red Meat Republic. Princeton University Press; 2019

[285] Ogle M. In Meat We Trust: An Unexpected History of Carnivore America. Houghton Mifflin Harcourt; 2013

[286] Lien ME. Becoming Salmon: Aquaculture and the Domestication of a Fish. University of California Press; 2015

[287] Stead V, Hinkson M. Beyond Global Food Supply Chains: Crisis, Disruption,

Regeneration. Springer Nature Singapore; 2022

[288] Gliessman SR. Agroecology: The Ecology of Sustainable Food Systems. 3rd ed. CRC Press; 2014

[289] Green T. The Covid Consensus: The New Politics of Global Inequality. Hurst Publishers; 2021

[290] Tooze A. Shutdown: How Covid Shook the World's Economy. Penguin Books Limited; 2021

[291] Andiman WA. Animals Viruses and Humans, A Narrow Divide: How Lethal Zoonotic Viruses Spill Over and Threaten Us. Paul Dry Books; 2018

[292] Honigsbaum M. The Pandemic Century: A History of Global Contagion from the Spanish Flu to Covid-19. Ebury Publishing; 2020

[293] Thomas M, Green P. The return of cosmopolitan capital: Globalization, the state and war. Historical Materialism. 2006;**14**(4):203-232

[294] Coulson M. The History of Mining: The Events, Technology and People Involved in the Industry that Forged the Modern World. Harriman House; 2012

[295] Pitron G, Jacobsohn B. The Rare Metals War: The Dark Side of Clean Energy and Digital Technologies. Scribe Publications Pty Limited; 2020

[296] Baldwin R. The Great Convergence: Information Technology and the New Globalization. Harvard University Press; 2016

[297] Williams AC, Hill LJ. Inequality: The dangers of meat haves and have-nots in a nicotinamide-adenine-dinucleotide world. Meat and Nutrition. 2021;**3**

[298] Levine S. School Lunch Politics. Princeton University Press; 2011

[299] Robertson C. The Time-Travelling Economist: Why Education, Electricity and Fertility Are Key to Escaping Poverty. Springer International Publishing; 2022

[300] Hyde L. The Gift: Imagination and the Erotic Life of Property. Vintage; 1999

[301] Brand U, Wissen M. The Imperial Mode of Living: Everyday Life and the Ecological Crisis of Capitalism. Verso Books; 2021

[302] Evans H. Good Times, Bad Times. BSB Publishers; 2013

[303] Bregman R. Utopia for Realists: How We Can Build the Ideal World. Little, Brown; 2018

[304] Standing G. The Blue Commons: Rescuing the Economy of the Sea. Penguin Books Limited; 2022

[305] Burnard T. Planters, Merchants, and Slaves: Plantation Societies in British America, 1650-1820. University of Chicago Press; 2015

[306] Chancel L, DeBevoise M. Unsustainable Inequalities: Social Justice and the Environment. Harvard University Press; 2020

[307] Health MC. Food and Social Inequality: Critical Perspectives on the Supply and Marketing of Food. Taylor & Francis; 2015

[308] Patterson O. Slavery and Social Death: A Comparative Study, With a New Preface. Harvard University Press; 2018

[309] Philcox R et al. The Wretched of the Earth. Grove Press; 2004

[310] Winchester S. Land: How the Hunger for Ownership Shaped the Modern World. HarperCollins Publishers; 2021

[311] Winchester S. Land: The Ownership of Everywhere. HarperCollins Publishers Limited; 2021

[312] Borgstrom G. The Hungry Planet: The Modern World at the Edge of Famine. Macmillan; 1972

[313] George S. Feeding the few: Corporate Control of Food. Washington DC: Institute for Policy Studies; 1979

[314] Hayter T, First TW. The Creation of World Poverty. Pluto; 1981

[315] Patel P. The Tyranny of Nations: How the Last 500 Years Shaped Today's Global Economy. Bifocal; 2021

[316] Stuckler D, Siegel K. Sick Societies: Responding to the Global Challenge of Chronic Disease. OUP Oxford; 2011

[317] Salzberger RP et al. Reparations for Slavery: A Reader. Rowman & Littlefield Publishers; 2004

[318] Darity WA, Mullen AK. From Here to Equality: Reparations for Black Americans in the Twenty-First Century. University of North Carolina Press; 2020

[319] Herman A. Restitution: The Return of Cultural Artefacts. Lund Humphries Publishers, Limited; 2021

[320] MacMillan M. Paris 1919: Six Months that Changed the World. Random House. p. 2007

[321] Snyder T. Black Earth: The Holocaust as History and Warning. Random House; 2015

[322] Adhikari M. Genocide on Settler Frontiers: When Hunter-Gatherers and Commercial Stock Farmers Clash. Berghahn Books; 2015

[323] Naimark NM. Genocide: A World History. Oxford University Press; 2017

[324] Kiernan B. Blood and Soil: A World History of Genocide and Extermination from Sparta to Darfur. Yale University Press; 2008

[325] Hancock G. Lords of Poverty: The Power, Prestige, and Corruption of the International Aid Business. Atlantic Monthly Press; 1989

[326] Keen D. The Benefits of Famine: A Political Economy of Famine and Relief in Southwestern Sudan, 1983-1989. James Currey Publishers. p. 2008

[327] Goldin I. Development: A Very Short Introduction. Oxford University Press; 2018

[328] Dercon S. Gambling on Development. Hurst Publishers; 2022

[329] Adorno TW, Hoban W. Aspects of the New Right-Wing Extremism. Wiley; 2020

[330] Rifkin J. The Age of Resilience: Reimagining Existence on a Rewilding Earth. St. Martin's Publishing Group; 2022

[331] Slaughter AM. The Chessboard and the Web: Strategies of Connection in a Networked World. Yale University Press; 2017

[332] Zheng Y, Qian J. Development and Poverty Reduction: A Global Comparative Perspective. Taylor & Francis; 2019

[333] Faloyin D. Africa Is Not A Country: Breaking Stereotypes of Modern Africa. Random House; 2022

[334] Taiwo O. Against Decolonisation: Taking African Agency Seriously. C Hurst & Company Publishers Limited; 2022

[335] Goldin I. Rescue: From Global Crisis to a Better World. Hodder & Stoughton; 2021

[336] Shapiro BJ. A Culture of Fact: England, 1550-1720. Cornell University Press; 2000

[337] Pardo RP. Shrimp to Whale: South Korea from the Forgotten War to K-Pop. Hurst Publishers; 2022

[338] Ball W. The Gates of Europe: The Eurasian Steppe and Europe's Border. East & West Pub.; 2015

[339] Allen LH, Dror DK. Effects of animal source foods, with emphasis on milk, in the diet of children in low-income countries. Milk and Milk Products in Human Nutrition. 2011;**67**:113-130

[340] Bhutta ZA et al. Evidence-based interventions for improvement of maternal and child nutrition: What can be done and at what cost? The Lancet. 2013;**382**(9890):452-477

[341] Black RE et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. The Lancet. 2013;**382**(9890):427-451

[342] De Beer H. Dairy products and physical stature: A systematic review and meta-analysis of controlled trials. Economics & Human Biology. 2012;**10**(3):299-309

[343] Fredriks AM et al. Continuing positive secular growth change in The Netherlands 1955-1997. Pediatric Research. 2000;**47**(3):316-323

[344] Galler JR et al. The influence of early malnutrition on subsequent behavioral development: II. Classroom behavior. Journal of the American Academy of Child Psychiatry. 1983;**22**(1):16-22

[345] Golden M. Trace elements in human nutrition. Human Nutrition Clinical Nutrition. 1982;**36**(3):185-202

[346] Grantham-McGregor SM, Cumper G. Jamaican studies in nutrition and child development, and their implications for national development. Proceedings of the Nutrition Society. 1992;**51**(1):71-79

[347] Grillenberger M et al. Food supplements have a positive impact on weight gain and the addition of animal source foods increases lean body mass of Kenyan schoolchildren. The Journal of Nutrition. 2003;**133**(11):3957S-3964S

[348] Hulett JL et al. Animal source foods have a positive impact on the primary school test scores of Kenyan schoolchildren in a cluster-randomised, controlled feeding intervention trial. British Journal of Nutrition. 2014;**111**(5):875-886

[349] Levitsky DA, Strupp BJ. Malnutrition and the brain: Changing concepts, changing concerns. The Journal of Nutrition. 1995;**125**(suppl_8):2212S-2220S

[350] Neisser U, Association AP. The Rising Curve: Long-term Gains in IQ and Related Measures. American Psychological Association; 1998

[351] Pollitt E et al. Nutrition in early life and the fulfillment of intellectual potential. The Journal of Nutrition. 1995;**125**(suppl_4):1111S-1118S

[352] Scotland GBDoHf et al. Milk Consumption and the Growth of School Children: Report on an Investigation in

Lanarkshire Schools. H.M. Stationery Office; 1930

[353] Winick M. Nutrition: Pre- and Postnatal Development. Springer US; 2012

[354] Bregman R. Utopia for Realists: And How We Can Get There. Bloomsbury Publishing Plc; 2018

[355] Coote A, Percy A. The Case for Universal Basic Services. Polity Press; 2020

[356] Fan S. Public Expenditures, Growth, and Poverty: Lessons from Developing Countries. International Food Policy Research Institute; 2008

[357] Lawrence M, Buller A. Owning the Future: Power and Property in an Age of Crisis. Verso Books; 2022

[358] Vinen R. Second City: Birmingham and the Forging of Modern Britain. Penguin Books Limited; 2022

[359] Stromquist S. Claiming the City: A Global History of Workers' Fight for Municipal Socialism. Verso Books; 2023

[360] Thompson H. Disorder: Hard Times in the 21st Century. Oxford University Press; 2022

[361] Silver N. Finance, Society and Sustainability: How to Make the Financial System Work for the Economy, People and Planet. Palgrave Macmillan UK; 2017

[362] Soper K. Post-Growth Living: For an Alternative Hedonism. Verso Books; 2020

[363] Delgado CL et al. Determinants and Implications of the Growing Scale of Livestock Farms in Four Fast-growing Developing Countries. International Food Policy Research Institute; 2008

[364] Fan S. Halving Hunger: Meeting the First Millennium Development Goal through" Business as Unusual". Intl Food Policy Res Inst; 2010

[365] Fanzo J et al. Diversifying Food and Diets: Using Agricultural Biodiversity to Improve Nutrition and Health. Taylor & Francis; 2013

[366] Mellor JW. Agricultural Development and Economic Transformation: Promoting Growth with Poverty Reduction. Springer; 2017

[367] Ohlson K. The Soil Will Save Us: How Scientists, Farmers, and Foodies Are Healing the Soil to Save the Planet. Rodale Books; 2014

[368] Perfecto I et al. Nature's Matrix: Linking Agriculture, Conservation and Food Sovereignty. Earthscan; 2009

[369] Sánchez PA et al. Halving Hunger: It Can be Done. Earthscan; 2005

[370] Vogler P. Scoff: A History of Food and Class in Britain. Atlantic Books; 2020

[371] Rawlence B. The Treeline: The Last Forest and the Future of Life on Earth. Random House; 2022

[372] Buscher B, Fletcher R. The Conservation Revolution: Radical Ideas for Saving Nature Beyond the Anthropocene. Verso Books; 2020

[373] Foster JB. The Return of Nature: Socialism and Ecology. Monthly Review Press; 2020

[374] Mardon A et al. Antibiotic Resistance: An Emerging Pandemic. Golden Meteorite Press; 2021

[375] Blaikie P, Brookfield H. Land Degradation and Society. Taylor & Francis; 2015

[376] Forsyth F. The Biafra Story: The Making of an African Legend. Pen & Sword Books; 2015

[377] Heerten L. The Biafran War and Postcolonial Humanitarianism: Spectacles of Suffering. Cambridge University Press; 2017

[378] Ignatieff M. Human Rights as Politics and Idolatry. Human Rights as Politics and Idolatry. Princeton University Press; 2011

[379] Wright W, Middendorf G. The Fight Over Food: Producers, Consumers, and Activists Challenge the Global Food System. Penn State Press; 2010

[380] Dunbar RI. The social brain hypothesis and its implications for social evolution. Annals of Human Biology. 2009;**36**(5):562-572

[381] Boltanski L et al. Distant Suffering: Morality, Media and Politics. Cambridge University Press; 1999

[382] Marmot M. The Health Gap: The Challenge of an Unequal World. Bloomsbury Publishing; 2015

[383] Chellaney B. Water, Peace, and War: Confronting the Global Water Crisis. Oxford University Press; 2014

[384] Sitwell W. Eggs or Anarchy: The Remarkable Story of the Man Tasked with the Impossible: To Feed a Nation at War. Simon & Schuster UK; 2016

[385] Hennessy P. A Duty of Care: Britain Before and After Covid. Penguin Books Limited; 2022

[386] Herbert B. Losing Our Way: An Intimate Portrait of a Troubled America. Knopf Doubleday Publishing Group; 2015

[387] Winders W, Scott JC. The Politics of Food Supply: U.S. Agricultural Policy in the World Economy. Yale University Press; 2012

[388] Narula H. Virtual Society: The Metaverse and the New Frontiers of Human Experience. Penguin Books Limited; 2022

[389] Lobel O. The Equality Machine: Harnessing Digital Technology for a Brighter, More Inclusive Future. PublicAffairs; 2022

[390] Harden KP. The Genetic Lottery: Why DNA Matters for Social Equality. Princeton University Press; 2021

[391] Blythman J. Bad Food Britain: [How a Nation Ruined Its Appetite]. Fourth Estate London; 2006

[392] Okun AM. Equality and Efficiency: The Big Tradeoff. Brookings Institution Press; 2015

[393] McKendrick N, Plumb JH. The Birth of a Consumer Society: The Commercialization of Eighteenth-Century England. Edward Everett Root; 2018

[394] Atkinson AB. Inequality. Harvard University Press; 2015

[395] Dorling D, Dorling D. Injustice: Why Social Inequality Still Persists. Policy Press; 2015

[396] Wilkinson R, Pickett K. The Spirit Level: Why Equality is Better for Everyone. Penguin Books Limited; 2010

[397] Wilkinson RG. Poverty and Progress: An Ecological Model of Economic Development. Methuen; 1973

[398] Parr T et al. Active Inference: The Free Energy Principle in Mind, Brain, and Behavior. MIT Press; 2022

[399] Rauch J. The Constitution of Knowledge: A Defense of Truth. Brookings Institution Press; 2021

[400] Shea N, Frith CD. The global workspace needs metacognition. Trends in Cognitive Sciences. 2019;**23**(7):560-571

[401] Sternberg RJ. Adaptive Intelligence: Surviving and Thriving in Times of Uncertainty. Cambridge University Press; 2021

[402] Van Schaik CP et al. Explaining brain size variation: From social to cultural brain. Trends in Cognitive Sciences. 2012;**16**(5):277-284

[403] Verschelden C, Pasquerella L. Bandwidth Recovery: Helping Students Reclaim Cognitive Resources Lost to Poverty, Racism, and Social Marginalization. Stylus Publishing; 2017

[404] Ward A. The Social Lives of Animals. Basic Books; 2022

[405] Warren WJ. Meat Makes People Powerful: A Global History of the Modern Era. University of Iowa Press; 2018

[406] Haskel J, Westlake S. Restarting the Future: How to Fix the Intangible Economy. Princeton University Press; 2022

[407] Outram AK, Bogaard A. Subsistence and Society in Prehistory: New Directions in Economic Archaeology. Cambridge University Press; 2019

[408] Poole S. You Aren't What You Eat: Fed Up with Gastroculture. Aurum Press; 2012

[409] Gabaccia DR, Gabaccia DR. We Are What We Eat: Ethnic Food and the Making of Americans. Harvard University Press; 2009

[410] Baughan E. Saving the Children: Humanitarianism, Internationalism, and Empire. University of California Press; 2021

[411] Tallis R. Aping Mankind. Routledge; 2016

[412] Rogan T. The Moral Economists: R. H. Tawney, Karl Polanyi, E. P. Thompson, and the Critique of Capitalism. Princeton University Press; 2019

[413] Cordain L. The Paleo Diet: Lose Weight and Get Healthy by Eating the Foods You Were Designed to Eat. Wiley; 2010

[414] Hinman RB, Harris RB. The Story of Meat. Swift; 1942

[415] Marcus E. Meat Market: Animals, Ethics, & Money. Brio Press; 2005

[416] Rimas A, Fraser E. Beef: The Untold Story of How Milk, Meat, and Muscle Shaped the World. HarperCollins; 2009

[417] Sykes N. Beastly Questions: Animal Answers to Archaeological Issues. Bloomsbury Publishing; 2014

[418] Weis T. The Ecological Hoofprint: The Global Burden of Industrial Livestock. Bloomsbury Publishing; 2013

[419] Winders B, Ransom E. Global Meat: Social and Environmental Consequences of the Expanding Meat Industry. MIT Press; 2019

[420] Zaraska M. Meathooked: The History and Science of Our 2.5-Million-Year Obsession with Meat. Basic Books; 2016

[421] Alverà M. The Hydrogen Revolution: A Blueprint for the Future of Clean Energy. Hachette UK; 2021

[422] George S. Another World Is Possible If. Verso Books; 2004

[423] Morland P. Tomorrow's People: The Future of Humanity in Ten Numbers. Pan Macmillan; 2022

[424] Edkins J. Whose Hunger?: Concepts of Famine, Practices of Aid. University of Minnesota Press; 2000

[425] George H. Progress and Poverty: An Inquiry Into the Cause of Industrial Depressions, and of Increase of Want with Increase of Wealth—the Remedy. Kegan Paul, Trench; 1883

[426] Nordman E. The Uncommon Knowledge of Elinor Ostrom: Essential Lessons for Collective Action. Island Press; 2021

[427] Nilakantan RS. South vs North: India's Great Divide. Juggernaut Publication; 2002. p. 280

[428] Cobb M. The Genetic Age: Our Perilous Quest To Edit Life. Profile; 2022

[429] Baylis F. Altered Inheritance: CRISPR and the Ethics of Human Genome Editing. Harvard University Press; 2019

[430] Metzl J. Hacking Darwin: Genetic Engineering and the Future of Humanity. Sourcebooks; 2019

[431] Church GM, Regis E. Regenesis: How Synthetic Biology Will Reinvent Nature and Ourselves. Basic Books; 2014

[432] Turkheimer E et al. Socioeconomic status modifies heritability of IQ in young children. Psychological Science. 2003;**14**(6):623-628

[433] Ferguson N. The Square and the Tower: Networks, Hierarchies and the Struggle for Global Power. Penguin Books Limited; 2017

[434] Foroohar R. Homecoming: The Path to Prosperity in a Post-Global World. Crown; 2022

[435] Stoller M. Goliath: The 100-Year War Between Monopoly Power and Democracy. Simon & Schuster; 2020

[436] Edwards J. The Great Fox Illusion. Walker Books Limited; 2022

[437] Siddons AR. Fault Lines. HarperCollins; 1996

[438] Pilger J. Freedom Next Time. Transworld; 2011

[439] Pim K. Endless Flight: The Life of Joseph Roth. Granta Books; 2022

[440] Gordon LR. Fear of Black Consciousness. Penguin Books Limited; 2022

[441] Rushkoff D. Survival of the richest. Medium. 2018;(July):5

[442] Malik K. The Meaning of Race: Race, History and Culture in Western Society. Macmillan Education UK; 1996

[443] Mansbridge JJ. Beyond Self-Interest. University of Chicago Press; 1990

[444] Warren S. Survival of the Richest. Book Beautiful; 2018

[445] DeLong JB. Slouching towards Utopia: An Economic History of the Twentieth Century. Basic Books; 2022

[446] Thackray A. Private Science: Biotechnology and the Rise of the Molecular Sciences. University of Pennsylvania Press; 1998

[447] Preston SD. The Altruistic Urge: Why We're Driven to Help Others. Columbia University Press; 2022

[448] McAfee A. More From Less: The Surprising Story of How We Learned to Prosper Using Fewer Resources—and What Happens Next. Simon & Schuster UK; 2019

[449] Appiah KA. The Honor Code: How Moral Revolutions Happen. W.W. Norton; 2011

[450] Putnam RD. Our Kids: The American Dream in Crisis. Simon & Schuster; 2016

[451] Mounk Y. The Great Experiment: How to Make Diverse Democracies Work. Bloomsbury Publishing Plc; 2022

[452] Klinenberg E. Palaces for the People: How To Build a More Equal and United Society. Random House; 2018

[453] Belich J. The World the Plague Made: The Black Death and the Rise of Europe. Princeton University Press; 2022

[454] Koram K. Uncommon Wealth: Britain and the Aftermath of Empire. John Murray Press; 2022

[455] Easterly W. The Tyranny of Experts: Economists, Dictators, and the Forgotten Rights of the Poor. Basic Books; 2014

[456] Coates TN. Between the World and Me. Text Publishing Company; 2015

[457] Malik K. Not So Black and White: A History of Race from White Supremacy to Identity Politics. Hurst Publishers; 2023

[458] Rich D. Everyday Hate How antisemitism is built into our world – and how you can change it. 2023

[459] Rosenberg AS. Undesirable Immigrants: Why Racism Persists in International Migration. Princeton University Press; 2022

Section 3

Vitamin E and Its Medicinal Values

Chapter 5

Medicinal Significance and Complications of Vitamin E

Naresh Podila, Sathish Kumar Konidala, Jithendra Chimakurthy, Srilatha Muddisetti, Suryaprabha Matangi, Natesh Gunturu, Yamarthi Venkateswara Rao and Mithun Rudrapal

Abstract

Vitamin E is a lipid-soluble substance that is the main component of the body's defense system against free radicals. It performs a range of important functions in the body as a result of its antioxidant action. Cancer, aging, and other diseases and ailments have all been related to oxidation. It has been shown that vitamin E protects against rheumatoid arthritis and cataracts. Additionally, vitamin E can help to prevent the production of prostaglandins like thromboxane, which encourage platelet clustering and hyper aggregation, which can lead to atherosclerosis. The present literature review examines the roles and functions of vitamin E in human health, different disorders, and the consequences of vitamin E deficiency. The tocopherol family of vitamers is the focus of the review's main points. In this review article, the part and actions of vitamin E are talked about, as well as the things that affect how well vitamin E treatment works. When given at the right time and for the right amount of time, Vitamin E should help people with oxidative stress caused by free radicals.

Keywords: vitamin E, health, antioxidants, tocopherols, free radicals

1. Introduction

A vitamin that dissolves in fat is vitamin E. Cereals, vegetable oils, meat, chicken, eggs, and fruits are just a few examples of the many meals that contain it. An essential vitamin, vitamin E is needed for the healthy operation of numerous organs in the body. As an antioxidant, it is also. RRR-alpha-tocopherol, a form of vitamin E that naturally occurs in foods, differs from the synthetic Supplemental vitamin E is available as all-rac-alpha tocopherol [1]. When patients have certain hereditary abnormalities or premature infants who were born very low in weight, vitamin E is used to treat vitamin E insufficiency, a condition that is uncommon but can occur. There is other more ailments for which vitamin E is utilized, however many of these other uses lack solid scientific backing. The antioxidant vitamin E has the potential to shield the body's cells from harm. Antioxidants may offer defense against major

illnesses including cancer and heart disease. Additionally essential for the production of vitamin E and red blood cells also aids in the utilization of vitamin K [2].

The liver absorbs vitamin E once it is absorbed in the small intestine and stores it there until it is required. At that time, the liver only secretes alpha-tocopherol again, which the body can identify. Your immune system benefits from vitamin E, which also supports healthy skin, eyes, and brain function. Despite the rarity of vitamin E deficiency, maintaining health and preventing and treating disease depend on achieving daily vitamin E needs. Several circumstances can lead to vitamin E insufficiency. Premature infants with low birth weight are one example. It is also possible among those who have an illness that impairs the body's ability to effectively absorb dietary fat, such as Crohn's disease or cystic fibrosis. Both require supplementation to reduce the risk of complications [3].

Those who struggle to adequately absorb fats may become vitamin E deficient. Serious vitamin E deficiency symptoms include [4].

- Vision problems
- Muscle weakness
- muscle density loss
- Unsteady walking
- Abnormal eye movements

Continuing deficiencies may also result in issues with the liver and kidneys. Although the majority of Americans do not have severe vitamin E deficiencies, many may have slightly low amounts. Edible vegetable oils are the best sources of vitamin E in the diet because they have the highest concentrations of all the different homologs (**Table 1**) Red blood cells and serum contain alpha- and gamma-tocopherols, with alpha-tocopherol having the highest quantity [5]. Only trace amounts of beta- and delta-tocopherols can be found in plasma. The higher metabolism of the other forms of tocopherol and the α-tocopherol possess protein are the causes of

Oils	Alpha (α)-Tocopherol	G-Tocopherol	D-Tocopherol	A-Tocopherol
Coconut oil	1.6	—	1.0	1.1
Maize	10.5	59.3	0.9	—
Palm	24.8	30.9	6.9	13.5
Olive	5.3	Trace amounts	0	0
Peanut	12.8	20.8	2.5	0
Soybean	11.00	58.5	27.0	0
Wheat germ	130.9	25.7	26.8	2.4
Sunflower	46.9	5.5	1.0	0

Table 1.
Vegetable oils contain vitamin E.

alpha-preferential tocopherol distribution in humans (alpha-TTP). The reason why alpha-tocopherol is largely removed in the urine while the majority of the absorbed beta-, gamma, and delta-tocopherols are released into the bile and excreted in the feces, is because of the binding affinity of α-tocopherol with alpha-TTP. In non-hepatic tissues, such as the endoplasmic reticulum and mitochondrial membranes of the heart and lungs and other organs with high amounts of free radical production, the alpha-tocopherol form also accumulates [6].

Oxidative stress has been linked to the pathogenesis of a number of diseases, including atherosclerosis, fatty liver disease, cancer, and neurodegenerative disorders [7, 8]. Oxidation of biological molecules such as lipids, proteins, and DNA, mediated by reactive oxygen species (ROS) and free radicals, results in injury to biological membranes, modification of proteins, inactivation of enzymes, and modification of DNA, according to an abundance of experimental evidence. Therefore, the function of antioxidants against oxidative stress in disease prevention and treatment has received considerable attention from both scientists and the general public [9]. If oxidative stress plays a causal role, it is expected that antioxidants will reduce the risk or be beneficial in the prevention and treatment of these diseases.

Several 1980s epidemiological studies suggested the health benefits of antioxidants such as vitamin E and carotenoids. Cancer incidence is negatively associated with the ingestion of fresh fruits and green-yellow vegetables [10]. This is attributable, at least in part, to the numerous phytochemical compounds found in plant foods, the majority of which are powerful antioxidants [11]. The Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) study revealed an inverse association between plasma vitamin E concentration and mortality due to ischemic heart disease and malignancy. Several large cohort studies have supported the protective function of antioxidants with overwhelmingly positive findings. Antioxidant-containing dietary supplements are very popular among a sizable fraction of the population, as a result of the heightened enthusiasm.

Large-scale randomized clinical trials and meta-analyses, on the other hand, have shown disappointing and contradictory data about vitamin E's effects. Not only have there been a number of "null" results, but some studies have shown that taking a lot of vitamin E may be bad for you, which has caused a lot of debate [12–14].

This article talks about the roles and effects of vitamin E and uses the scientific data to answer the following questions. Are oxidative harm and diseases caused by free radicals? Does vitamin E stop damage caused by free radicals and diseases that come with it? Why do controlled, randomized human studies of vitamin E give mixed and disappointing results?

1.1 Chemistry of vitamin E

Vitamin E is not the same thing as tocopherol; rather, Tocopherol refers to tocol derivatives with a methyl substitution. The two homologous sets of natural tocochromanols are Unsaturated tocotrienols and tocopherols with saturated side chains are two types of tocopherols. (**Figure 1**) depicts the fundamental chemical structure of tocopherols and tocotrienols; it has two places on a 6-chromanol ring where a lengthy isoprenoid side chain is connected. In contrast to tocopherols, which have a saturated isoprenoid C16 side chain, tocotrienols have a farnesyl side chain. Natural tocopherols have the RRR-configuration, but all-racalpha-tocopherol, which is the synthesized version, has eight distinct stereoisomers. Natural tocotrienols only have the 2R, 3′E and 7′E structure, and tocotrienols only have the chiral stereo center at C-2 [7]. Chiral

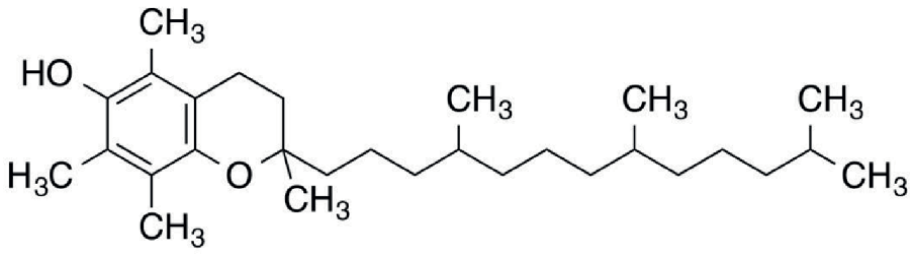

Figure 1.
Structure of tocopherol.

recognition is the process by which the enzymes and body's receptors solely communicate with the enantiomers of the one of chiral compounds. As a consequence, only one of the two enantiomers has the desired effect on the body, while the other two may either have no effect or a negative effect. E- Vitamin cannot be converted to one another within the human [15, 16].

1.2 Sources and recommended intakes

Various foods and oils contain vitamin E. Alpha-tocopherol is present in substantial quantities in vegetable oils, fortified cereals, green leafy vegetables, nuts, seeds.

food intake guidelines	amount of -tocopherol in each serving, in milligrams	Percent daily value
Spinach, raw, 1 cup	21.2	102
Almonds, dry roasted, 1 ounce	6.4	32.9
Kiwifruit, 1 medium	5.5	26.8
Hazelnuts, dry roasted, 1	4.1	23.1
Tomato, raw, 1 medium	2.72	14.2
Peanuts, dry roasted, 1 ounce	2.5	10
Spinach, boiled, ½ cup	1.6	9.8
Corn oil, 1 tablespoon	1.5	11
Broccoli, chopped, boiled, ½ cup	1.6	5.6
Sunflower oil,	1.0	6.1
Safflower oil,	3.8	24.5
Soybean oil,	0.9	5.4
Wheat germ oil, 1 tablespoon	0.9	4.1
Peanut butter, 2 tablespoons	1.0	3
Mango, sliced, ½ cup	0.5	2.5

Table 2.
Food that contain vitamin E found in some foods.

Age	RDA in mg (IU)	
	Females	**Males**
0 to 5 months	3.9 (2)	5 (7)
7 to 12 months	4 (9.5)	6. (6.2)
1 to 3 years	6 (10)	6 (7)
4 to 8 years		
9 to 13 years	11 (14.9)	7 (8.9)
>14 years	14 (45.8)	10 (15.2)
In pregnancy	16 (26.5)	16 (20.4)
If lacting	20 (26.7)	

Table 3.
Guidelines for intake of E vitamin.

(**Tables 1** and **2**) lists the top resources of vitamin E and their tocopherol quantity, and their percentage of daily values. The ideal supplementation number of mixed tocopherols is yet unknown, and no official recommendations has been established addressing the consumption of vitamin E. Vitamin E may not appear to be hazardous when only received from food sources. However, it has been discovered that supplements might cause pro-oxidant damage, but often only at high levels (for instance, >1000 mg/day) [17]. Listed below are the recommended daily amounts (RDAs) for vitamin E (alpha-tocopherol) (**Table 3**).

1.3 Dietary factors interaction

The breakdown of vitamin E is significantly influenced by selenium, glutathione, vitamin B3, and vitamin C. For a diet high in vitamin E to be successful, it must also contain foods that are high in these other nutrients. Beta-carotene and vitamin E have a potential cooperative connection, but vitamin C and beta-carotene have a very high likelihood of having one [3]. It has been discovered that the interactions between tocopherols, Thiols increase the potency of cellular antioxidant protection mechanisms [18]. Findings in the year of 2007 the study from the Women's Health manifestation that E vitamin and alpha-tocopherol supplementation lower the risk of dying from thromboembolism in healthy normal women [19]. Additionally, it was shown that vitamin E supplementation increased prothrombin's under-carboxylation in humans, which suggests that vitamin E lowers people's levels of vitamin K [20].

2. Vitamin E's functions

2.1 Controlling oxidative stress

The E Vitamin, a potent antioxidant that disrupts chemical bonds, stops the synthesis of reactive oxygen species molecules when fat is subjected to oxidation and during the spread of free radical reactions [21]. even though the phospholipid concentration level may only be one molecule for every 2000 of it, it is mostly found in the membranes of cells and organelles where it can exert its possessive impact.

To prevent lipid peroxidation, it serves as the first line of defense, shielding the cell membranes from oxidative damage. According to studies, alpha tocopherol alone is not as effective at inhibiting lipid peroxidation in human erythrocytes as a mixture of tocopherols is [22]. The polyunsaturated fatty acids found in membrane phospholipids and plasma lipoproteins are additionally safeguarded through its peroxyl radical scavenging action [23–25]. The resulting tocopheroxyl radicals can then go on to oxidize other lipids, go through extra oxidation to form tocopheryl quinones, combine with another radical to form non-reactive tocopherol dimers, or be reduced by additional antioxidants to tocopherol. It has been discovered that although gamma-tocopherol captures and neutralizes the free radicals already present, α-tocopherol primarily suppress the generation of anew free radicals. Numerous possible outcomes have been connected to oxidation, including illnesses and disorders, cataracts, cancer, aging, and cancer. As a result, E vitamin might aid in preventing or delaying the Reactive oxygen species molecules have been related to the emergence of chronic illnesses.

2.2 Evidence for in-vivo lipid peroxidation and its link to disease

Highly susceptible to oxidation are polyunsaturated fatty acids such as linoleic acid and arachidonic acid, as well as their esters. They are oxidized into numerous compounds, some of which are cytotoxic and reactive enough to modify proteins and DNA bases [26]. Enzymes, free radicals, and nonenzymatic, nonradical oxidants oxidize lipids. Frequently, lipoxygenase, cyclooxygenase, and cytochrome P450 induce oxidation in a regulated manner to produce specific physiologically essential products. In contrast, lipid peroxidation, which is oxidation mediated by free radicals, occurs arbitrarily and nonspecifically.

Free radicals attack proteins, DNA, and lipids without discrimination. Therefore, when free radicals are generated in vivo, as a result of high-energy irradiation or ischemia–reperfusion injury, the levels of oxidation products of proteins and DNA, as well as lipid peroxidation, are elevated. In addition, secondary lipid peroxidation products, such as unsaturated aldehydes, readily react with protein thiols, leading to the loss of protein function and cellular homeostasis. Among the lipid peroxidation products, hydroxy octadecadienoic acid (HODE) from linoleic acid and hydroxy eicosatetraenoic acid (HETE) and isoprostanes from arachidonic acid are frequently used as biomarkers of lipid peroxidation in vivo [27]. Vitamin E is a powerful radical-scavenging antioxidant that inhibits lipid peroxidation mediated by free radicals but not enzymatic oxidation by lipoxygenase and cyclooxygenase, as will be discussed in greater detail below. Both enzymatic and free radical oxidation produce HODE and HETE, but their isomer distribution depends on the type of oxidant. To evaluate the effects of vitamin E, it is crucial to understand the mechanisms and oxidants of lipid oxidation. The mechanisms of lipid oxidation have been thoroughly studied and are currently well understood [28, 29]. Trans, trans-forms of HODE and HETE have been shown to be specific products of lipid peroxidation mediated by free radicals.

Numerous studies have demonstrated that the levels of lipid peroxidation products, such as HODE, HETE, and isoprostanes, in biological fluids and tissues of diseased patients are generally, if not always, greater than those of healthy individuals. In addition, clinical research has established a connection between disease states and lipid peroxidation products.

2.2.1 Liver diseases

The importance of lipid peroxidation mediated by free radicals in liver injury induced by carbon tetrachloride and other halogenated alkanes has been investigated since the 1960s and documented in detail [30]. It was once thought that carbon tetrachloride affects the liver by the action of a simple solvent, but it is now understood that carbon tetrachloride must undergo metabolic activation to trichloromethyl radical by cytochrome P450, primarily by cytochrome P450 2E1, to exert its toxic effect [31]. The trichloromethyl radical reacts rapidly with oxygen to yield the trichloromethyl peroxyl radical, which attacks lipids and induces their peroxidation. Lipid peroxidation mediated by free radicals is involved in alcoholic liver disease caused by chronic alcohol ingestion [32, 33]. Plasma levels of several lipid oxidation products, including oxysterols and isoprostanes, have been shown to be elevated in alcoholic liver disease patients [34, 35].

Nonalcoholic fatty liver disease (NAFLD), a hepatic manifestation of metabolic syndrome, is now the most common liver disorder, affecting a high proportion of the global population. The incidence of NAFLD is increasing due to increases in the prevalence of two major risk factors, obesity, and type 2 diabetes, which are related to lifestyle and diet. The characteristic feature of NAFLD is an excessive accumulation of fat, notably triglyceride, in the liver, and it encompasses a wide spectrum from benign steatosis to nonalcoholic steatohepatitis (NASH), liver cirrhosis, liver failure, and hepatocellular carcinoma [36].

NAFLD and NASH are multifactorial diseases and oxidative stress has been implicated in their pathogenesis. Several human and animal studies have reported an association between NAFLD/NASH disease state and biomarkers of lipid peroxidation [37]. One such study reported that levels of 9- and 13-HODE, major products of linoleic acid peroxidation, were significantly elevated in patients with NASH compared to those with steatosis, and a strong correlation was observed between these oxidation products and liver histopathology such as inflammation, fibrosis, and steatosis [38]. These HODEs were racemic, suggesting them to be produced by free radical oxidation.

Numerous studies have reported a beneficial effect of vitamin E on NAFLD and NASH [39]. In one such study, the effects of vitamin E at a dose of 800 IU/day or placebo for 96 weeks were examined in adults with NASH and without diabetes; there was improvement in the histological features of NASH [40]. Another study reported measurable differences in the metabolic profile of subjects likely to respond to vitamin E treatment for NASH and those who experienced histological improvements following treatment [41]. In a recent retrospective study of the effects of 300 mg/day vitamin E for 2 or more years in patients with biopsy-proven NASH, vitamin E ameliorated NASH fibrosis, especially in those who showed improved transaminase activities and insulin resistance [42, 43].

2.2.2 Atherosclerosis

Atherosclerosis is a leading cause of cerebral infarction, myocardial infarction, coronary artery disease, and peripheral arterial disease. It is a chronic inflammatory disease characterized by excessive cholesterol deposition in the arterial wall and sluggish progression. It begins in childhood and remains asymptomatic for decades, but it is the primary cause of death in developed nations [44, 45]. It is generally recognized

that oxidative modification of low-density lipoprotein (LDL) is a crucial initial event in the development of atherosclerosis. Incubation of macrophages with oxidized LDL, but not with native LDL, results in accumulation of cholesteryl esters within the cell. Oxidation of low-density lipoprotein increases its pro-atherogenic effect, whereas oxidation of high-density lipoprotein decreases its anti-atherogenic effect [46, 47].

In the 1990s, extensive research was conducted on the oxidative modification of LDL, and its mechanisms and products were elucidated; however, the epitope responsible for recognition by macrophage scavenger receptors has not yet been identified. However, it has been demonstrated that macrophages take up oxidatively modified LDL, which is the first step in the formation of foam cells. LDL oxidation generates diverse byproducts. Cholesteryl esters and phosphatidylcholine (PC) are the predominant lipids in LDL particles of humans. The oxidation of linoleic acid and arachidonic acid esters of cholesterol and PC produces the corresponding hydroperoxides, hydroxides, and degradation products [48]. Plasma levels of lipid peroxidation products are higher in atherosclerotic patients than in healthy individuals. LDL isolated from diabetic patients has higher levels of HODE and HETE than LDL isolated from healthy subjects. In addition, the molecular ratios of HODE and HETE to the primary lipids (linoleates and arachidonates, respectively) are greater in diabetic LDL than in control LDL [49]. In addition, the levels of oxysterols such as 7-b-hydroxycholesterol, 7-ketocholesterol, and cholesterol-5,6-epoxide rise in the order normal artery fatty streak advanced lesion [50]. Moreover, hydroperoxide and hydroxide forms of cholesteryl linoleate are frequently found in human atherosclerotic plaque [51, 52].

The oxidative modification of LDL is mediated by multiple oxidants and distinct mechanisms, it should be noted. LDL is oxidized by both free radicals and nonradical oxidants, including lipoxygenases, cytochrome P450 enzymes, and hypochlorite. Singlet oxygen could also be a factor [53]. Importantly, various oxidants generate distinct oxidation products, necessitating the use of distinct antioxidants. No single antioxidant is capable of preventing all forms of oxidation.

2.3 Safeguarding the cell membranes

As a result of vitamin E's improved lipid packing orderliness, the membrane can be packed more tightly, which increases cell stability. Vitamin E was demonstrated to be essential for preserving the balance of skeletal muscle by Howard et al. in 2011. and that introducing alpha-tocopherol to cultured myocytes makes it easier to repair plasma membranes. This occurs because phospholipids in the membrane are frequently the target of oxidants, and vitamin E efficiently prevents lipid peroxidation. Contrarily, when cultivated cells are exposed to an oxidant assault without alpha-tocopherol supplementation, the repair is notably inhibited. Comparative measurements show that an antioxidant needs to join the membranes, like α-tocopherol does, or be able to regenerate α-tocopherol, to promote the repair [54]. As a result, vitamin E aids in membrane repair by reducing the oxidation of phospholipids, which might hypothetically obstruct membrane fusion processes.

2.4 Regulation of protein kinase c activation and platelet aggregation

It has been discovered that elevating alpha-tocopherol levels in endothelial cells prevents platelet aggregation and causes the endothelium to release prostacyclin. to reduce the components of blood cells' adherence to the endothelium, it was hypothesized that the vascular cell adhesion molecule and the intracellular cell adhesion

molecule (ICAM-1) (VCAM-1) were downregulated. Additionally, vitamin E-induced up regulation of the arachidonic acid cascade enzymes cytosolic phospholipase [55] cyclooxygenase-1 and A2 [56] leads to the generation of prostacyclin, a strong vasodilator that prevents platelet clumping in people [57]. Earlier studies advise that tocopherols may prevent protein kinase C (PKC) [58] and increase the activity of nitric oxide synthase [59] in order tocopherols may inhibit platelet aggregation.

When it comes to lowering PKC activity, alpha-tocopherol in its natural RRR version has been shown to be twice as effective as other all-racemic (synthetic) alpha-tocopherols [60]. This is caused by how alpha-attenuating tocopherols affect the synthesis of diacylglycerol, a lipid that makes PKC more mobile and thus activates it. The activity of protein phosphatase type 2A is also increased by alpha-tocopherol, while PKC autophosphorylation and subsequently its activity is decreased. Compared to mixed tocopherols, alpha-tocopherol is less efficient at preventing platelet aggregation. Gamma-tocopherol-enriched vitamin E (100 mg of gamma-tocopherol, 40 mg of delta-tocopherol, and 20 mg of alpha-tocopherol per day) significantly reduced adenosine diphosphate-induced platelet aggregation in healthy people, but not in those taking pure alpha-tocopherol alone. (100 mg per day) [61].

3. Preventing disease with vitamin E

Due to its role as an antioxidant, its contribution to the reduction of inflammation, due to its immune-stimulating properties and suppression of platelet aggregation, many disease outcomes have been found to be prevented and reversed with the aid of vitamin E.

3.1 Cardiovascular diseases

Body's low-density lipoproteins are oxidized, which causes inflammation, which in turn leads to cardiovascular issues [62]. Gamma-tocopherol has been shown to enhance functions of cardiovascular by boosting the nitric oxide synthase activity, which generates nitric oxide that relaxes blood vessels [63]. This is accomplished by trapping molecules of peroxynitrite, a reactive nitrogen species, and improving endothelial function. Humans who take 100 milligrams of gamma-tocopherol daily have shown to have fewer arterial clotting risk factors, such as cholesterol, platelet aggregation [64].

Different research revealed that combined tocopherols were more successful than individual tocopherols at preventing lipid peroxidation and human platelet aggregation, indicating a cooperative platelet-inhibitory action. Tocotrienols were also discovered to reduce cholesterol production by inhibiting 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, in addition to tocopherols, which causes the liver cells to produce less cholesterol [65]. Contrary to what has been reported, the majority of recent large interventional clinical trials suggest that vitamin E use was related to a considerably elevated risk of hemorrhagic stroke in the participants [66]. It was therefore proposed that further extensive research including younger subjects could be necessary to fully comprehend the vitamin E's possibility for preventing coronary heart disease.

3.2 Cancer

Additionally, vitamin E has anti-cancer qualities. This may be due to vitamin E's several effects, which include activating heat shock proteins, down-regulating

mutant p53 proteins, stimulating the p53 tumor suppressor gene, and having an anti-angiogenic action via the inhibition of transforming growth factor alpha [67]. As vitamin E compounds, alpha-, gamma-, and delta-tocopherols have developed, each with specific roles and anti-cancer properties. The development of PKC and collagenase [68], which promotes the proliferation of cancer cells, was found to be inhibited by alpha-tocopherol. Gamma-tocopherol was identified as superior to α-tocopherol in this situation for its capacity to suppress the proliferation of human prostate cancer cell lines, whereas delta-tocopherol has exhibited growth inhibitory efficacy against mouse mammary cancer cell lines [69]. In the culture, gamma-tocopherol suppress the cancer cells growth in a variety of methods.

The reactive nitrogen species of the compounds that modify the DNA strands and provide cells with cancerous changes are among the free radicals that are captured by it [70]. Additionally, it inhibits the activity of the cyclins, which stop the midst of the cancerous cell cycle and block the spread of the cancerous cells [71]. Additionally, it has been discovered that gamma-tocopherol performs better than alpha-tocopherol at inducing apoptosis, encouraging the activity of the peroxisome proliferators-activated receptor gamma, especially in colon cancer cells, and triggering several pathways that cause cell death [72, 73], inhibiting the growth of new blood vessels in tumors, and preventing tumors from receiving the supplements they require to grow. Tocotrienols was also found to have apoptotic and antiproliferative effects on both healthy and cancerous human cells in this setting [74]. This could be because apoptosis is induced by a mitochondria-mediated pathway or because cyclin D is suppressed, which would cause the cell cycle to be arrested [39]. Additionally, they impede vascularization and reduce 3-hydroxy-3-methyl coenzyme A (HMG-CoA) reductase activity, which stops the growth of cancer.

3.3 Cataracts

One of the most common causes of significant vision loss in older individuals is cataracts. They develop as a result of the buildup of proteins that have been harmed by free radicals. There may be a connection between vitamin E supplements and the likelihood of developing cataracts, according to several observational studies. *Leske et al*., discovered that those who took vitamin E supplements and those with greater blood levels of vitamin [40]. Had clearer lenses. a sustained vitamin E treatment was linked in a different study [75] to a slower evolution of age-related lens opacification. Vitamin E, however, did not appear to have any impact on the onset or 6.3 years on average, the randomized Age-Related Eye Disease Study (AREDS) tracked the development of cataracts [76].

3.4 Alzheimer's disease

Through a mechanism involving oxidative stress and hydrogen peroxide, the beta-amyloid protein causes cytotoxicity, which eventually leads to the death of neuronal cells and AD. This process is what causes Alzheimer's disease (AD), which, through a free radical process, is brought on by protein oxidation and lipid peroxidation. Vitamin E can prevent hydrogen peroxide production and the cytotoxicity it produces. It lessens the cell mortality brought on by beta-amyloid in PC12 cells and rat hippocampus cell cultures [77, 78], as well as the neuroblastoma cell toxicity brought on by excitatory amino acids [79]. Vitamin E may decrease the progression of the disease in those with moderately severe Alzheimer's disease, according to the

cooperative study on Alzheimer's from 1997.High vitamin E doses prevented the patient from losing the capacity to perform daily tasks and postponed their placement for several months in a private facility [80]. Another study revealed that people with AD had lower plasma levels of antioxidant supplements, indicating that the condition may be influenced by insufficient antioxidant activity. The neuroprotective impact of multiple vitamin E forms combined rather than just alpha-tocopherol alone is linked to older patients with high vitamin E plasma levels having a lowering risk of AD [81]. In a 2009 study, the effects of giving 847 individuals with and without taking an AD treatment 2000 IU of E vitamin were examined. It was discovered that combining an E vitamin with a cholinesterase inhibitor may be more advantageous than taking either medication by itself [82].

Using automated magnetic resonance imaging (MRI) measures and plasma levels of tocopherols and tocotrienols, Mangialasche et al. showed that it is possible to distinguish between Alzimers disease patients, people with moderate cognitive impairment, and healthy controls, as well as to predict the progression of with moderate cognitive impairment into Alzimers disease at the biomarker level. This demonstrates that plasma tocopherols and tocotrienols, which are nutritional indicators, may act as a surrogate for AD pathology [83]. However, due to its potential for harmful drug interactions in high doses, particularly those for lowering cholesterol, experts advise against patients taking vitamin E for AD treatment without a doctor's supervision.

3.5 Acute immunodeficiency syndrome and HIV

Although it is frequently discovered that Human immunodeficiency virus carriers (HIV) are low in E vitamin, unknown is whether E vitamin minerals is advantageous at any point during HIV infection. It has been shown that vitamin E to boost the growth of T helper cells (CD4 T-cells) and to restore delayed cutaneous hypersensitivity reactions at doses of 400 IU and higher [84]. Tang et al. examined the relationship between vitamin E and A levels and the development of HIV-1 illness in 1997. E vitamin levels in men above 24.2 m/l had a noticeably lower chance of illness development, according to this study. High amounts of vitamin E in the blood were shown to be strongly correlated with the consumption of vitamin E supplements at the time of study admission in this cohort [85].

The correction of immunological markers that are disrupted in HIV/AIDS was demonstrated in a study on the mouse acquired immunodeficiency syndrome utilizing a micronutrient intake rose by 15 times [86]. In addition, it has been demonstrated that increasing dietary vitamin E can guard against azidothymidine adverse effects such as bone marrow toxicity [87]. Similar findings were obtained from related research utilizing d-alpha-tocopherol supplementation on bone marrow cells from stage IV acquired immunodeficiency syndrome patients [88]. But it has also been observed that a higher fatality rate was associated with lower pre-infection vitamin E levels. As a result, more investigation is required to clarify the part of role of E vitamin E in the development of human immune deficiency virus-1 [89].

3.6 Immunity

It is now established that E vitamin boosts phagocytic activity, humoral immunological responses, and cell immunity in addition to stimulating the body's defenses. When immunological phagocytosis is engaged in infectious disorders, it has a noticeable impact, but it has less of an impact on cell-mediated immune defenses. Humans'

cell-mediated and humoral immunological functions are markedly improved by its supplementation, especially in the adults. In healthy individuals' daily intake of 200 mg of E vitamin, who did not experience any adverse side effects increased the antibody response to several vaccines [90]. Higher plasma levels of E vitamin were linked with fewer infections throughout a three-year period [91], and additionally, vitamin E increased resilience to viral infections.in aged patients. According to *Kutty et al.* demonstrated that taking vitamin E supplements daily can improve the immunological reaction to a specific antigen [92]. When combined with vitamin CE has been proven to help treat a variety of illnesses, including photo dermatitis, pre-eclampsia/dysmenorrhea, and tardive dyskinesia, menstrual pain in addition to the conditions already listed [93].

3.7 Vitamin E deficiency

1. It is relatively uncommon for people to lack vitamin E. People who are unable to absorb dietary fat, suffer from uncommon disorders of the metabolism of fat, or acquire or acquired conditions that restrict their ability to absorb the vitamin are the main ones who are affected, as well as individuals who have these conditions (such as bowel syndrome, cystic fibrosis).

2. Recent studies have demonstrated that alpha-TTP controls the liver cells' production of alpha-tocopherol and that severe vitamin E shortage in humans can result from missense mutations of specific residues of arginine on the protein surface [94]. The target membrane's PIPs (phosphatidylinositol phosphates) made it easier for alpha-TTP to transfer alpha-tocopherol than it was for the arginine mutants. The arginine mutant a-alpha-TTPs failed to bind PIPs, in contrast to the wild-type alpha-TTP.

3. Muscle weakness, poor vision, immune system issues, tremors, trouble walking. Numbness and unsteadiness are all symptoms of vitamin E deficiency.

4. Dysarthria may accompany other deficit-related symptoms such as the lack of positive babinski reflexes, the loss of vibratory sensations, deep tendon reflexes and other symptoms, as well as neuromuscular conditions such spinocerebellar ataxia and myopathies.

5. Red blood cells are harmed by reactive stress, which leads to retinopathy [95–98], and the immune system is compromised;

6. A vitamin E deficit can also result in anemia. A E vitamin shortage will cause irreversible nerve damage, blindness, heart disease, and if neglected, cognitive impairment will occur.

7. According to certain research, a E-vitamin deficiency may be a factor in male infertility.

3.8 Complications of vitamin E

3.8.1 Safety and adverse effects

Oral vitamin E use is typically regarded as safe when administered in the proper dosages. Occasionally, taking vitamin E orally can result in:

- Gonadal dysfunction
- Rash
- Fatigue
- Weakness
- Headache
- Blurred Vision.
- Intestinal Cramps
- Increased Creatine Concentration in Urine (creatinuria).

Higher vitamin E dosages could make side effects more likely. Furthermore, there is a worry that those who consume high amounts of vitamin E but are in bad health-care more likely to pass away. Numerous illnesses can interact with vitamin E use. For instance, studies indicate that consuming vitamin E orally may raise the risk of prostate cancer. According to additional research, taking vitamin E may make it more likely that a person will pass away if they have a history of severe heart diseases, such as a stroke or heart attack. If any of the following apply to you before using vitamin E:

A lack of vitamin K, retinitis pigmentosa, a condition that damages the retina in the eyes, and bleeding issues.

Diabetes, a prior history of a heart attack or stroke, head and neck malignancy, liver illness, and diabetes.

Your risk of bleeding may go up if you take the supplement. You should stop taking vitamin E two weeks before surgery if you are planning on having it. If you are about to undergo or have recently undergone a technique to unblock arteries and restart your heart's regular blood flow, talk to your doctor about using vitamin E.

Several studies have documented adverse effects of vitamin E supplements in high doses. As stated previously, a meta-analysis of 19 clinical trials involving 135,968 participants indicated that high-dose vitamin E supplements (400 IU) may increase all-cause mortality. In contrast, a recent review article reported that a pooled analysis of 18 randomized controlled trials conducted in individuals who appeared to be healthy found no effect of vitamin E supplementation at doses ranging from 23 to 800 IU/day on all-cause mortality. In addition, meta-analyses of 33 and 57 trials found no correlation between vitamin E supplementation and mortality.

Unknown is the mechanism underlying the increased risk associated with high-dose vitamin E supplementation. The phenomenon may be attributable to the induction of cytochrome P450, an enzyme that speeds up the metabolism of other substances [99]. Vitamin E has eight isoforms, with -tocopherol being the most potent and abundant in humans, despite -tocopherol being ingested in equal amounts. High-dose -tocopherol supplementation accelerates the metabolism of non-tocopherol forms. It has not been established whether or not the different isoforms of vitamin E have specific functions in vivo that could be compromised by -tocopherol supplementation. In certain in vitro systems, —tocopherol has been found to act as a pro-oxidant. In the absence of reducing agents such as vitamin C, —tocopherol accelerates the oxidation of LDL because the a-tocopheroxyl radical induces LDL oxidation.

Nevertheless, vitamin C absolutely inhibits this pro-oxidant action by decreasing -tocopheroxyl radical levels [100]. Therefore, it is improbable that vitamin E functions as a pro-oxidant in vivo.

3.8.2 Interactions

Your levels of vitamin E may change if you use certain medications. Several interactions are possible:

- **Anti-tumor antibiotics and alkylating drugs**: High vitamin E dosages are feared to have an impact on how well this chemotherapy drug works.
- **Medicines and supplements that inhibit clotting and platelet function**: The risk of bleeding may increase if vitamin E is used along with these medications, supplements and herbs to reduce blood clotting.
- **Substrates for Cytochrome P450 3A4 (CYP3A4):** When using omeprazole, a medication impacted by these enzymes, as well as vitamin E, proceeds with caution (Prilosec, Zegerid).
- **Niacin and statins:** Niacin's effects may be diminished if taken with statins or vitamin E, which may help those with high cholesterol.
- **K-vitamin:** Combining vitamin K and vitamin E may lessen vitamin K's effects.

4. Conclusion

The doctor's Shute and Shute employed vitamin E as a supplement for the first time in Canada; as a result of the successful outcomes, they started utilizing it frequently in their offices. Since then, carefully planned clinical and experimental investigations have progressively advanced and advanced our understanding of E-vitamin. Vitamin E's antioxidant capabilities have been proven to be essential in the fight against a number of illnesses, including cancer, oxidative stress, atherosclerosis cataracts and AD, among others. Additionally, demonstrated to be efficient against diabetes, allergies, asthma, and other illnesses in addition to these. The emphasis of this review was on the vital roles that E-vitamin plays in a number of infections.

A side from the extensive advantages claimed, there has always been disagreement on the precise of E vitamin role and its connection to certain ailments. In the literature, there are several contradictory accounts of both favorable and unfavorable outcomes for the same biological processes. The absence of reliable indicators for monitoring E vitamin consumption and status, which would link intakes to potential clinical outcomes, is the main obstacle to understanding the functions in human health of E vitamin. In conclusion, despite the inconsistent facts surrounding vitamin E, the present body of research seems to be in favor of the idea that the advantages outweigh the drawbacks.

Vitamin E inhibits lipid peroxidation both in vivo and in vitro. These findings suggest that vitamin E may reduce the risk of diseases mediated by free radicals or be beneficial in their prevention and treatment. Numerous epidemiological studies have supported this theory, but the results of clinical intervention studies and

meta-analyses have been controversial; some have reported positive findings, while others have reported null or negative findings.

To attain optimal results, numerous factors must be taken into account. Vitamin E should be beneficial for subjects enduring oxidative stress mediated by free radicals if administered at the appropriate dose, time, and duration.

Conflict of interest

The authors declare no conflict of interest.

Author details

Naresh Podila[1*], Sathish Kumar Konidala[1], Jithendra Chimakurthy[1], Srilatha Muddisetti[2], Suryaprabha Matangi[1], Natesh Gunturu[2], Yamarthi Venkateswara Rao[3] and Mithun Rudrapal[1]

1 Department Pharmaceutical Sciences, School of Biotechnology and Pharmaceutical Sciences, Vignan's Foundation for Science, Technology and Research, Guntur, A.P., India

2 Vikas College of Pharmaceutical Sciences, Suryapet, Telangana, India

3 Vignan Pharmacy College, Guntur, A.P., India

*Address all correspondence to: nareshtrcp10@gmail.com

IntechOpen

References

[1] Abner EL, Schmitt FA, Mendiondo MS, Marcum JL, Kryscio RJ. Vitamin E and all-cause mortality: A meta-analysis. Current Aging Science. 2011;**4**(2):158-170

[2] Abraham GE. Nutritional factors in the etiology of the premenstrual tension syndromes. The Journal of Reproductive Medicine. 1983;**28**(7):446-464 View abstract

[3] National Institutes of Health Office of Dietary Supplements. Vitamin E, Niki E, Noguchi N, Tsuchihashi H, Gotoh N. Interaction among vitamin C, vitamin E, and beta-carotene. The American Journal of Clinical Nutrition. 1995;**62**:1322S-1326S

[4] Ames BN. Micronutrient deficiencies: A major cause of DNA damage. Annals of the New York Academy of Sciences. 2000;**889**:87-106

[5] Chow CK. Distribution of tocopherols in human plasma and red blood cells. The American Journal of Clinical Nutrition. 1975;**28**:756-760

[6] Drotleff AM, Ternes W. Determination of RS, E/Z-tocotrienols by HPLC. Journal of Chromatography A. 2001;**909**:215-223

[7] Halliwell B, Gutteridge JM. Free Radicals in Biology and Medicine. 4th. Oxford: Clarendon Press; 2007

[8] Sugamura K, Keaney JF. Jr reactive oxygen species in cardiovascular disease. Free Radical Biology & Medicine. 2011;**51**:978-999

[9] Niki E. Assessment of antioxidant capacity in vitro and in vivo. Free Radical Biology & Medicine. 2010;**49**:503-515

[10] Palmer S. Diet, nutrition, and cancer. Progress in Food & Nutrition Science. 1985;**9**:283-341

[11] Gey KF, Brubacher GB, Stahelin HB. Plasma levels of antioxidant vitamins in relation to ischemic heart disease and cancer. The American Journal of Clinical Nutrition. 1987;**45**(5 Suppl):1368-1377

[12] Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: Systematic review and meta-analysis. Journal of the American Medical Association. 2007;**297**:842-857

[13] Traber MG, Frei B, Beckman JS. Vitamin E revisited: Do new data validate benefits for chronic disease prevention? Current Opinion in Lipidology. 2008;**19**:30-38

[14] Niki E. Do free radicals play causal role in atherosclerosis? Low density lipoprotein oxidation and vitamin E revisited. Journal of Clinical Biochemistry and Nutrition. 2011;**48**:3-7

[15] Zingg JM. Molecular and cellular activities of vitamin E analogues. Mini Reviews in Medicinal Chemistry. 2007;**7**:543-558

[16] Ball GFM. Vitamins in Foods: Analysis, Bioavailability, and Stability. Boca Raton, Florida: CRC Press; 2006. pp. 119-136

[17] Brown KM, Morrice PC, Duthie GG. Erythrocyte vitamin E and plasma ascorbate concentrations in relation to erythrocyte peroxidation in smokers and non-smokers: Dose response to vitamin E supplementation. The American Journal of Clinical Nutrition. 1997;**65**:496-502

[18] Di Mascio P, Murphy ME, Sies H. Antioxidant defense systems: The role of carotenoids, tocopherols, and thiols. The American Journal of Clinical Nutrition. 1991;**53**:194S-200S

[19] Glynn RJ, Ridker PM, Goldhaber SZ, Zee RY, Buring JE. Effects of random allocation to vitamin E supplementation on the occurrence of venous thromboembolism: Report from the Women's health study. Circulation. 2007;**116**:1497-1503

[20] Booth SL, Golly I, Sacheck JM, Roubenoff R, Dallal GE, Hamada K, et al. Effect of vitamin E supplementation on vitamin K status in adults with normal coagulation status. The American Journal of Clinical Nutrition. 2004;**80**:143-148

[21] Burton GW, Ingold KU. Autoxidation of biological molecules: 1. The antioxidant activity of vitamin E and related chainbreaking phenolic antioxidants in vitro. Journal of the American Chemical Society. 1981;**103**:6472-6477

[22] Liu M, Wallin R, Wallmon A, Saldeen T. Mixed tocopherols have a stronger inhibitory effect on lipid peroxidation than alpha-tocopherol alone. Journal of Cardiovascular Pharmacology. 2002;**39**:714-721

[23] Burton GW, Joyce A, Ingold KU. Is vitamin E the only lipidsoluble, chain-breaking antioxidant in human blood plasma and erythrocyte membranes? Archives of Biochemistry and Biophysics. 1983;**221**:281-290

[24] Howard AC, Anna K, McNeil AK, McNeil PL. Promotion of plasma membrane repair by vitamin E. Nature Communications. 2011;**20**:597

[25] Tran K, Wong JT, Lee E, Chan AC, Choy PC. Vitamin E potentiates arachidonate release and phospholipase A2 activity in rat heart myoblastic cells. The Biochemical Journal. 1996;**319**:385-391

[26] Niki E. Lipid peroxidation: Physiological levels and dual biological effects. Free Radical Biology & Medicine. 2009;**47**:469-484

[27] Niki E. Biomarkers of lipid peroxidation in clinical material. Biochimica et Biophysica Acta. 2014;**1840**:809-817

[28] Yin H, Xu L, Porter NA. Free radical lipid peroxidation: Mechanisms and analysis. Chemical Reviews. 2011;**111**:5944-5972

[29] Cheeseman KH, Albano EF, Tomasi A, Slater TF. Biochemical studies on the metabolic activation of halogenated alkanes. Environmental Health Perspectives. 1985;**64**:85-101

[30] Recknagel RO. Carbon tetrachloride hepatotoxicity. Pharmacological Reviews. 1967;**19**:145-208

[31] Smathers RL, Galligan JJ, Stewart BJ, Petersen DR. Overview of lipid peroxidation products and hepatic protein modification in alcoholic liver disease. Chemico-Biological Interactions. 2011;**192**:107-112

[32] Sid B, Verrax J, Calderon PB. Role of oxidative stress in the pathogenesis of alcohol-induced liver disease. Free Radical Research. 2013;**47**:894-904

[33] Adachi J, Asano M, Ueno Y, Naito T. Identification of 7-hydroperoxycholesterol in human liver by liquid chromatography-mass spectrometry. Alcoholism, Clinical and Experimental Research. 2000;**24** (Suppl. 4):21S-25S

[34] Aleynik SI, Leo MA, Aleynik MK, Lieber CS. Increased circulating products

of lipid peroxidation in patients with alcoholic liver disease. Alcoholism, Clinical and Experimental Research. 1998;**22**:192-196

[35] Wierzbicki AS, Oben J. Nonalcoholic fatty liver disease and lipids. Current Opinion in Lipidology. 2012;**23**:345-352

[36] Sumida Y, Niki E, Naito Y, Yoshikawa T. Involvement of free radicals and oxidative stress in NAFLD/NASH. Free Radical Research. 2013;**47**:869-880

[37] Feldstein AE, Lopez R, Tamimi TA, et al. Mass spectrometric profiling of oxidized lipid products in human nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Journal of Lipid Research. 2010;**51**:3046-3054

[38] Terao K, Niki E. Damage to biological tissues induced by radical initiator 2,2′-azobis(2-amidinopropane) dihydrochloride and its inhibition by chain-breaking antioxidants. Journal of Free Radicals in Biology & Medicine. 1986;**2**:193-201

[39] Morita M, Ishida N, Uchiyama K, et al. Fatty liver induced by free radicals and lipid peroxidation. Free Radical Research. 2012;**46**:758-765

[40] Yoshida Y, Hayakawa M, Cynshi O, Jishage K, Niki E. Acceleration of lipid peroxidation in alpha-tocopherol transfer protein-knockout mice following the consumption of drinking water containing a radical initiator. Journal of Oleo Science. 2008;**57**:577-583

[41] Sanyal AJ, Chalasani N, Kowdley KV, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. The New England Journal of Medicine. 2010;**362**:1675-1685

[42] Cheng J, Joyce A, Yates K, Aouizerat B, Sanyal AJ. Metabolomic profiling to identify predictors of response to vitamin E for non-alcoholic steatohepatitis (NASH). PLoS One. 2012;**7**(9):e44106

[43] Sumida Y, Naito Y, Tanaka S, et al. Long-term (>=2 yr) efficacy of vitamin E for non-alcoholic steatohepatitis. Hepatogastroenterology. 2013;**60**:1445-1450

[44] Steinberg D. The LDL modification hypothesis of atherogenesis: An update. Journal of Lipid Research. 2009;**50**(Suppl):S376-S381

[45] Barter PJ, Nicholls S, Rye KA, Anantharamaiah GM, Navab M, Fogelman AM. Antiinflammatory properties of HDL. Circulation Research. 2004;**95**:764-772

[46] Noguchi N, Numano R, Kaneda H, Niki E. Oxidation of lipids in low density lipoprotein particles. Free Radical Research. 1998;**29**:43-52

[47] Colas R, Pruneta-Deloche V, Guichardant M, et al. Increased lipid peroxidation in LDL from type-2 diabetic patients. Lipids. 2010;**45**:723-731

[48] Garcia-Cruset S, Carpenter KL, Guardiola F, Stein BK, Mitchinson MJ. Oxysterol profiles of normal human arteries, fatty streaks and advanced lesions. Free Radical Research. 2001;**35**:31-41

[49] Niu X, Zammit V, Upston JM, Dean RT, Stocker R. Coexistence of oxidized lipids and alpha-tocopherol in all lipoprotein density fractions isolated from advanced human atherosclerotic plaques. Arteriosclerosis, Thrombosis, and Vascular Biology. 1999;**19**:1708-1718

[50] Suarna C, Dean RT, May J, Stocker R. Human atherosclerotic plaque contains both oxidized lipids and relatively

large amounts of alpha-tocopherol and ascorbate. Arteriosclerosis, Thrombosis, and Vascular Biology. 1995;**15**:1616-1624

[51] Kuhn H, Romisch I, Belkner J. The role of lipoxygenase-isoforms in atherogenesis. Molecular Nutrition & Food Research. 2005;**49**:1014-1029

[52] Malle E, Marsche G, Arnhold J, Davies MJ. Modification of low-density lipoprotein by myeloperoxidase-derived oxidants and reagent hypochlorous acid. Biochimica et Biophysica Acta. 2006;**1761**:392-415

[53] Wagner JR, Motchnik PA, Stocker R, Sies H, Ames BN. The oxidation of blood plasma and low density lipoprotein components by chemically generated singlet oxygen. The Journal of Biological Chemistry. 1993;**268**:18502-18506

[54] Szczeklik A, Gryglewski RJ, Domagala B, Dworski R, Basista M. Dietary supplementation with vitamin E in hyperlipoproteinemias: Effects on plasma lipid peroxides, antioxidant activity, prostacyclin generation and platelet aggregability. Thrombosis and Haemostasis. 1985;**54**:425-430

[55] Freedman JE, Farhat JH, Loscalzo J, Keaney JF Jr. Alphatocopherol inhibits aggregation of human platelets by a protein kinase C-dependent mechanism. Circulation. 1996;**94**:2434-2440

[56] Li D, Saldeen T, Romeo F, Mehta JL. Different isoforms of tocopherols enhance nitric oxide synthase phosphorylation and inhibit human platelet aggregation and lipid peroxidation: Implications in therapy with vitamin E. Journal of Cardiovascular Pharmacology and Therapeutics. 2001;**6**:155-161

[57] Brigelius-Flohé R, Traber MG. Vitamin E: Function and metabolism. The FASEB Journal. 1999;**13**:1145-1155

[58] Liu M, Wallmon A, Olsson-Mortlock C, Wallin R, Saldeen T. Mixed tocopherols inhibit platelet aggregation in humans: Potential mechanisms. The American Journal of Clinical Nutrition. 2003;**77**:700-706

[59] Steinberg D, Parthasarathy S, Carew TE, Khoo JC, Witztum JL. Beyond cholesterol: Modifications of low-density lipoprotein that increase its artherogenicity. The New England Journal of Medicine. 1989;**320**:915-924

[60] Li D, Saldeen T, Romeo F, Mehta JL. Relative effects of alphaand gamma-tocopherol on low-density lipoprotein oxidation and superoxide dismutase and nitric oxide synthase activity and protein expression in rats. Journal of Cardiovascular Pharmacology and Therapeutics. 1999;**4**:219-226

[61] Singh I, Turner AH, Sinclair AJ, Li D, Hawley JA. Effects of gamma-tocopherol supplementation on thrombotic risk factors. Asia Pacific Journal of Clinical Nutrition. 2007;**16**:422-428

[62] McAnally JA, Gupta J, Sodhani S, Bravo L, Mo H. Tocotrienols potentiate lovastatin-mediated growth suppression in vitro and in vivo. Experimental Biology and Medicine (Maywood, N.J.). 2007;**232**:523-531

[63] Sesso HD, Buring JE, Christen WG, Kurth T, Belanger C, MacFadyen J, et al. Vitamins E and C in the prevention of cardiovascular disease in men: The physicians' health study II randomized controlled trial. JAMA. 2008;**300**:2123-2133

[64] Shklar G, Oh SK. Experimental basis for cancer prevention by vitamin E. Cancer Investigation. 2000;**18**:214-222

[65] Ricciarelli R, Maroni P, Ozer N, Zingg JM, Azzi A. Agedependent

increase of collagenase expression can be reduced by alpha-tocopherol via protein kinase C inhibition. Free Radical Biology & Medicine. 1999;**27**:729-737

[66] McIntyre BS, Briski KP, Gapor A, Sylvester PW. Antiproliferative and apoptotic effects of tocopherols and tocotrienols on preneoplastic and neoplastic mouse mammary epithelial cells. Proceedings of the Society for Experimental Biology and Medicine. 2000;**224**:292-301

[67] Christen S, Woodall AA, Shigenaga MK, Southwell-Keely PT, Duncan MW, Ames BN. Gamma-tocopherol traps mutagenic electrophiles such as NO(X) and complements alphatocopherol: Physiological implications. Proceedings of the National Academy of Sciences of the United States of America. 1997;**94**:3217-3222

[68] Gysin R, Azzi A, Visarius T. Gamma-tocopherol inhibits human cancer cell cycle progression and cell proliferation by down-regulation of cyclins. The FASEB Journal. 2002;**16**:1952-1954

[69] Takahashi S, Takeshita K, Seeni A, Sugiura S, Tang M, Sato SY, et al. Suppression of prostate cancer in a transgenic rat model via gamma-tocopherol activation of caspase signaling. Prostate. 2009;**69**:644-651

[70] Stone WL, Krishnan K, Campbell SE, Qui M, Whaley SG, Yang H. Tocopherols and the treatment of colon cancer. Annals of the New York Academy of Sciences. 2004;**1031**:223-233

[71] Wells SR, Jennings MH, Rome C, Hadjivassiliou V, Papas KA, Alexander JS. Alpha-, gamma- and delta-tocopherols reduce inflammatory angiogenesis in human microvascular endothelial cells. The Journal of Nutritional Biochemistry. 2010;**21**:589-597

[72] Wada S. Chemoprevention of tocotrienols: The mechanism of antiproliferative effects. Forum of Nutrition. 2009;**61**:204-216

[73] Jiang Q, Wong J, Fyrst H, Saba JD, Ames BN. Gamma-tocopherol or combinations of vitamin E forms induce cell death in human prostate cancer cells by interrupting sphingolipid synthesis. Proceedings of the National Academy of Sciences of the United States of America. 2004;**101**:17825-17830

[74] Chen CS. Study Shows How Vitamin E Can Help Prevent Cancer. Available from: www.researchnews.osu.edu/archive/silenceakt.htm [Accessed: Dec 2013]

[75] Lonn E, Bosch J, Yusuf S, Sheridan P, Pogue J, Arnold JM, et al. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: A randomized controlled trial. JAMA. 2005;**293**:1338-1347

[76] Goodman Y, Mattson MP. Secreted forms of beta-amyloid precursor protein protect hippocampal neurons against amyloid beta-peptide-induced oxidative injury. Experimental Neurology. 1994;**128**:1-12

[77] Behl C, Davis J, Cole GM, Schubert D. Vitamin E protects nerve cells from amyloid beta protein toxicity. Biochemical and Biophysical Research Communications. 1992;**186**:944-950

[78] Murphy TH, Schnaar RL, Coyle JT. Immature cortical neurons are uniquely sensitive to glutamate toxicity by inhibition of cystine uptake. The FASEB Journal. 1990;**4**:1624-1633

[79] Sano M, Ernesto C, Thomas RG, Klauber MR, Schafer K, Grundman M, et al. A controlled trial of selegiline, alphatocopherol, or both as treatment

for Alzheimer's disease. The Alzheimer's disease cooperative study. The New England Journal of Medicine. 1997;**336**:1216-1222

[80] Mangialasche F, Kivipelto M, Mecocci P, Rizzuto D, Palmer K, Winblad B, et al. High plasma levels of vitamin E forms and reduced Alzheimer's disease risk in advanced age. Journal of Alzheimer's Disease. 2010;**20**:1029-1037

[81] Pavlik VN, Doody RS, Rountree SD, Darby EJ. Vitamin E use is associated with improved survival in an Alzheimer's disease cohort. Dementia and Geriatric Cognitive Disorders. 2009;**28**:536-540

[82] Mangialasche F, Westman E, Kivipelto M, Muehlboeck JS, Cecchetti R, Baglioni M, et al. Classification and prediction of clinical diagnosis of Alzheimer's disease based on MRI and plasma measures of α−/γ-tocotrienols and γ-tocopherol. Journal of Internal Medicine. 2013;**273**:602-621

[83] Meydani M, Vitamin E. Lancet. 1995;**345**:170-175

[84] Tang AM, Graham NM, Semba RD, Saah AJ. Association between serum vitamin a and E levels and HIV-1 disease progression. AIDS. 1997;**11**:613-620

[85] Wang Y, Huang DS, Watson RR. Vitamin E supplementation modulates cytokine production by thymocytes during murine AIDS. Immunologic Research. 1993;**12**:358-366

[86] Ganser A, Greher J, Volkers B, Staszewski A, Hoelzer D. Azidothymidine in the treatment of ATDS. The New England Journal of Medicine. 1988;**318**:250-251

[87] Geissler RG, Ganser A, Ottmann OG, Gute P, Morawetz A, Guba P, et al. In vitro improvement of bone marrow-derived hematopoietic colony formation in HIV-positive patients by alpha-D-tocopherol and erythropoietin. European Journal of Haematology. 1994;**53**:201-206

[88] Graham SM, Baeten JM, Richardson BA, Bankson DD, Lavreys L, Ndinya-Achola JO, et al. Higher pre-infection vitamin E levels are associated with higher mortality in HIV-1-infected Kenyan women: A prospective study. BMC Infectious Diseases. 2007;**7**:63

[89] Meydani SN, Meydani M, Blumberg JB, Leka LS, Siber G, Loszewski R, et al. Vitamin E supplementation and in vivo immune response in healthy elderly subjects: A randomized controlled trial. JAMA. 1997;**277**:1380-1386

[90] Chavance M, Herbeth B, Fournier C, Janot C, Vernhes G. Vitamin status, immunity and infections in an elderly population. European Journal of Clinical Nutrition. 1989;**43**:827-835

[91] Radhakrishnan AK, Mahalingam D, Selvaduray KR, Nesaretnam K. Supplementation with natural forms of vitamin E augments antigen-specific TH1-type immune response to tetanus toxoid. BioMed Research International. 2013;**2013**:782067

[92] University of Maryland Medical Center. Vitamin E. Available from: www.umm.edu/health/medical/altmed/supplement/vitamine#ixzz2c7gfq93R [Accessed: Dec 2013]

[93] Kono N, Ohto U, Hiramatsu T, Urabe M, Uchida Y, Satow Y, et al. Impaired a-TTP-PIPs interaction underlies familial vitamin E deficiency. Science. 2013;**340**:1106-1110

[94] Office of Dietary Supplements, National Institutes of Health. Dietary Supplement Fact Sheet: Vitamin E.

Available from: www.ods. od.nih.gov/factsheets/vitamine.asp [Accessed: Aug 2010]

[95] Food and Nutrition Board, Institute of Medicine. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. Washington, DC: National Academy Press; 2000

[96] Kowdley KV, Mason JB, Meydani SN, Cornwall S, Grand RJ. Vitamin E deficiency and impaired cellular immunity related to intestinal fat malabsorption. Gastroenterology. 1992;**102**(6):2139-2142

[97] Slover HT. Tocopherols in foods and fats. Lipids. 1971;**6**:291-296

[98] United States Department of Agriculture (USDA), Agricultural Research Service. USDA National Nutrient Database for Standard Reference, Release 25. Available from: www.ars.usda.gov/SP2UserFiles/Place/12354500/Data/SR25/nutrlist/sr25a323.pdf [Accessed: Dec 2013]

[99] Colombo ML. An update on vitamin E, tocopherol and tocotrienol: Perspectives. Molecules. 2010;**15**:2103-2113

[100] Rathore GS, Suthar M, Pareek A, Gupta RN. Nutritional antioxidants: A battle for better health. Journal of Natural Pharmaceuticals. 2011;**2**:2-14

Chapter 6

Vitamin E Inhibits Osteoclastogenesis in Protecting Osteoporosis

Chen Yongjie, Yu Naichun, Zhou Daguo, Li Zongguang, Gong Fengqing, Yi Weijiang, Chen Botao and Ji Guangrong

Abstract

The most common orthopedic condition affecting senior adults is osteoporosis, which is defined by a decrease in bone mass and strength as well as microstructural degradation that leads to fragility fractures. Bone remodeling is a well-planned, ongoing process that replaces deteriorated, old bone with new, healthy bone. Bone resorption and bone creation work together during the cycle of bone remodeling to preserve the bone's volume and microarchitecture. The only bone-resorbing cells in the human body, mononuclear preosteoclasts fuse to form osteoclasts, are multinucleated cells. In numerous animal models or epidemiological studies, vitamin E's anti-osteoporotic characteristics have been extensively described. This review aims to summarize recent developments in vitamin E's molecular features as a bone-protective agent. In RANKL/RANK/OPG signaling pathway, vitamin E inhibits synthesis of RANKL, stimulation of c-Fos, and increase level of OPG. Vitamin E also inhibits inflammatory cytokines, such as TNF-α, IL-1, IL-6, IL-27, and MCP-1, negative regulating the JAK–STAT, NF-κB, MAPK signaling pathways. Additionally, vitamin E decreases malondialdehyde and increases superoxide dismutase, GPx and heme oxygenase-1, in suppressing osteoclasts. In this article, we aim to give readers the most recent information on the molecular pathways that vitamin E uses to enhance bone health.

Keywords: vitamin E, osteoclast, osteoporosis, RANKL, inflammatory, oxidative stress

1. Introduction

The most common orthopedic condition affecting elderly people is osteoporosis, which is characterized by a decline in microarchitecture and a loss of bone mass and strength. Approximately 25% of all women aged 65 or older are affected by osteoporosis, which results in the lifetime fracture risk of patients with osteoporosis being as high as 40% [1]. Osteoporosis fractures involving the hip, vertebrae, and wrist reduce life expectancy or quality of life. Some drugs classified as antiresorptive or anabolic have been used in the treatment of osteoporosis [2, 3].

Antiresorptive drugs, which include bisphosphonates, estrogens, denosumab, and selective estrogen receptor modulators (SERMs), increase bone mineral density

(BMD) and reduce fragility fractures. Bisphosphonates are the most widely used antiresorptive drug, which bind avidly to bone mineral and have a continual effect in months to years. However, bisphosphonates have low bioavailability and induce gastrointestinal problems, myalgia, and flu-like symptoms. Osteoclast activity and development are significantly decreased by the monoclonal antibody denosumab, which specifically targets RANKL. Every six months, denosumab is given by subcutaneous injection. Denosumab's anti-fracture effects are comparable to those of bisphosphonates; however starting 7 months after the last injection, there is a noticeable reduction of anti-resorptive action, which can lead to clusters of rebound vertebral fractures. SERMs exhibit estrogen agonist or antagonist qualities and bind to the estrogen receptor with high affinity to prevent bone loss. However, SERMs can induce venous thromboemboembolism, stroke and hot flashes, which limit their use [4].

Anabolic agents, including teriparatide and abaloparatide, promote bone formation to reduce the risk of fractures. Teriparatide and abaloparatide are both limited to a maximum of 24 months of therapy due to elevated osteosarcoma incidence in rats treated with these medications for their entire lives. These drugs similarly induce some adverse effects, including dizziness, leg cramps, nausea, postural hypotension, and headache. Another anabolic agent is romosozumab, which blocks the actions of sclerostin to reduce bone resorption. However, the romosozumab group in the ARCH study had a higher rate of a composite endpoint that included cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. In general, different drugs have been used to treat osteoporosis (**Table 1**), but their different adverse reactions limit their long-term use against osteoporosis [2, 3, 5, 6].

Vitamin E has shown great potential in the treatment of osteoporosis. There are two subclasses of the lipid-soluble vitamin E: tocopherol (TF) and tocotrienol (T3). Each isoform can further be separated into four unique analogs, namely, alpha (α), beta (β), gamma (γ), and delta (δ). Some researchers have investigated the impact of vitamin E (TF) on osteoblast differentiation in a previous study. Early osteoblast development

Drugs	Administration	Dosage	Side effects
Anti-resorptive Bisphosphonates			
Alendronate	Oral	70 (or 35) mg/week; 10 (or 5) mg/day	Upper gastrointestinal symptoms/osteonecrosis of the jaw (ONJ)/atypical femoral fracture (AFF)
Risedronate	Oral	5 mg/day; 35 mg/ week; 75 mg twice per month. 150 mg/ month.	Upper gastrointestinal symptoms, ONJ, or AFF.
Ibandronate	Oral or intravenous	150 mg/month orally or 3 mg/ month	Upper gastrointestinal Symptoms, flu-like illness ONJ or AFF.
Zoledronate or Zoledronic acid	Intravenous	Intravenously 5 mg/year	Flu-like illness ONJ or AFF.
SERMs			
Raloxifene	Oral	60 mg/day	Venous thromboembolism, stroke and flashes

Drugs	Administration	Dosage	Side effects
Monoclonal antibody against RANKL			
Denosumab	Subcutaneously	60 mg every 6 months	Hypocalcaemia, rebound vertebral fractures, and AFF
Anabolic agents			
Teriparatide	Subcutaneously	20 μg/day	Hypercalcemia
Abaloparatide	Subcutaneously	80 μg/day	Dizziness, leg cramp, nausea, headache, hypercalcemia
Romosozumab	Subcutaneously	210 μg/day	Serious cardiovascular events, AFF and ONJ

Table 1.
Principal medications for treatment of osteoporosis.

was demonstrated to be hindered by TF, as evidenced by a decrease in alkaline phosphatase (ALP) activity and osteocalcin expression (OCN) [7]. In another study, another researcher showed that incubating human mesenchymal stem cells (MSCs) with TF boosted their proliferation. ALP and runt-related transcription factor-2 (Runx-2) expression was markedly increased in cells treated with TF. Gamma-T3 has been shown to decrease apoptosis and increase osteoblastic cell proliferation, differentiation, and mineralization. When αTF and δT3 were compared to TF and T3, αTF and δT3 had superior effects on inhibiting osteoblast differentiation. In a biomechanical strength test, bone scaffolds treated with all types of vitamin E isomers, particularly αTF and δT3, displayed enhanced elasticity [8]. According to this study, αTF and δT3 may be the isomers that affect bone most actively. Many researchers have focused on the effect of vitamin E on osteoblasts. In contrast, few *in vitro* studies have examined how vitamin E affects osteoclasts. This chapter emphasizes recent developments in our knowledge of vitamin E's molecular actions in inhibiting osteoclasts, particularly through interactions between multiple signaling pathways and signal transduction molecules.

2. Osteoclasts in bone homeostasis

Bone is a dynamic tissue that changes regularly during the course of life. During the process of bone remodeling, osteoclasts remove old or damaged bone and osteoblasts replace it with fresh bone. Without appreciably altering the net bone mass and mechanical strength, the ratio of osteoblast-mediated bone formation to osteoclast-mediated bone resorption is tightly regulated in homeostatic situations [9]. However, when this equilibrium is dysregulated, aberrant bone remodeling occurs, leading to postmenopausal and secondary types of osteoporosis. Osteoclasts are the only bone-resorbing cells in the human body, which is significant since they are essential for reconstructing the skeletal system. Numerous cells originating from blood-circulating monocytes combine to become osteoclasts. They themselves come from the bone marrow. Although the majority have only 5 to 20 nuclei, osteoclasts can have up to 200 nuclei. The active area of osteoclasts is formed by numerous tiny projections (microvilli) that protrude into the surface of the bone on the side of the cell that is closest to the bone. One of the many enzymes produced by osteoclasts,

acid phosphatase dissolves both the organic collagen and the inorganic calcium and phosphorus found in bone. The osteoclast then engulfs and digests the broken-down pieces of mineralized bone inside the cytoplasmic vacuoles. Communication between osteoblasts and osteoclasts is crucial for optimizing bone remodeling during bone homeostasis. In addition to M-CSF, RANKL, and WNT5A, osteoblasts also release OPG and WNT16, which limit osteoclast activity. In contrast, S1P, CTHRC1, and C3, which encourage osteoblast differentiation, as well as SEMA4D, which inhibits osteoblast differentiation, are secreted by osteoclasts.

A hematopoietic growth factor called M-CSF enables mononuclear phagocyte lineages, which include osteoclasts, to survive, proliferate, differentiate, and move around. M-CSF binds to its specific receptor, C-FMS, on the surface of osteoclasts and monocytes/macrophages after being produced by osteoblasts and bone marrow stromal cells. Significant amounts of RANKL are expressed in lymph nodes, activated T lymphocytes, osteoblasts, and osteocytes. The main regulatory transcription factors and enzymes are activated as a result of RANKL activation of RANK, which promotes osteoclast differentiation, fusion, and proliferation. For instance, RANKL binding to RANK activates TRAF6, which has been discovered to activate the protein kinase TGF-activated kinase (TAK1). The classical IB kinase (IKK) complex is then activated by TAK1. IKK activation results in the activation of NF-κB, protein kinase Tp12, and mitogen-activated protein (MAP) kinase (MKK) kinases. MKKs trigger the activity of p38 MAP kinases and c-Jun N-terminal kinases. Extracellular signal-regulated kinase 1 (ERK1) and ERK2 are stimulated by activated Tp12, which in turn activates MEK1 and MEK2. Eventually, the MAPK and NF-κB signaling pathways are activated, increasing NFATc1, a crucial regulator of osteoclastogenesis. OPG has been shown to be a secreted glycoprotein made by numerous cell types, including osteoblasts, cells living in the liver or lungs, and B lymphocytes in the bone marrow. Due to the suppression of the development of osteoclasts, overexpression of OPG causes severe osteopetrosis. OPG is thought to act as a decoy receptor for RANKL, blocking the RANKL-RANK interaction and impairing osteoclast development and activation. Because it controls osteoblastogenesis and osteoclastogenesis through both catenin-dependent (canonical) and catenin-independent (noncanonical) pathways, the WNT pathway is essential for preserving bone homeostasis. By increasing RANK expression in osteoclasts and activating the MAPK pathway, WNT5A promotes RANKL-induced osteoclastogenesis, which is also inhibited by WNT16 both directly and indirectly. A direct method of preventing osteoclastogenesis is provided by WNT16-induced phosphorylation of JUN, which increases OPG expression in osteoblasts in addition to directly inhibiting osteoclastogenesis *via* the noncanonical JNK/MAPK pathway (**Table 2**) [10].

	Osteoblast	**Osteoclast**
Transcription factors	RUNX 1/2, OSX, ATF 4, SATB 2, AP-1	NFATc 1, AP-1, CREB, MITF, NF-κB, c-FOS
Activating cytokines	IL-10, IL 11, IL 18, IFN-γ CT-1, OSM, S1P, CTHRC 1, C3 BMP-2, TGF-β, FGF, PTH	RANKL, TNF-α, IL-1, IL-6, IL-7, IL-8, IL-11, IL-15, IL-17, IL-23, IL-34
Activating signaling pathways	Wnt, Smad, MAPK, PI3K/ AKT, ERK, cAMP/PKA/CREB, Hedgehog	Akt, ERK, NF-κB, MAPK, JNK, STAT3/Smad 7 DAP12/ FCRγ-Syk-PLCγ

	Osteoblast	**Osteoclast**
Inhibiting factors	TNF-α, TNF-β, IL-1α, IL-4, IL-7, IL 12, IL-13, IL-23, IFN-α, IFN-β, SEMA4D	OPG, IFN-α, IFN-β, IFN-γ, IL-3, IL-4, IL-10, IL-12, IL-27, IL-33
Inhibiting signaling pathways	ERK/JNK/P2YR, JNK/P38 MAPK, STAT 1/3, NF-κB	JAK1/STAT3/c-Fos, STAT 6, Fas/FasL

RANX 1/2, runt-related transcription factor 1/2; CT-1, Cardiotrophin-1; OSM, oncostatin M; OSX, osterix; ATF 4, activating transcription factor 4; SATB 2, special AT-rich sequence-binding protein 2; AP-1, activator protein-1; IFN-γ, interferon-γ; TNF-α/β, tumor necrosis factor-α/β; MITF, microphthalmia transcription factor.

Table 2.
Key factors and signaling pathways of osteoblastogenesis or osteoclastogenesis.

3. The effects of vitamin E on bone cells

In the past, researchers have looked at the direct effects of vitamin E on bone cells. In a prior study, Soeta et al. looked at the effects of vitamin E (αTF and δT3) on osteoblast differentiation. It was demonstrated that whereas TF initially hindered osteoblast differentiation, at a later stage, osteoblast differentiation reverted to normal [7]. Ahn et al. discovered in another investigation that incubation with αTF increased the proliferation of MSCs. In cells treated with αTF, the expression of ALP and Runx-2 was dramatically upregulated. Gamma-T3 has been demonstrated to enhance osteoblastic cell proliferation, differentiation, and mineralization, as well as reduce apoptosis [11]. According to prior research, α T3's protective effects on osteoblastic cells were consistent, while TF's effects were varied. Osteoclastogenesis was inhibited by both the γT3 and αT3 isomers, with the latter showing a more significant suppression of osteoclast production and activity than the former [12].

Vitamins also affect osteoclastogenesis. Johnson showed that vitamin E administration inhibits osteoclastogenesis, potentially by preventing the development of monocytes and lymphocytes. In their study, the Ovx control group had a much higher number of osteoclasts, which were strongly inhibited by all three dosages of vitamin E, although more efficiently in the Ovx group that received 300 mg of vitamin E per kg of food. Vitamin E also reduced the increase in monocyte and lymphocyte production induced by Ovx [13]. Woon Kim discovered that tocotrienol reduced the amount of RANKL that IL-17 stimulated FLS generation. Tocotrienol reduced the activation of extracellular signal-regulated kinase, kappa B-alpha inhibitor, and mammalian target of rapamycin caused by IL-17. Osteoclasts were differentiated when monocytes were incubated with IL-17, RANKL, FLS that had been treated with IL-17, or Th17 cells, and tocotrienol inhibited this osteoclast differentiation. Tocotrienol decreased IL-17 and sRANKL synthesis as well as Th17 cell differentiation [14]. Polyethylene has been shown by Hazir et al. to increase the number of TRAP-positive cells and the expression of genes related to osteoclasts. TF therapy markedly decreased the quantity of TRAP-positive osteoclasts, bone resorption activity, antioxidant-related gene expression and mitochondrial function [15]. In Walker 256/B tumor osteolytic rats, Badraoui et al. investigated the effects of vitamin E supplementation on osteoclast resorbing activity and cytomorphometry. The results indicate that fewer osteolytic lesions were visible in W256VE. In addition, the W256VE group had less alteration of bone microarchitecture and OC activity [16]. Quercetin and vitamin E have been studied by Vakili et al. in relation to ovariectomy-induced osteoporosis.

The results showed that ovariectomy increased the total number of osteoclasts and serum osteocalcin and lowered the bone weight, bone volume, trabeculae volume, and total number of osteocytes and osteoblasts. The expression of LC3, beclin1, and caspase 3 was also upregulated in the tibia, while bcl2 expression was downregulated. Treatment with Q and vitamin E significantly improved osteoporosis by reversing these alterations [17]. In a double-blinded, randomized, placebo-controlled human trial study, vitamin E has significantly decreased the serum C-terminal telopeptide of type I collagen (CTX) [18]. These studies have indicated that vitamin E could inhibit osteoclastogenesis in the treatment of osteoporosis.

4. The molecular mechanism of vitamin E in osteoclastogenesis

4.1 The effect of vitamin E on the M-CSF and RANKL/RANK/OPG signaling pathways

The RANK/RANKL/OPG trimolecular complex system and M-CSF exert a considerable influence on osteoclast production and the regulation of bone resorption. The maturation of osteoclast precursor cells into mature osteoclasts in the presence of RANKL depends on the production of M-CSF by osteoblastic stromal cells. Other names include osteoclast differentiation factor (ODF), tumor necrosis factor-related activation-induced cytokine, and OPG ligand (TRANCE). When RANKL binds to its receptor, RANK, on myeloid cells, a series of intracellular signaling events are triggered, including interactions with TRAF6 adaptor molecules and the activation of NF-κB, nuclear factor of activated T cells cytoplasmic 1 (NFATc1), MAPK, and PI3K. It has been demonstrated that NF-κB regulates RANKL-induced osteoclast development, activating the Fos proto-oncogene (c-Fos) before NFATc1. The presence of NFATc1, which has been dubbed the "master regulator of osteoclast development," is critical for stem cells differentiate into osteoclasts. If RANKL and NF-κB p65 interact, it becomes transiently active in osteoclast precursors within an hour. Additionally, the c-Fos is also vital for osteoclastogenesis induced by M-CSF and RANKL. OPG is a protein that is largely secreted by osteoblast lineage cells, and it functions as a key endogenous regulator of the RANK/RANKL/OPG pathway. The same ligand, RANKL, has affinity for the receptors OPG and RANK as well. In order to stop osteoclastogenesis and the survival of existing osteoclasts, OPG acts as a decoy receptor by interacting with RANK. The ratio of RANKL/OPG may play a significant role in regulating bone resorption because OPG expression is normally downregulated and not as active as RANKL. Cortical and cancellous bone mass is considerably increased by OPG overexpression, while osteoclast levels are decreased.

Ambroszkiewicz et al. observed that children with cystic fibrosis (CF), the most prevalent deadly autosomal recessive genetic illness that results in a range of long-term health issues, including bone ailments, have lower average levels of fat-soluble vitamins (A, D, and E). Children with CF have significantly lower levels of the markers for bone production (osteocalcin) and bone resorption (CTX, TRACP5b) than children without the condition. In comparison with healthy individuals, CF patients had serum levels of OPG that were much lower and RANKL that were approximately two times greater. This finding suggested a link between vitamin E and RANKL or OPG in various bone diseases [19]. In another study, Kim et al. showed that RANKL synthesis was promoted by IL-17 in fibroblast-like synoviocytes (FLS) and was inhibited by tocotrienol. Tocotrienol reduced the activation of NF-kappaB,

extracellular signal-regulated kinase, and mammalian target of rapamycin caused by IL-17. Osteoclasts were differentiated when monocytes were incubated with IL-17, RANKL, FLS that had been treated with IL-17, or Th17 cells, and tocotrienol inhibited this osteoclast differentiation [14]. Trolox is a water-soluble vitamin E analog that has been studied for its effects on osteoclastogenesis and RANKL signaling by Kim et al. By preventing RANKL production in osteoblasts, trolox effectively prevented interleukin-1-induced osteoclast development in bone marrow cell-osteoblast coculture. This decrease in RANKL was ascribed to a downregulation of cyclooxygenase-2 activity, which in turn resulted in less prostaglandin E [2] being produced. Trolox also reversibly reduced the production of osteoclasts by bone marrow macrophages stimulated by RANKL and M-CSF. Trolox targets early osteoclast precursors since its effectiveness depends on its presence early in the culture process. Trolox pretreatment had no effect on the early signaling pathways activated by RANKL, such as the MAPK, NF-κB, and Akt pathways. By inhibiting its translation, Trolox reduced the stimulation of the c-Fos protein by RANKL. Trolox's suppression of osteoclastogenesis in bone marrow macrophages was reversed by ectopic overexpression of c-Fos [20]. In cocultures of osteoblasts and bone marrow cells stimulated by either IL-1 or a combination of 1,25(OH)(2) vitamin D(3) and prostaglandin E, Ha et al. discovered that vitamin E inhibits osteoclastogenesis. This is supported by the finding that only tocotrienols prevented RANKL in osteoblasts. Additionally, c-Fos expression was suppressed by α-tocotrienols but not α-tocopherols, which may have been accomplished by preventing ERK and NF-κB activation. This may have prevented RANKL-induced osteoclast development from precursors. When c-Fos or an active version of NFATc1, a crucial downstream target of c-Fos during osteoclastogenesis, was overexpressed, this anti-osteoclastogenic impact was reversed [21]. Human osteoblastic SaOS2 cells were treated with wear particles from vitamin E-doped and regular UHMWPE, and the gene expression and protein synthesis of IL-6, RANKL, OPG, DKK-1, and Sclerostin were then evaluated. When compared to standard UHMWPE, vitamin E-blended UHMWPE lowered RANKL while increasing OPG [22]. According to research by Mohammed, annatto tocotrienol (AT) and self-emulsified annatto tocotrienol (SEAT) both increased the number of osteoblasts and the pace at which trabecular mineralization occurred. In OVX animals, AT also reduced the expression of skeletal sclerostin. Only SEAT significantly boosted the bone formation rate and decreased the RANKL/OPG ratio. SEAT increases bone growth, inhibits sclerostin expression, and lowers the RANKL/OPG ratio in rats with estrogen shortage, all of which may have skeletal anabolic effects [23].

Overall, the RANK/RANKL/OPG system is a crucial signaling channel involved in communication between bone cells, and there is substantial evidence that altering this signaling pathway has significant consequences for bone remodeling. While OPG inhibits osteoclast-induced bone resorption by negatively regulating RANKL binding to RANK and shortening the half-life of membranous RANKL, RANKL mediates osteoclastogenesis and activates mature osteoclasts. According to growing research, T3 therapy has the potential to protect bones by regulating this route. However, more research is required to support these conclusions.

4.2 Vitamin E suppresses inflammation in preventing bone loss

Inflammation, which is defined by the activation of immune cells and the consequent release of inflammatory cytokines, is the first line of defense against illnesses for both the innate and adaptive immune systems. The removal of damaged tissues

and the beginning of tissue repair are both essential functions of inflammation. Continued inflammation, however, also promotes bone resorption and inhibits bone development. The main controllers of the inflammatory response seen in metabolic bone disorders, such as osteoporosis, are cytokines. Interferon, interleukin (IL), and tumor necrosis factor-alpha (TNF-α) are only a few of these cytokines. Previous research has shown that proinflammatory mediators can both positively and adversely affect osteoclast and osteoblast activities. Significant stimulators of bone resorption include TNF-α, IL-1, and IL-6. After TNF-α and IL-6 are recognized by their corresponding receptors on bone marrow stromal cells, the inhibition of MAPK, the activation of suppressor of mothers against decapentaplegic ubiquitylation regulatory factor 1 (SMURF1) and SMURF2, and the activation of signal transducers and activators of transcription (STAT) all work together to cause the downregulation of osteoblast gene products. Through the overexpression of Dickkopf-related protein 1 (DKK1) and sclerostin (SOST), proinflammatory cytokines block the transcription of osteogenic factors to block the Wnt/β-catenin pathway. Additionally, due of the link among inflammatory factors and their receptors, which promotes osteoclast development, proliferation, and activation, osteoblasts create more M-CSF and RANKL. TNF-α, IL-1, and IL-6 signal in osteoclasts and osteoclast precursors through the NF-κB, MAPK, and Janus kinase (JAK)-STAT pathways to upregulate osteoclast-related genes and intensify osteoclastogenesis. The downregulation of c-Fos, NFATc1, and TRAF6, as well as the subsequent impairment of the activation of downstream targets, including NF-κB and JNK, has been hypothesized as the underlying mechanisms of IFN-γ in suppressing osteoclast development. Additionally, IFN-γ increases the interaction between Fas and Fas ligands to promote osteoclast precursor death and induces osteoblasts to create nitric oxide. On the other hand, IFN-γ indirectly encourages osteoclast development by promoting T-cell activation and the release of osteoclastogenic substances, including TNF-α and RANKL, by T cells. Additionally, IFN-γ stimulates the production of DC-STAMP, which is in charge of fusing mononucleated osteoclasts into mature, functioning osteoclasts. It is speculated that inflammatory cytokines play an important role in bone homeostasis.

Several different laboratory experiments have shown how vitamin E can reduce systemic inflammation. In children with biopsy-proven NAFLD, hydroxytyrosol (HXT) and vitamin E may reduce oxidative stress, insulin resistance, and steatosis, according to Mosca. Children participating in the HXT + VitE experiment had their plasma levels of IL-6, IL-1, IL-10, TNF, 4-hydroxy-2-nonenal (4-HNE), and 8-hydroxy-2'deoxyguanosine (8-OHdG) analyzed. This study showed that both the placebo (Pla) group and the HXT + VitE group exhibited changes in indicators of systemic inflammation. Levels of IL-1 and TNF were decreased in both groups; however, IL-6 and IL-10 increased significantly only in the HXT + VitE group. Systemic inflammation in children caused by NAFLD was reduced by HXT and VitE therapy [24]. Hashem pretreated rats with vitamin E (60 mg/kg) and continued giving them vitamin E until the experiment was complete to test the hypothesis that acute pancreatitis (AP) and the regulation of the TNF-AMPK axis in the presence and absence of vitamin E are related. Infiltration of inflammatory cells and severe pancreatic tissue damage, which were significantly shielded by vitamin E, served as evidence that AP had occurred. Additionally, L-arginine injections markedly lowered phospho-AMPK, IL-10 mRNA, and protein expression, which were markedly protected by vitamin E [25]. Amevor et al. exposed 400 Tianfu breeders to 0.4 g/kg quercetin (Q) and 0.2 g/kg vitamin E, Q (0.4 g/kg) and vitamin E (0.2 g/kg) for 14 weeks to study the effects of dietary combinations of Q and vitamin E on the intestinal structure and barrier

integrity in aged breeder chickens. The findings demonstrated that Q + vitamin E had synergistic effects on intestinal morphology by increasing villus height and crypt depth and by reducing inflammatory damage to the intestines of elderly chickens. Additionally, Q + vitamin E boosted the mRNA expression of intestinal tight junction proteins, such as occludin, ZO1, and claudin-1. Additionally, Q + vitamin E boosted the expression of anti-inflammatory genes (IL-10 and IL-4) while decreasing the mRNA expression of pro-inflammatory genes (TNF-α, IL-6, and IL-1) [26]. Cell-based, preclinical, and clinical intervention studies have investigated the mechanisms behind the impact of vitamin E on the immune system and inflammation. Vitamin E affects inflammatory mediators produced by other immune cells, which in turn affects the integrity of T-cell membranes, signal transduction, and cell division both directly and indirectly. Since it impacts the host's susceptibility to infectious diseases including respiratory infections as well as allergy and infectious diseases like asthma, vitamin E's control of immune function has therapeutic importance. In many responses to infection, inflammation, and immunological activation, IL-1 is a key player. In addition to osteoporosis and cancer-induced osteolysis, IL-1 has a role in the etiology of rheumatoid arthritis and osteolysis of orthopedic implants. It promotes osteoclast development and activity, which results in excessive bone resorption. Without the assistance of osteoblasts or stromal cells, IL-1 may directly encourage the development of osteoclasts. It works by activating NF-κB in osteoclasts and inhibiting apoptosis. It was shown that vitamin E has the capacity to prevent activated monocytes from producing IL-1. Both hemopoietic and nonhematopoietic cells produce IL-6 in response to diverse forms of stimulation. Under the control of parathyroid hormone, vitamin D3, growth factor, and other cytokines, stromal cells and osteoblasts release IL-6 during bone remodeling in nanomolar amounts. The production of IL-6 by osteoblasts in response to IL-1, TNF-α, and LPS stimulation has also been documented. Osteoclastogenesis would be encouraged, and NF-κB would be activated as a result of high cytokine levels.

Animals with ovariectomy-induced estrogen shortage had higher levels of IL-1 and IL-6. Treatment with palm-derived T3 at 60 mg/kg was successful in preventing cytokine levels from increasing. In addition to enhancing bone microstructure in MetS mice, palm-derived T3 and annatto-derived T3 decreased inflammatory marker levels (IL-1 and IL-6). Researchers found that annatto T3 improved trabecular and cortical microstructure, raised serum procollagen I intact N-terminal propeptide while decreasing serum carboxyl-terminal telopeptide of type I collagen, and inhibited the expression of inflammation markers (MCP-1, IL-2, IL-23, IFN-γ, and TNF-α) in a distinct investigation [27–29]. Animals treated with free radicals and nicotine were also used to clarify the unique ways that vitamin E affects inflammatory indicators. Free radicals produced by ferric nitrilotriacetate increased the levels of OCN, IL-1, and IL-6 and negatively affected bone histomorphometry. By supplementation with a palm oil T3 combination at a rate of 100 mg/kg, these unfavorable alterations were reversed. Inflammatory cytokines and markers of bone resorption were both elevated after two months of nicotine administration, whereas a marker of bone production was decreased. Vitamin E at a dose of 60 mg/kg demonstrated effectiveness in enhancing all these parameters when compared to the control group. In a different investigation, it was found that 60 mg/kg of a palm T3 combination might prevent the rise in IL-1 and IL-6 caused by nicotine administration [30]. In contrast, in experimental animal models, ultrahigh molecular weight polyethylene (VE-UHMWPE) combined with vitamin E has been shown to have higher mechanical performance and less unfavorable cellular responses than ordinary polyethylene.

	TT	TF
Inflammatory cytokines	TNF-α, IL-1β, IL-6, IL-8 PGE2, COX-2, MCP-1, 5-LOX	LTB4, exotoxin 3, TNF-α MCP-1, 5-LOX, MPO, MDA TNF-α, IL-1β, IL-6
Signaling pathway	NF-κB, IRE1α, PPAR caspase-4, Nrf2, MPK, PI3K/Akt/mTOR, Ras–Raf–MEK–ERK, JAK/STAT	JAK/STAT, NF-κB, JNK/p38, Nrf2, ERK1/2, PPAR

Table 3.
Inflammatory factor and related signaling pathways which vitamin E regulated.

Human macrophages stimulated by VE-UHMWPE particles showed a different transcriptional program from macrophages stimulated by UHMWPE particles. IL-27 was one of the upregulated genes, and it was discovered that in macrophages cultivated with VE-UHMWPE particles as opposed to those cultivated with UHMWPE particles, its levels were much higher. IL-27 decreased the inflammatory response induced by standard UHMWPE particles *in vitro* and prevented osteoclasts from differentiating [31].

When combined, the information from these previous articles showed that vitamin E had anti-inflammatory characteristics that can protect against osteoporosis (TNF-α, IL-1, IL-6, IL-27, MCP-1) (**Table 3**) [32]. Furthermore, other inflammatory cytokines, including IL-7, IL-8, IL-11, and IL-34, IL-3, IL-4, IL-10, IL-12, and IL-33, whether regulated by vitamin E in osteoclastogenesis need further research.

4.3 Vitamin E suppresses oxidative stress in preventing bone loss

Reactive oxygen species (ROS) and reactive nitrogen species are the two types of free radicals that are most frequently mentioned when discussing oxidative stress. An imbalance among these free radical oxidants and the cells' antioxidant defenses leads to cellular damage. Chain reactions affecting DNA, proteins, cell wall lipoproteins, and other biological components are triggered by damage from free radical molecules such as superoxide (O_2–). Additionally, NF-κB and other pathways are activated, which upregulate the TNF-α and IL-1 downstream cytokines. Through inhibition or activation of several cellular pathways, changes in the cell and its organelles modify cellular function. These alterations result in inflammation (through IL-4, IL-6, TNF-α, and other factors), changes to crucial cellular processes, and even mitochondria-initiated cell death and apoptosis, which, in severe cases, can result in organ damage. According to the mitochondrial theory of aging, chronic cumulative oxidative stress encourages disease conditions and early aging. Oxidative stress has been linked to a wide range of chronic diseases, including osteoporosis, in a significant body of literature ever since the mitochondrial theory of aging was first proposed [33]. The mitochondria of the cell are where ROS are typically present. An oxygen molecule (O_2) is combined with four electrons and four protons to create two water molecules during the electron transport process in the mitochondria of the cell. This transfer results in the formation of a superoxide ion (O_2^-) or, less frequently, a hydroxide (OH-) or peroxide ion (O_2^{2-}), each of which is a reactive-free radical in ROS form. Normally, the antioxidant enzymes superoxide dismutase (SOD) and peroxidase convert these ROS into the less reactive molecules hydrogen peroxide (H_2O_2) and water (H_2O). The nicotinamide adenine dinucleotide phosphate (NADP-NADPH) cycle, which neutrophils use to destroy

viruses and bacteria, xanthine oxidase reactions during purine catabolism, nitric oxide synthase reactions during nitric oxide synthesis, and cyclooxygenases (COX) in the pathway for prostaglandin synthesis are some additional cellular pathways that produce ROS. Despite having the potential to cause damage, ROS and RNS are essential for healthy cell function because they play a role in cellular messaging that controls processes including gene transcription and transduction, differentiation, apoptosis, and repair. To minimize the negative effects of unchecked oxidative stress, natural cellular defenses against ROS and RNS work to preserve equilibrium rather than eliminate them. Oxidative stress is accelerated by anything that speeds up mitochondrial metabolism in the cell. Examples include fractures, surgery, and trauma injuries, infections, the detoxification of drugs or alcohol, high oxygen conditions, smoke inhalation, elevated salt concentrations, and heavy metal exposure. Oxidative stress is also heightened by radiation from radiographic, solar, cosmic, or electromagnetic sources. Even consuming foods devoid of naturally occurring antioxidants, such as processed sugars and some fatty acids, increases oxidative stress. Additional factors that may contribute to an increase in oxidative stress include dehydration, stress, anxiety, and possibly inadequate sleep. OPG and RANKL expression are both susceptible to the oxidative state, which lowers OPG expression and raises RANKL expression, tipping the scales in favor of bone loss. In response to excessive oxidative stress, sclerostin and DKK-1, two WNT pathway inhibitors, involved in the osteoimmunological regulation of bone remodeling, are increased, while OPG production is decreased. Aging, which is characterized by an increase in oxidative stress, and inflammatory mediators appear to be the two situations that most strongly promote the production of WNT pathway inhibitors. Increases in pro-oxidants have been associated with decreased osteoprogenitor development into the osteoblast cell lineage. Oxidative stress inhibits rabbit bone marrow stromal cells and calvarial osteoblasts differentiate into osteoblasts, according to research by Bai et al. Differentiation markers for this include decreased levels of ALP, type-I collagen, and nuclear phosphorylation of Runx2. OPG production is lowered as a result of decreased osteoblast activity. This decrease further modifies the overall RANKL/OPG ratio, which is essential for maintaining the balance of osteoblastic and osteoclastic activity. Oxidative stress causes an increase in apoptosis in osteoblasts and osteocytes. The cytokines for osteoblastic activity are reduced with osteocyte death, which further favors osteoclastogenesis. Additionally, osteocytes that are dead or dying induce osteoclastogenesis. Antioxidants, such as GSH, N-acetylcysteine, and alpha-lipoic acid, reduce these effects.

Given the rapidly changing potential role of oxidative stress in osteoporosis, reducing oxidative stress with an antioxidative agent may be a practical way to prevent osteoporosis. Strong free radical scavenger vitamin E has been shown to have bone-protective properties by reducing oxidative stress. Osteoblasts were protected against the negative effects of H_2O_2 by treatment with tocotrienol (1 μM) for 24 hours in a study using an H_2O_2-induced osteoblast model. In ovariectomized models, tocotrienol treatments both short-term and long-term successfully increased femur bone mineral density, bone formation, and strength. In addition, osteocalcin, bone morphogenetic protein 2 (BMP-2), and RUNX-2 mRNA expression in the tibia increased after tocotrienol treatments [34]. In an *in vitro* study that looked at the effects of tocotrienol on lipid peroxidation, antioxidant enzyme activities, and apoptosis of osteoblasts exposed to H_2O_2, tocotrienol was able to prevent malondialdehyde (MDA) elevation, decrease osteoblast apoptosis, and increase SOD, GPx, and CAT activities. It has also been shown that other natural compounds, including tocotrienols, rice protein, melatonin, and others, lower ROS by increasing heme oxygenase-1 (HO-1)

activity, which may potentially counteract the negative effects of oxidative stress [35]. Nuclear respiratory factor 2(NRF2) significantly controls the transcription of these antioxidants. Under normal circumstances, NRF2 is recruited by Kelch-like ECH-associated protein 1 (KEAP1) into the Cul3-containing E3 ubiquitin ligase complex, where it is ubiquitylated and degraded. In contrast, oxidative stress inhibits the function of the E3 ubiquitin ligase, which causes NRF2 and KEAP1 to separate. The transcription of SOD, CAT, HO-1, GPxs is then activated once Nrf2 enters the nucleus and forms a heterodimer with tiny Maf proteins in antioxidant response elements (AREs), a conserved gene sequence in target gene promoter regions. By triggering the NRF2-KEAP1-ARE pathway, tocotrienols, rice protein, melatonin, and other naturally occurring substances that are NRF2 activators may reduce ROS. However, in Fujita's investigation, treatment with α-tocopherol had no effect on the proliferation of osteoclast precursors or the survival of mature osteoclasts. Instead, it increased the number of tartrate-resistant acid phosphatase (TRAP)-positive multinucleated osteoclasts. Additionally, they examined whether vitamin E's antioxidant characteristics were necessary for it to trigger the fusion of osteoclasts. None of the vitamin E isoforms, with the exception of α-tocopherol, induced osteoclast fusion [36]. This result indicated that vitamin E decreases bone mass by stimulating osteoclast fusion.

Vitamin E has shown tremendous promise in the treatment of postmenopausal osteoporosis because it is an efficient source for halting bone loss by suppressing oxidative stress.

4.4 Other mechanisms of vitamin E in preventing bone loss

Initially, a hormone mostly made by adipose tissue, leptin, regulates satiety and energy expenditure by acting on the hypothalamus. Leptin has a variety of effects, including the promotion of hemopoietic and osteoblastic differentiation, which it uses to control bone mass. Prior studies have shown that leptin has distinct effects on bone metabolism through both central and peripheral pathways. The brain's hypothalamic leptin receptors were activated in groundbreaking *in vivo* research, which showed that doing so decreased osteoblast formation and function and boosted osteoclast activity [37]. Two downstream molecular cascades are active: (a) an increase in RANKL through the PKA signaling pathway to encourage osteoclasts' effects on bone resorption; and (b) a decrease in c-myc expression, which encourages the production of cyclin D and prevents osteoblast development. An earlier study found that compared to healthy control animals fed a standard chow diet, rats on a high-carb, high-fat diet displayed symptoms of MetS, hyperleptinemia, and hypoadiponectinemia as well as damage to the trabecular microarchitecture. The increased leptin was decreased by palm and annatto T3 treatments [28, 29]. MicroRNA (miRNA) is a small, highly conserved endogenous noncoding RNA molecule with 20–22 bases that controls the expression of proteins. The differentiation of osteoclasts and miRNA expression are closely related processes. Several miRNAs inhibit osteoclast development and function by targeting the RANK/RANKL/OPG pathway. The expression of RANKL was suppressed by miR-17/20a and miR-26a. In bone marrow-derived macrophages, other miRNAs displayed suppression on osteoclast development through the TGF-β/SMAD signaling pathway. Insufficient vitamin E led to lower levels of miR-122a and miR-125b in the rat liver. These results suggest that vitamin E may regulate miRNA expression, which may be crucial for the regulation of bone homeostasis. The precise mechanism needs to be further researched [38, 39].

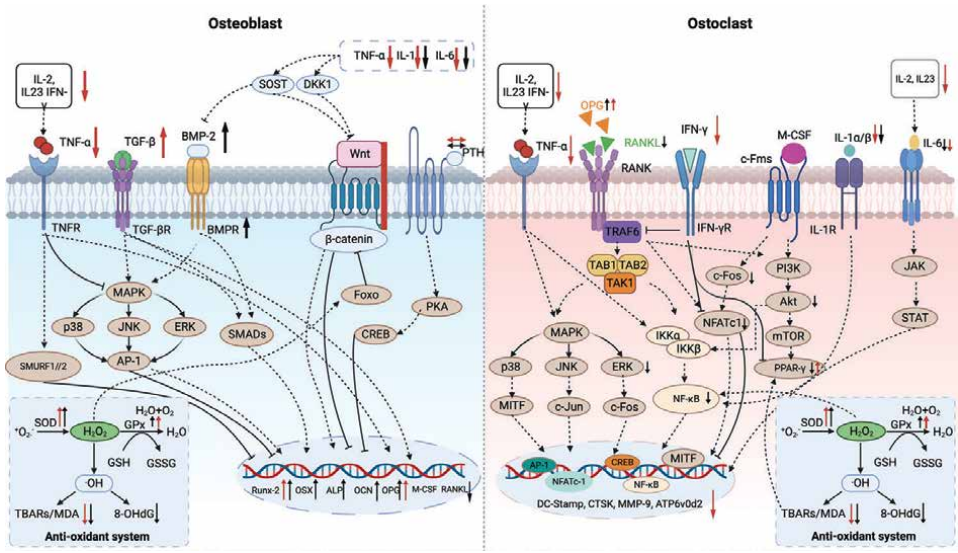

Figure 1.
The molecular mechanism of vitamin E on osteoblast or osteoclast. The effects of TF (red arrows) and TT (black arrows) on osteoblast and osteoclast are indicated.

5. Conclusion

Osteoporosis is the most prevalent orthopedic disease in elderly people. Vitamin E has shown great potential in treating osteoporosis. The close synchronization between bone resorption and formation is facilitated by the activation or inhibition of numerous downstream signaling pathways, which are controlled by endocrine and paracrine regulators. The molecular targets of vitamin E in regulating bone metabolism have been identified by numerous scientific studies (**Figure 1**). In order to inhibit osteoclasts, vitamin E altered the levels of inflammatory mediators, ROS, and hormones as well as the RANK/RANKL/OPG, NF-κB, MAPK, and oxidative stress signaling pathways. Vitamin E could be selected as a novel therapy against osteoporosis.

Acknowledgements

Chen YJ, Yu NC, and Zhou DG gathered literatures and drafted this manuscript. Li ZG, Gong FQ, Yi WJ, and Chen BT provided valuable opinions and assistance in the process of the research. GJ supervised this study and revised this manuscript. This study was supported by the National Natural Science Foundation of China (82074233), Starting Package of Xiang'an Hospital of Xiamen University (PM201809170009), National Natural Science Foundation of Xiamen, China (3502Z20227119), and Young Investigator Research Program of Xiang'an Hospital of Xiamen University (PM202103050009).

Conflict of interest

The authors declare no conflict of interest.

Author details

Chen Yongjie, Yu Naichun, Zhou Daguo, Li Zongguang, Gong Fengqing, Yi Weijiang, Chen Botao and Ji Guangrong*
Department of Orthopedics Surgery, Xiang'an Hospital of Xiamen University, School of Medicine, Xiamen University, Xiamen, China

*Address all correspondence to: jiguangrong@sina.cn

IntechOpen

References

[1] Ensrud KE, Crandall CJ. Osteoporosis. Annals of Internal Medicine. 2017;**167**(3):Itc17-itc32

[2] Reid IR, Billington EO. Drug therapy for osteoporosis in older adults. Lancet. 2022;**399**(10329):1080-1092

[3] Song S, Guo Y, Yang Y, Fu D. Advances in pathogenesis and therapeutic strategies for osteoporosis. Pharmacology & Therapeutics. 2022;**237**:108168

[4] Anam AK, Insogna K. Update on osteoporosis screening and management. The Medical Clinics of North America. 2021;**105**(6):1117-1134

[5] Sánchez A, Blanco R. Osteonecrosis of the jaw (ONJ) and atypical femoral fracture (AFF) in an osteoporotic patient chronically treated with bisphosphonates. Osteoporosis International. 2017;**28**(3):1145-1147

[6] Khosla S, Hofbauer LC. Osteoporosis treatment: Recent developments and ongoing challenges. The Lancet Diabetes and Endocrinology. 2017;**5**(11):898-907

[7] Soeta S, Higuchi M, Yoshimura I, Itoh R, Kimura N, Aamsaki H. Effects of vitamin E on the osteoblast differentiation. The Journal of Veterinary Medical Science. 2010;**72**(7):951-957

[8] Wan Hasan WN, Abd Ghafar N, Chin KY, Ima-Nirwana S. Annatto-derived tocotrienol stimulates osteogenic activity in preosteoblastic MC3T3-E1 cells: A temporal sequential study. Drug Design, Development and Therapy. 2018;**12**:1715-1726

[9] Amarasekara DS, Kim S, Rho J. Regulation of osteoblast differentiation by cytokine networks. International Journal of Molecular Sciences. 2021;**22**(6):3288

[10] Amarasekara DS, Yun H, Kim S, Lee N, Kim H, Rho J. Regulation of osteoclast differentiation by cytokine networks. Immune Network. 2018;**18**(1):e8

[11] Abd Manan N, Mohamed N, Shuid AN. Effects of low-dose versus high-dose γ-Tocotrienol on the bone cells exposed to the hydrogen peroxide-induced oxidative stress and apoptosis. Evidence-based Complementary and Alternative Medicine. 2012;**2012**:680834

[12] Brooks R, Kalia P, Ireland DC, Beeton C, Rushton N. Direct inhibition of osteoclast formation and activity by the vitamin E isomer gamma-tocotrienol. International Journal for Vitamin and Nutrition Research. 2011;**81**(6):358-367

[13] Johnson SA, Feresin RG, Soung do Y, Elam ML, Arjmandi BH. Vitamin E suppresses ex vivo osteoclastogenesis in ovariectomized rats. Food & Function. 2016;**7**(3):1628-1633

[14] Kim KW, Kim BM, Won JY, Min HK, Lee SJ, Lee SH, et al. Tocotrienol regulates osteoclastogenesis in rheumatoid arthritis. The Korean Journal of Internal Medicine. 2021;**36**(Suppl. 1): S273-Ss82

[15] Mohamad Hazir NS, Yahaya NHM, Zawawi MSF, Damanhuri HA, Mohamed N, Alias E. Changes in metabolism and mitochondrial bioenergetics during polyethylene-induced osteoclastogenesis. International Journal of Molecular Sciences. 2022;**23**(15):8331

[16] Badraoui R, Ben-Nasr H, Amamou S, El-May MV, Rebai T. Walker

256/B malignant breast cancer cells disrupt osteoclast cytomorphometry and activity in rats: Modulation by α-tocopherol acetate. Pathology, Research and Practice. 2014;**210**(3):135-141

[17] Vakili S, Zal F, Mostafavi-Pour Z, Savardashtaki A, Koohpeyma F. Quercetin and vitamin E alleviate ovariectomy-induced osteoporosis by modulating autophagy and apoptosis in rat bone cells. Journal of Cellular Physiology. 2021;**236**(5):3495-3509

[18] Vallibhakara SA, Nakpalat K, Sophonsritsuk A, Tantitham C, Vallibhakara O. Effect of vitamin E supplement on bone turnover markers in postmenopausal osteopenic women: A double-blind, randomized, placebo-controlled trial. Nutrients. 2021;**13**(12):4266

[19] Ambroszkiewicz J, Sands D, Gajewska J, Chelchowska M, Laskowska-Klita T. Bone turnover markers, osteoprotegerin and RANKL cytokines in children with cystic fibrosis. Advances in Medical Sciences. 2013;**58**(2):338-343

[20] Lee JH, Kim HN, Yang D, Jung K, Kim HM, Kim HH, et al. Trolox prevents osteoclastogenesis by suppressing RANKL expression and signaling. The Journal of Biological Chemistry. 2009;**284**(20):13725-13734

[21] Ha H, Lee JH, Kim HN, Lee ZH. α-Tocotrienol inhibits osteoclastic bone resorption by suppressing RANKL expression and signaling and bone resorbing activity. Biochemical and Biophysical Research Communications. 2011;**406**(4):546-551

[22] Galliera E, Ragone V, Marazzi MG, Selmin F, Banci L, Corsi Romanelli MM. Vitamin E-stabilized UHMWPE: Biological response on human osteoblasts to wear debris. Clinica Chimica Acta. 2018;**486**:18-25

[23] Mohamad NV, Ima-Nirwana S, Chin KY. Self-emulsified annatto tocotrienol improves bone histomorphometric parameters in a rat model of oestrogen deficiency through suppression of skeletal sclerostin level and RANKL/OPG ratio. International Journal of Medical Sciences. 2021;**18**(16):3665-3673

[24] Mosca A, Crudele A, Smeriglio A, Braghini MR, Panera N, Comparcola D, et al. Antioxidant activity of Hydroxytyrosol and vitamin E reduces systemic inflammation in children with paediatric NAFLD. Digestive and Liver Disease. 2021;**53**(9):1154-1158

[25] Al-Hashem F, Abd Ellatif M, ShamsEldeen AM, Kamar SS, Al-Ani B, Haidara MA. Vitamin E protects against the modulation of TNF-α-AMPK axis and inhibits pancreas injury in a rat model of L-arginine-induced acute necrotising pancreatitis. Archives of Physiology and Biochemistry. 2023;**129**(1):148-156

[26] Amevor FK, Cui Z, Du X, Ning Z, Deng X, Xu D, et al. Supplementation of dietary quercetin and vitamin E promotes the intestinal structure and immune barrier integrity in aged breeder hens. Frontiers in Immunology. 2022;**13**:860889

[27] Muhammad N, Luke DA, Shuid AN, Mohamed N, Soelaiman IN. Tocotrienol supplementation in postmenopausal osteoporosis: Evidence from a laboratory study. Clinics (São Paulo, Brazil). 2013;**68**(10):1338-1343

[28] Wong SK, Chin KY, Suhaimi FH, Ahmad F, Ima-Nirwana S. The effects of vitamin E from Elaeis guineensis (oil palm) in a rat model of bone loss due

to metabolic syndrome. International Journal of Environmental Research and Public Health. 2018;**15**(9):1828

[29] Wong SK, Chin KY, Suhaimi FH, Ahmad F, Ima-Nirwana S. Exploring the potential of tocotrienol from Bixa orellana as a single agent targeting metabolic syndrome and bone loss. Bone. 2018;**116**:8-21

[30] Norazlina M, Lee PL, Lukman HI, Nazrun AS, Ima-Nirwana S. Effects of vitamin E supplementation on bone metabolism in nicotine-treated rats. Singapore Medical Journal. 2007;**48**(3):195-199

[31] Terkawi MA, Kadoya K, Takahashi D, Tian Y, Hamasaki M, Matsumae G, et al. Identification of IL-27 as potent regulator of inflammatory osteolysis associated with vitamin E-blended ultra-high molecular weight polyethylene debris of orthopedic implants. Acta Biomaterialia. 2019;**89**:242-251

[32] Ungurianu A, Zanfirescu A, Nițulescu G, Margină D. Vitamin E beyond its antioxidant label. Antioxidants (Basel). 2021;**10**(5):634

[33] Kimball JS, Johnson JP, Carlson DA. Oxidative stress and osteoporosis. The Journal of Bone and Joint Surgery. American Volume. 2021;**103**(15):1451-1461

[34] Shen CL, Klein A, Chin KY, Mo H, Tsai P, Yang RS, et al. Tocotrienols for bone health: A translational approach. Annals of the New York Academy of Sciences. 2017;**1401**(1):150-165

[35] Wang Z, Liang M, Li H, Cai L, Yang L. Rice protein exerts anti-inflammatory effect in growing and adult rats via suppressing NF-κB pathway. International Journal of Molecular Sciences. 2019;**20**(24):6164

[36] Fujita K, Iwasaki M, Ochi H, Fukuda T, Ma C, Miyamoto T, et al. Vitamin E decreases bone mass by stimulating osteoclast fusion. Nature Medicine. 2012;**18**(4):589-594

[37] Takeda S, Elefteriou F, Levasseur R, Liu X, Zhao L, Parker KL, et al. Leptin regulates bone formation via the sympathetic nervous system. Cell. 2002;**111**(3):305-317

[38] Kim K, Kim JH, Kim I, Lee J, Seong S, Park YW, et al. MicroRNA-26a regulates RANKL-induced osteoclast formation. Molecules and Cells. 2015;**38**(1):75-80

[39] Shi C, Qi J, Huang P, Jiang M, Zhou Q, Zhou H, et al. MicroRNA-17/20a inhibits glucocorticoid-induced osteoclast differentiation and function through targeting RANKL expression in osteoblast cells. Bone. 2014;**68**:67-75

Edited by Juber Akhtar, Mohammad Ahmad, Mohammad Irfan Khan and Badruddeen

Vitamin B is a water-soluble vitamin that plays important roles in cell metabolism and synthesis of red blood cells. Many foods contain B vitamins, including meat, poultry, and fish, among others. Vitamin E is a fat-soluble vitamin with antioxidant properties that can be found in vegetable oils, cereals, meat, poultry, eggs, and fruits. Both vitamins B and E are important for human health. This book provides a comprehensive overview of vitamins B and E. It is organized into three sections on the role of vitamin B on body health and gut flora, vitamin B deficiency and its association with the disease pellagra, and the medicinal significance and complications associated with vitamin E deficiency.

Published in London, UK

IntechOpen

ISBN 978-1-83768-380-2